Supplementary Material

Incidence trends and relative survival of colorectal neuroendocrine neoplasms - A population-based study using German cancer registry data

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Supplementary materials & methods

Imputation model

Multiple imputation by chained equations (MICE) assuming missingness at random was performed to handle the high proportion of missing values of UICC stages (see table 1). In the first step, the missing T-, N-, and M-stages were imputed using age at diagnosis, sex, year of diagnosis, status of morphological verification, grading, anatomic subsite, morphology group (NET, NEC, or MINEN), vital status at the end of the period (i.e. alive or deceased), and cumulative baseline hazard as predictor variables. T-, N-, and M-stages were also included as predictors, because they were associated with each other and their missing patterns were not completely overlapping. The imputation method for T- and N-values was polytomous regression, while M-stages were imputed by logistic regression. The Nelson-Aalen estimator was used to approximate the cumulative baseline hazard[1]. The number of imputed datasets was set to 100, and the number of maximum iterations was 20. Convergence was diagnosed by plotting the mean and standard deviation of each imputed variable against the iteration number for each parallel stream. The UICC-stages were derived from the imputed TNM-values in a subsequent step (passive imputation)[2]. Age-standardized incidence rates, annual percentage changes and relative 5-year survival were calculated for each imputed dataset stratified by UICC stages, morphology groups and primary site. As the estimates were normally distributed across the imputed datasets, the untransformed outcomes were pooled using the mean value as a point estimate and the standard error was obtained according to Rubin's rule[3]. The imputation was performed with R 4.3.2[4] using the mice package (version 3.16.0) [5].
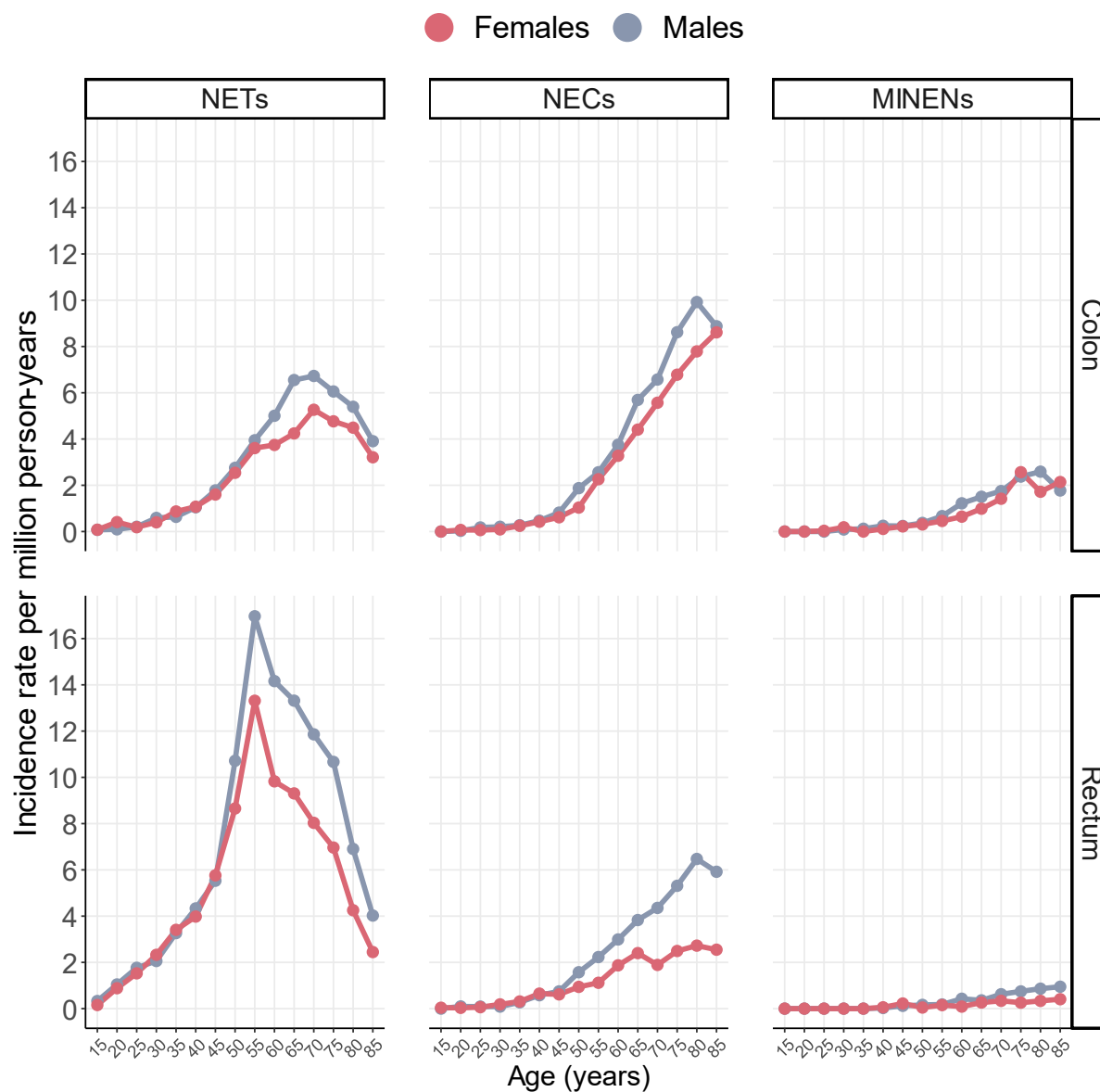
Supplement Figure 1 Age-specific incidence