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ORIGINAL ARTICLE

The other colon cancer: a population-based cohort study of appendix tumour trends and prognosis

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Abstract

Aim: Appendiceal neoplasms are rare subtypes of colorectal tumours that mainly affect younger patients some 20 years earlier than other colon tumours. The aim of this study was to gain more insight into the histological subtypes of this rare disease and include cases previously excluded, such as mucinous neoplasia.

Method: The cohort study included 1097 patients from the Munich Cancer Registry (MCR) diagnosed between 1998 and 2020. Joinpoint analysis was used to determine trend in incidence. Baseline demographic comparisons and survival analyses using competing risk and univariate/multivariate methods were conducted according to tumour histology:

[Correction added on 17 March 2023, after first online publication: The first and last names of the first four authors were inadvertently swapped and have now been corrected in this version.]

adenocarcinoma (ADENO), neuroendocrine neoplasia (NEN), mixed adeno-neuroendocrine carcinoma (MANEC), and low- (LAMN) and high-grade mucinous neoplasia (HAMN).

Results: Up to 2016 the number of cases increased significantly [annual per cent change (APC) = 6.86, $p < 0.001$] followed by a decline in the following years (APC = −14.82, $p = 0.014$; average APC = 2.5, $p = 0.046$). Comparison of all patients showed that NEN (48.4%) and mucinous neoplasms (11.6%) had a considerably better prognosis than ADENO (36.0%) and MANEC (3.0%, $p < 0.0001$). A multivariate analysis within the NEN and ADENO subgroups revealed that further histological classification was not prognostically relevant, while older age and regional tumour spread at diagnosis were associated with a poor prognosis. ADENO histology with high tumour grade and appendectomy only was also associated with poorer survival.

Conclusion: Appendiceal neoplasms are histologically heterogeneous; however, this diversity becomes less relevant compared with the marked difference from cancers of the remaining colon. The previously observed increase in cases appears to be abating; fewer cases of appendicitis and/or appendectomies or changes in histopathological assessment may be behind this trend.

KEYWORDS
appendiceal neoplasia, appendix tumour, cancer epidemiology, rare cancer, survival analysis

INTRODUCTION

The most common affliction of the appendix is appendicitis, with an approximate incidence in Germany of 100 per 100000 (2021) [1]. During the surgical treatment and the pathological inspection of the removed organ an incidental diagnosis of appendiceal neoplasia may be made. While this disease is rare, a trend of increasing case numbers continues to be reported with no known cause [2–4]. Although the organ is small it gives rise to a wide variety of neoplasms. These are broadly classified according to their histopathological characteristics into neuroendocrine, adenocarcinoma, mixed adenocarcinoma and neuroendocrine, as well as different subtypes of mucinous neoplasia [5].

Regardless of the underlying histopathology, there is increasing evidence that these tumours may behave distinctly differently from other colorectal cancers (CRCs). However, due to the rarity of the disease and its heterogeneous manifestation several aspects of its clinical management have been adopted from CRC, and most advanced tumours are treated similarly to metastatic CRC [6]. Apart from mucinous neoplasms with peritoneal dissemination, in which intraoperative hyperthermic intraperitoneal chemotherapy (HIPEC) is used as a treatment modality, no treatment regimen has yet proven superior [7]. To date there is only a small number of publications on this disease. The largest published population-based study on appendiceal neoplasms was conducted using Surveillance, Epidemiology and End Results (SEER) data in 2002 and 2015, a more recent study from 2020 used SEER and Canadian Cancer Registry data from 1992 to 2016 [2, 3, 8]. In these reports a significant increase in cases was seen in patients from North America. However, in the latest publication from 2020, the categories mixed adeno-neuroendocrine carcinoma (MANEC), goblet cell adenocarcinoma and mucinous neoplasia were not considered separately and were analysed together with neuroendocrine tumours (NET) and mucinous adenocarcinomas, respectively, in accordance to the previous WHO classification of Tumours of the Digestive System 4th edition [9]. In addition, there are only a few reports that used European population-based data on the appendix in its entirety [10]. The primary objective of this study was therefore to quantify the time trends in overall cases of appendiceal neoplasms within a population-based setting and determine prognostic and predictive factors affecting time to progression and survival [11].

What does this paper add to the literature?

This paper gives and in-depth analysis of the clinical and prognostic features of histological subtypes of appendiceal tumours in a representative cohort of patients. Previous studies were nearly all based on Surveillance, Epidemiology, and End Results data and did not include mucinous neoplasia. In addition, our study provides prognostic results based on multivariate and competing risk analysis.

METHODS

Data collection

The catchment area of the Munich Cancer Registry (MCR) currently encompasses a population of approximately 4.9 million inhabitants [12]. Pathology reports of solid tumours from all pathology laboratories in this catchment area are available and provide the total

number of malignant cases in the region and the respective prognostic factors. In parallel, patient demographics, prognostic factors, treatment and follow-up information are reported from clinicians. In addition, life status of patients with a cancer diagnosis is maintained systematically through death certificates.

Out of this population, a total of 1252 cases with a diagnosis of appendiceal neoplasm between 1998 and 2020 were retrieved from the MCR Oracle database in October 2021. The life status follow-up was available up until June 2021.

Definition of diagnoses and patient sample

Cases were identified according to the International Classification of Diseases (ICD-10; GM Version 2020) and based on the diagnosis code (C18.1, D12.1 and D37.3). Participants not living within the MCR catchment area ($n = 184$), age at diagnosis below 18 years ($n = 50$), missing date of diagnosis ($n = 3$) or sarcoma histology ($n = 1$) were excluded, resulted in a final study cohort of 1097 patients for incidence analysis. For demographic analyses based on the tumour histology, a further two patients with a missing histology finding were excluded, leading to a total of 1095 patients. Histological subgroups were defined according to the WHO Classification of Tumours, 5th edition, 2019 [5]. The respective ICD-O-3 codes are listed in supplementary Table S1. Although signet ring-cell adenocarcinoma is not consistently regarded as a separate subgroup within the adenocarcinoma category, it does show a distinctly poorer prognosis compared with other subtypes. Therefore the results below consider these data separately, and these tumours are hereafter referred to as adenocarcinoma with signet ring-cell involvement [13]. Histological subtypes of adenocarcinoma, namely mucinous, colonic-type, goblet cell and those with signet ring-cell involvement are collectively referred to as ADENO from here on. Similarly, neuroendocrine neoplasia (NEN) collectively refers to neuroendocrine carcinomas (NEC) and NET.

Endpoints and statistical analyses

In order to assess the change in incidence of appendiceal neoplasms over time, a Joinpoint regression analysis was conducted. The crude rate per 100000 and its standard error were calculated and subsequently adjusted to the German standard population. Joinpoint regression analysis and graphic visualization were completed in the Joinpoint Regression Program, version 4.9.0.0, provided by the Statistical Research and Applications Branch of the National Cancer Institute [14]. Regression model selection was done using the weighted Bayesian information criterion (p-value = 0.05), confidence intervals for the reported annual per cent change and average annual per cent change (APC/AAPC) were calculated using the parametric method.

Excluding patients with a previous or simultaneous tumour diagnosis ($n = 230$) resulted in a total 865 patients for survival analyses.

Univariate overall survival (OS) from date of diagnosis until date of death was estimated using the Kaplan–Meier method and tested using the log-rank test. Relative survival (RS) as an estimation of cancer-specific survival was calculated using the ratio of the observed to the expected survival rate. The latter was estimated using the Ederer II method and age- and sex-matched life tables of the German population. Significant differences were determined according to the 95% confidence intervals (CIs) of the individual subgroups at defined time points. For multivariate analysis of independent survival factors, a Cox proportional hazards model was used, with proportional hazard assumption being tested by plotting the log(−log(survival)) against the log of the follow-up time. Time to progression data were calculated from the date of diagnosis until the first progression. To account for the competing risk of death by any cause, a cumulative incidence analysis was used to calculate the time to progression. Differences among subgroups were assessed using the Fine–Grey test for equality of cumulative incidence functions [15]. A multivariate analysis of independent factors was assessed using the Fine–Grey subdistribution hazard model [16]. In all multivariate analyses, baseline variables were entered simultaneously as independent predictive variables for a multivariate analysis of risk for death or progression.

Pearson's chi-square or Fisher's exact test was used to compare categorical, and the Mann–Whitney U and Wilcoxon test for numerical variables between individual subgroups. Percentages for individual subgroups consider available data only, and missing values are given in relation to the underlying cohort or subgroup for the respective category. Unless otherwise stated, medians with upper and lower quartiles are reported for numerical variables. For all analyses, a two-sided p-value of 0.05 or less was considered statistically significant. Statistical Analysis Software version 9.4 (SAS Institute, Cary, NC) was used for data analysis.

RESULTS

Time trend analysis

The overall age-standardized incidence per 100000 for appendiceal neoplasia during the study period was 1.1 (1.2 in women and 1.1 in men). The results of the Joinpoint analysis for all analysed cases of appendiceal neoplasms are shown in Figure 1. Overall, the AAPC showed a slight increase in patients of 2.5 (95% CI [0.0–5.1]; $p = 0.046$) for the entire time period, 2.7 (95% CI [0.6–5.0]; $p = 0.013$) in men and 2.4 (95% CI [−1.9 to 6.8]; $p = 0.274$) in women.

Patient demographics, clinical treatment and outcome

Baseline demographic and tumour characteristics are summarized in Table 1. Over half of all patients were diagnosed with T3/T4 disease (62.4%), lymph node involvement was seen in 24.6% and metastasis in 16.8% of patients whose data were available. Missing T/N or TX/

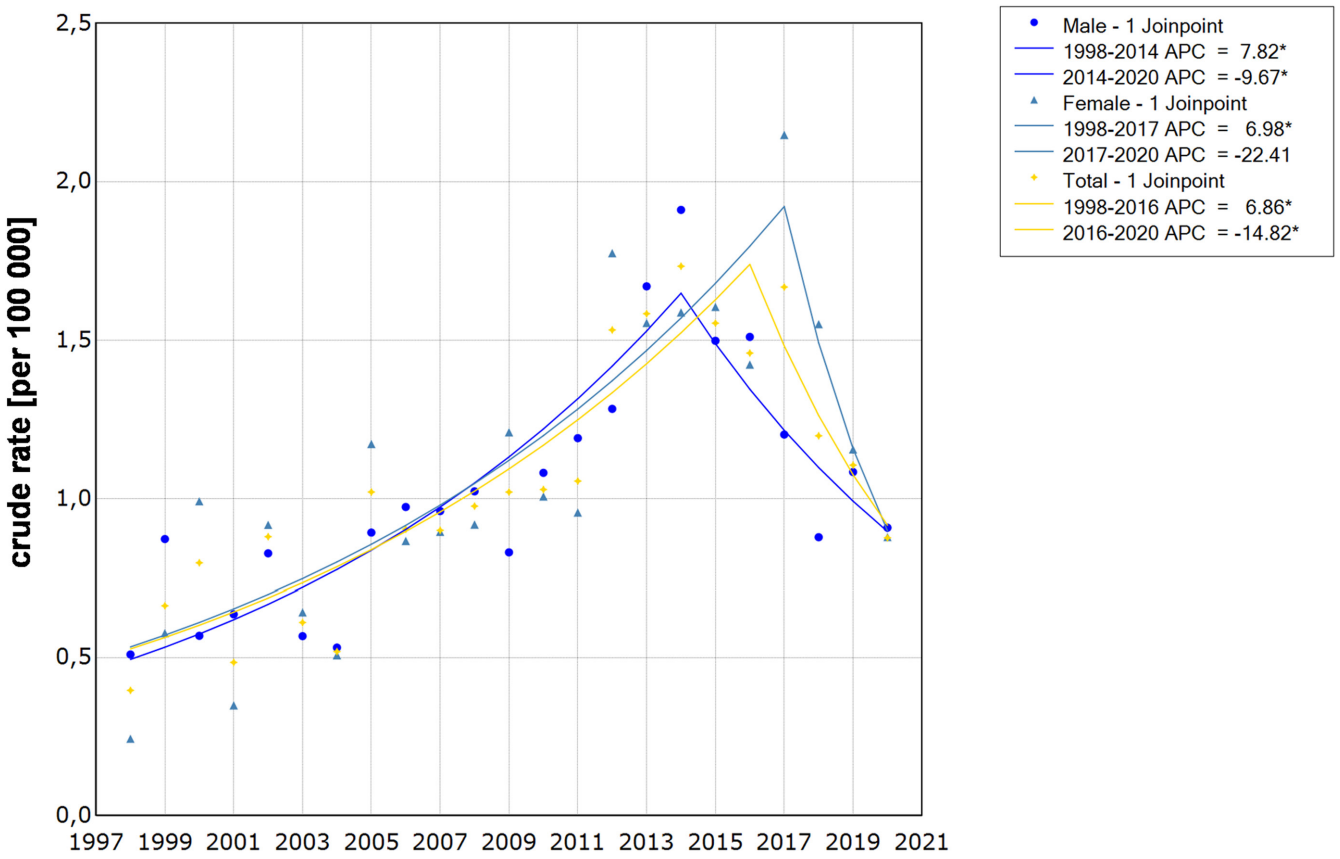

FIGURE 1 Joinpoint regression model for all appendiceal neoplasms recorded in the MCR database between 1998 and 2020. The crude rate per 100000 of the German standardized population per year is shown stratified by sex.

NX values were categorized as T1/2 and N0, respectively ($T_{Missing}$/TX, $n = 271$; $N_{missing}$/NX, $n = 581$), which were mainly attributed to cases of NEN, where only 18.1% underwent lymph node dissection. Observed metastatic sites lay mostly in the retroperitoneum. The current diagnosis represented the first tumour diagnosis in 81.3% of patients.

Comparison of tumour treatment showed a relatively similar strategy over all histological groups, which mainly consisted of the surgical removal of the tumour (surgery only 81.7%). A smaller percentage of patients also received chemotherapy (14.5%; Table 2).

The surgical tumour resection procedure was categorized as hemi-/sub- or total colectomy, segment resection, appendectomy or appendectomy plus or other surgical approaches. The appendectomy plus category ($n = 19$) includes cases where surgical tumour removal consisted of an appendectomy in addition to another surgical technique such as tumour/colon resection not otherwise specified ($n = 13$), omentectomy ($n = 4$) or Hartmann's procedure ($n = 2$).

After a median follow-up time of 6.9 years (95%CI [6.5–7.5]), comparison of histological subgroups showed the worst prognosis for patients diagnosed with MANEC and ADENO; NEN and mucinous neoplasia fared considerably better ($p < 0.0001$; Figure 2). In the multivariate analysis summarized in Figure 4 (Model 1), age and histological type were significant prognostic factors. ADENO and MANEC, as well as patients aged over 50 years at diagnosis, had a significantly worse prognosis.

Histological subgroups

Mucinous neoplasia and MANEC

Mucinous neoplasia was frequently diagnosed in Stage IV (28.4%) and exhibited a large tumour diameter (72 mm, 95% CI [22–100 mm]). This was mainly attributed to the presence of pseudomyxoma in 41.7% of cases. Mucinous neoplasms were mainly treated with surgery followed by chemotherapy. Women were more likely to undergo appendectomy or appendectomy plus/other than men (male 29.2%, female 63.8%; $p = 0.0003$).

The respective 5-year overall survival was 84.6% (95% CI [76.0–93.3]) for mucinous neoplasms. In mucinous neoplasia, sex, UICC or the presence of pseudomyxoma were not prognostically relevant (sex $p = 0.4854$; UICC $p = 0.9755$; pseudomyxoma $p = 0.6285$). Undergoing chemotherapy also did not affect survival ($p = 0.3389$), whereas age at diagnosis proved to be a significant factor ($p = 0.0020$).

Due to the low incidence of MANEC, the number of analyses was limited. Although MANEC patients were more likely to be male

TABLE 1 Baseline demographics separately for each histological group.

	All		Other		NEN		ADENO		MANEC		Mucinous neoplasia		
	(*N* = 1 095)		(*n* = 11, 1.0%)		(*n* = 530, 48.4%)		(*n* = 394, 36.0%)		(*n* = 33, 3.0%)		(*n* = 127, 11.6%)		
Patient characteristics	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%	*p*-value*
Sex													
Male	513	46.8	7	63.6	217	40.9	214	54.3	20	60.6	55	43.3	0.0002
Female	582	53.2	4	36.4	313	59.1	180	45.7	13	39.4	72	56.7	
Median age (years)													
Median (Q1–Q3)	57.4 (40.8–71.3)		70.9 (60.8–81.4)		47.0 (30.0–64.5)		64.2 (53.5–74.4)		56.3 (49.2–65.1)		60.3 (49.0–74.0)		<0.0001
Age at diagnosis (years)													
18–49	413	37.7	1	9.1	288	54.3	77	19.5	10	30.3	37	29.1	<0.0001
50–69	388	35.4	4	36.4	145	27.4	179	45.4	15	45.5	45	35.4	
70+	294	26.9	6	54.5	97	18.3	138	35.0	8	24.2	45	35.4	
UICC													
0/I	503	45.9	3	27.3	372	70.2	74	18.8	3	9.1	51	40.2	<0.0001
II	319	29.1	5	45.4	100	18.9	161	40.9	13	39.4	40	31.5	
III	89	8.1	0	-	37	7.0	48	12.2	4	12.1	0	-	
IV	184	16.8	3	27.3	21	4.0	111	28.2	13	39.4	36	28.3	
Grade													<0.0001
G1	482	61.5	3	37.5	356	92.7	68	21.8	3	11.5	52	96.3	
G2	164	20.9	3	37.5	21	5.5	134	42.9	4	15.4	2	3.7	
G3-4	138	17.6	2	25.0	7	1.8	110	35.3	19	73.1	-	-	
Missing/GX	311	28.4	3	27.3	146	27.5	82	20.8	7	21.2	73	57.5	
Tumour diameter (mm)													
Median (Q1 – Q3)	8.0 (4.0–15.0)		27.5 (20.0–35.0)		6.0 (4.0–12.0)		20.5 (10.0–40.0)		40.0 (15.5–61.5)		72.0 (22.0–100.0)		<0.0001
R stage													
R0	717	90.5	5	83.3	376	97.7	257	84.8	22	73.3	57	83.8	<0.0001**
R1/R2	75	9.5	1	16.7	9	2.3	46	15.2	8	26.7	11	16.2	
Missing/RX	303	27.7	5	45.5	145	27.4	91	23.1	3	9.1	59	46.5	
Histology													
NET	-	-	-	-	492	92.8	-	-	-	-	-	-	
NEC	-	-	-	-	38	7.2			-	-	-	-	
Mucinous	-	-	-	-	-	-	141	35.8	-	-	-	-	
Colonic-type	-	-	-	-	-	-	123	31.2	-	-	-	-	

(Continues)

TABLE 1 (Continued)

Patient characteristics	All (N = 1 095)		Other (n = 11, 1.0%)		NEN (n = 530, 48.4%)		ADENO (n = 394, 36.0%)		MANEC (n = 33, 3.0%)		Mucinous neoplasia (n = 127, 11.6%)		p-value*
	n	%	n	%	n	%	n	%	n	%	n	%	
Goblet cell	-	-	-	-	-	-	90	22.8	-	-	-	-	
Signet-ring cell	-	-	-	-	-	-	40	10.2	-	-	-	-	
LAMN	-	-	-	-	-	-	-	-	-	-	124	97.6	
HAMN	-	-	-	-	-	-	-	-	-	-	3	2.4	
Pseudomyxoma													
Yes	76	6.9	2	18.2	-	-	21	5.3	-		53	41.7	-
Simultaneous tumour													
Yes	123	11.2	1	9.1	80	15.1	26	6.6	2	6.1	14	11.0	-

Note: *p*-value compares main histological groups.

Abbreviations: HAMN, high-grade mucinous neoplasia; LAMN, low-grade mucinous neoplasia; MANEC, mixed adeno-neuroendocrine carcinoma; NEC, neuroendocrine carcinoma; NET, neuroendocrine tumor; UICC, Union for International Cancer Control.

*Chi-square comparison between NEN, ADENO, MANEC and mucinous neoplasia only.; **Comparison between R0 and R1/R2 only.

(60.6%), metastatic disease was more common in women (male 25%, female 61.5%; $p = 0.0358$). Similar survival results could not be calculated for the MANEC group due to the small number of cases.

Neuroendocrine neoplasia

Patients with NEN presented with the most favourable characteristics. Men were more frequently diagnosed with metastatic disease (male 7.4%, female, 1.6%; $p = 0.0008$). In patients with NET, men were a median 53.6 years (range 33.5–66.6 years) old at diagnosis compared with women, who were almost 10 years younger at diagnosis (42.4 years, range 27.7–62.4 years; $p = 0.0131$). Only 3% of patients presented with metastatic disease at initial diagnosis. The age difference was even more pronounced in NEC patients with men diagnosed at a median age of 58.3 years (range 53.1–77.0 years) compared with women diagnosed at 36.8 years (range 31.6–59.6 years; $p = 0.0126$). Here the rate of initial metastasis was 13.2%.

The respective 5-year overall survival of NEN was 89.9% (95% CI 86.7%–93.1%). Within the NEN subgroup, disseminated disease, older age at diagnosis and a more extensive surgical tumour resection procedure were associated with a poor prognosis (Figure 3).

Age and UICC continued to be major factors in a separate multivariate model for NEN (Figure 4, Model 2). NEC tumour biology was much more likely to result in disease progression within the following years compared with NET ($p = 0.0084$; Figure 3G).

Adenocarcinoma

In the ADENO subgroup over half of the patients were diagnosed with Stage III or IV disease (59.6%) and 30.0% had high-grade tumour biology. Where data on biomarkers were available, tumours were mainly KRAS mutated (19/34, 55.9%) and were microsatellite stable (MSI–; 41/44, 93.2%). Comparisons of histological subgroups within the ADENO category showed similar patterns, as reported elsewhere. Namely that patients with goblet-cell adenocarcinoma were majorly characterized with UICC stage 0/1/2 (83.3%) in contrast to colonic-type (58.5%), mucinous (50.3%) and adenocarcinoma with signet ring-cell involvement (42.5%, $p < 0.0001$). The distribution of high- versus low-grade tumour biology followed a similar pattern ($p < 0.0001$). The highest proportion of cases with lymph node involvement was observed in adenocarcinoma with signet ring-cell involvement (42.5%), followed by colonic-type (29.3%), mucinous (14.2%) and goblet-cell adenocarcinoma (10.0%, $p < 0.0001$). Metastatic disease was found most frequently in mucinous adenocarcinoma (44.0%) and adenocarcinoma with signet ring-cell involvement (37.5%). Colonic-type and goblet-cell adenocarcinoma presented with metastases in 19.5% and 11.1% of cases ($p < 0.0001$).

Female colonic-type and mucinous adenocarcinoma patients were approximately 7 years older than men at diagnosis (colonic-type $p = 0.0107$, mucinous $p = 0.0310$). Women with goblet-cell

TABLE 2 Treatment characteristics for each histological subgroup.

	Other		NEN		Adenocarcinoma		MANEC		Mucinous neoplasm	
	(*n* = 11)		(*n* = 530)		(*n* = 394)		(*n* = 33)		(*n* = 127)	
Treatment characteristics	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**	***n***	**%**
Treatment mode[a]										
Surgery only	7	70.0	500	98.2	277	72.3	22	68.8	89	72.4
Chemotherapy	3	30.0	8	1.6	105	27.4	9	28.1	34	27.6
Radiation therapy	0	-	2	0.4	5	1.3	1	3.1	0	–
Missing	1	9.1	21	4.0	11	2.8	1	3.0	4	3.2
Surgical tumour resection										
Hemi-/sub−/total colectomy	5	45.4	121	28.1	235	66.0	22	71.0	40	34.2
Segment resection	2	18.2	35	8.1	55	15.4	4	12.9	19	16.2
Appendectomy	1	9.1	257	59.6	43	12.1	5	16.1	50	42.7
Appendectomy plus/other	1	9.1	18	4.2	23	6.5	0	-	8	6.8
Missing	2	18.2	99	18.7	38	9.6	2	6.1	10	7.9
Lymph node dissection										
Yes	3	33.3	78	18.1	173	48.6	16	51.6	24	20.5
Surgery mode										
Elective	11	100	491	92.6	379	96.2	29	87.9	121	95.3
Emergency	0	-	39	7.4	15	3.8	4	12.1	6	4.7

Abbreviations: CTX, chemotherapy; MANEC, mixed adeno-neuroendocrine carcinoma; NEN, neuroendocrine neoplasms.
[a]Multiple mentions possible.

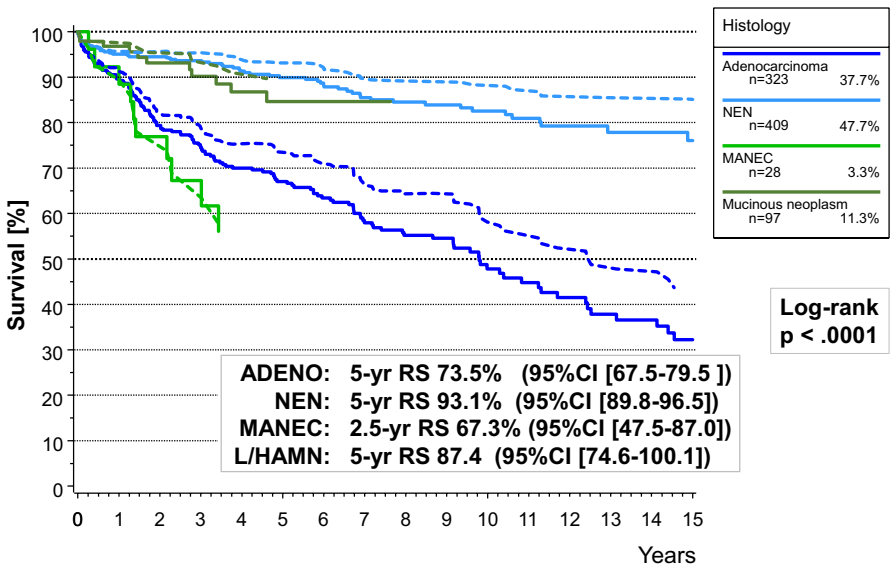

FIGURE 2 Overall and relative survival according to histological subgroup. Point estimates are given after 5 years. The number of patients in the MANEC cohort was small, and due to the low prognosis, a valid point estimate could only be reported after 2.5 years.

adenocarcinoma were more likely to present with advanced disease stages (Stage III/IV, 35.1%) than men (3.8%, $p = 0.0001$). Women in the ADENO group were more likely to undergo appendectomy or appendectomy plus/other (28.1%) rather than hemicolectomy or sub−/total colectomy or segment resection (72.0%) compared with men (10.4%, $p < 0.0001$). Women were also less likely to undergo chemotherapy (68.9%), although the difference was not significant (male 77.1%, $p = 0.0662$).

The respective 5-year overall survival of ADENO patients was 67.1% (95% CI 61.6%–72.5%). Sex, age and the histological subtype proved to be prognostically relevant in univariate analysis of ADENO patients (Figure 3).

Age continued to be a major factor in a multivariate model of ADENO cases (Figure 4). Besides older age, higher UICC stage, high grade and surgical tumour resection emerged as significant prognostic factors (Model 3). Regarding tumour resection procedure,

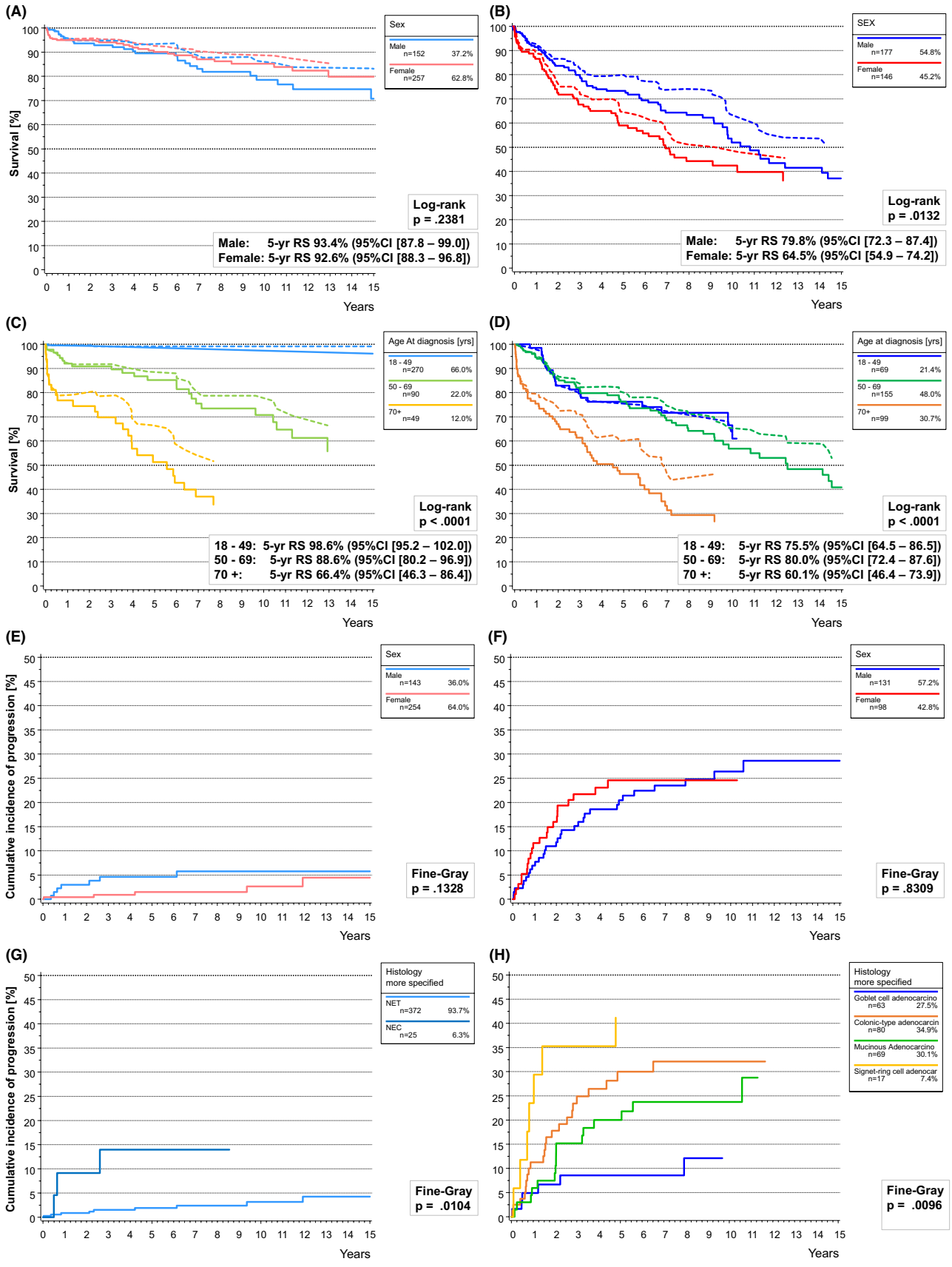

FIGURE 3 Overall and relative survival for NEN and ADENO according to clinical subgroups. Stratified by sex (A and B) and according to age at diagnosis (C and D). Cumulative incidence of progression in nonmetastasized patients only and considering competing risk of death by any cause (E–H). The risk for progression is shown according to sex and histology in both NEN (E, G) and ADENO (F, H) patients.

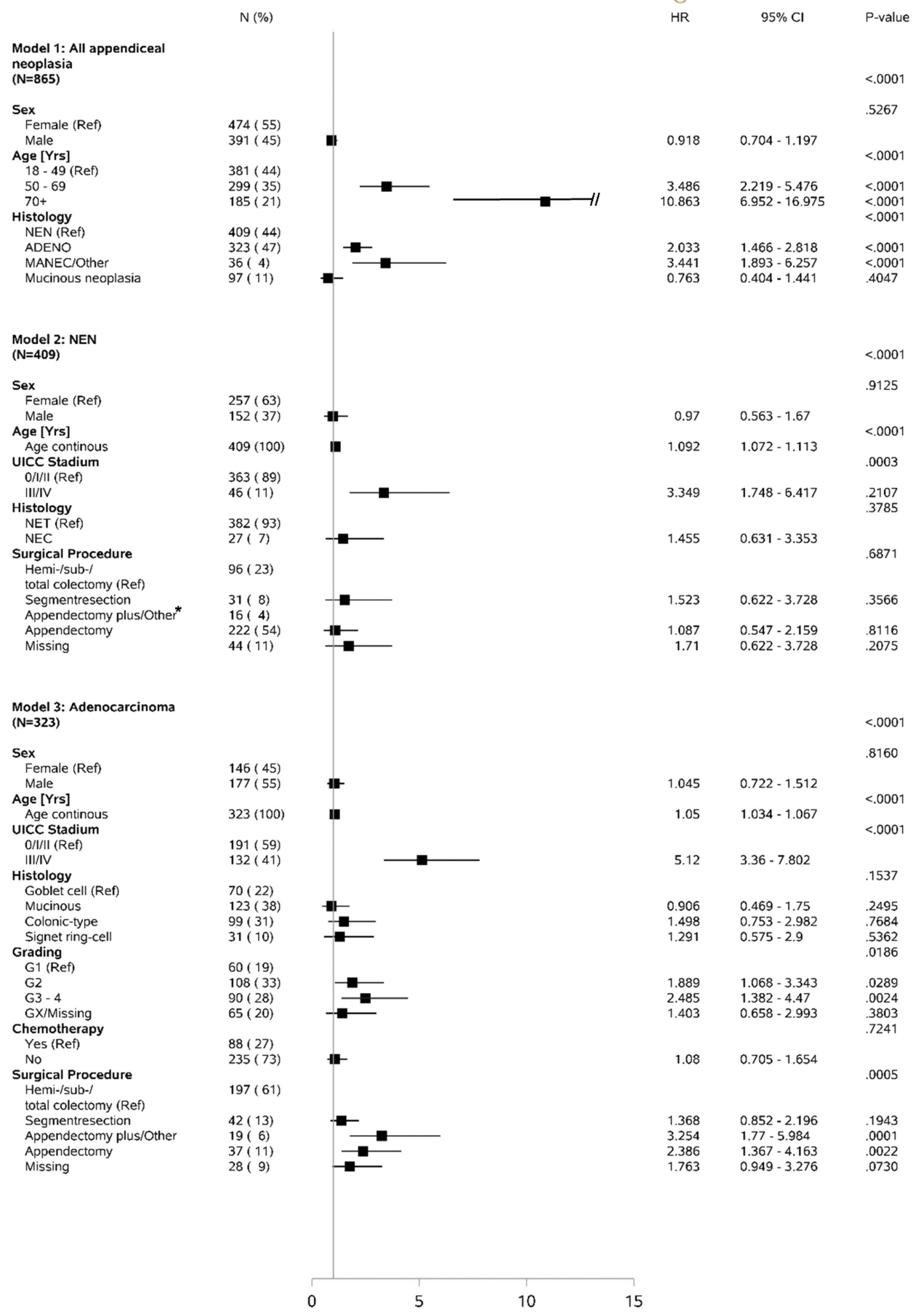

FIGURE 4 Multivariate Cox regression models. *No events in this category.

appendectomy only and appendectomy plus/other had a significantly poor prognosis. Histological subtypes, sex and chemotherapy were not significant in the model. However, the proportional hazard assumption for the variable chemotherapy was not met, since the number of patients receiving chemotherapy was time dependent. Histological subtypes within the ADENO subgroup were associated with differences in the risk of progression ($p = 0.0065$; Figure 3H). Approximately one-third of patients with either signet ring-cell involvement, colonic-type and mucinous adenocarcinoma developed a disease progression within the time of observation.

DISCUSSION AND CONCLUSIONS

In this study, all available cases of appendiceal neoplasia from the population-based Munich cancer registry were combined to gain further insight into the epidemiology, tumour characteristics and patient prognosis. To our knowledge this is the first study on this group of tumours affecting the appendix vermiformis conducted using population-based European data which incorporates the most recent WHO histology criteria. Time trend analysis showed that there was a rise in total cases up to 2016 followed by a subsequent decline, with numbers still elevated but nearly returning to their previous levels in 1998. Potentially the decreasing rate of appendectomies and appendicitis may be responsible for this trend reversal. Comparison of the individual histological types of neoplasia showed distinct characteristics in each group, in both demographic and prognostic factors. After 10 years, over 80% of NEN patients are still alive. These numbers are in clear contrast to the ADENO group with a rate of surviving patients below 50% in the same time span. Although the initial diagnosis showed sex-based patterns, especially regarding the age of diagnosis, this difference lost its relevance on prognosis when controlling for confounders. Older age was the only common patient characteristic that was prognostically relevant for all cases, regardless of histology. The type of tumour resection surgery played a role in patient survival, although the number of patients with a diagnosis of ADENO undergoing localized appendix surgery was small. Especially in incidental cases where only an appendectomy was performed, patients may profit from a more extensive revision surgery to improve prognosis. Overall, these findings are clearly distinct from tumours in the remaining colon. In comparison, there was a clear predominance of cases with NEN histology, which had to a slightly higher proportion of female patients, a lower age of diagnosis and a generally more favourable clinical disease presentation [11].

Interestingly, there was a significant gap in age of diagnosis between men and women in NET, with men being a decade older than women. The difference in age grew to over 20 years in NEC patients. This indicates that there may be different pathways of carcinogenesis involved. Also, in the ADENO category mucinous adenocarcinoma showed a relatively high proportion of cases that directly spread to distant metastasis without affecting regional lymph nodes (N0/M1, 35.5%). In 17 out of these 50 cases pseudomyxoma was present (34%).

The number of studies looking into this disease are small, yet the overall findings regarding the overall incidence are similar to those detailed in this study. There are several population-based studies using SEER data, namely the studies by McCusker from 2002, Marmon from 2015 and the more recent study by Singh from 2020, who also used data from Canada [2, 3, 8]. Comparing the results of these studies with our data shows a similar time trend up until 2016 when the period of observation of the study by Singh et al. ends.

However, in our data a shift in time trends becomes apparent in the mid-2010s. The cause of this is most likely a common change in either practice or diagnosis, since nearly all subgroups are equally affected. One reason may be that the rate of both appendectomy and appendicitis have been decreasing, in contrast to the reported data by Singh et al. [8] where both rates remained steady until 2016. Cases of appendicitis are increasingly treated nonsurgically using antibiotics. Considering that a small proportion (about 1%) of cases of appendiceal neoplasia are discovered incidentally during surgery, this may lead to a delayed diagnosis. In several studies older patients appear to be more at risk for a missed diagnosis when treated for a presumed appendicitis or during an interval appendectomy [17, 18]. In a recent publication from the UK, Orchard et al. similarly examined time trends in appendiceal tumours [19]. The authors determined that the main increase in cases was seen in low-grade NET and argue that this may either be associated with the overall rate of appendectomy or rather the handling of the appendix specimen. The latter offers a valid explanation for the reported changes in trends, possibly due to a greater awareness of potential neoplasms and closer histopathological assessment of surgical specimens [20].

Limitations of this study are similar to those of other cancer registry studies and are mainly due to the observational nature of any such study. Time trend analysis specifically may be affected by a lag in documentation. More recent years in particular may be undercounted. However, a potential artificial decrease in cases due to a lag in documentation would only account for the last 2–3 years. The shift in the study data lies several years back and is not found for all subgroups. Another limitation may be an underreporting of NEN cases. The cause may lie in the frequently benign histology. In these cases, data are not always reported or recorded in similar depth to ADENO cases, which is also the case for SEER data. Also, due to the borderline malignancy of mucinous neoplasia it is unclear if all cases are reported and if before 2016 these cases may have been classified in another histological category. Since these cases are more likely to be associated with favourable characteristics, comparisons between this group and the ADENO group may lack validity.

Both the variety and small numbers of each histological subtype make studying this disease rather complicated, which explains why nearly all clinical procedures and treatment approaches are directly adapted from standard of care for the remaining colon. However, this may not be suitable, since the discrepancy in demographic and prognostic data is relatively large. The results of this study and other previously conducted studies show that within the ADENO and NEN groups the individual histology is not as relevant as older age and regional or distant tumour dissemination. This indicates that these smaller subgroups may be combined in large nationwide or international prospective trials to determine the best treatment course.

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AUTHOR CONTRIBUTIONS

Study conception, design, and data interpretation were made by Halfter Kathrin, Anne Schlesinger-Raab, Schubert-Fritschle Gabriele, and Jutta Engel. Data curation and statistical analysis were performed by Halfter Kathrin and Anne Schlesinger-Raab. Patient care, data collection and curation were made by Klauschen Frederick, Werner Jens, Julia Mayerle, Wilko Weichert, Helmut Friess, Roland Schmid, Marcus Kremer, Reinhard Ruppert, Jürgen Hoelzl, Detlef Krenz, Andreas Nerlich, Ayman Agha, Martin Fuchs, Ingrid Becker, Kai Nowak. The first draft of the manuscript was written by Halfter Kathrin and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

Only preexisting retrospective data with no personal identifiers was used in the study making it exempt from review and approval by an ethics committee or competent authority.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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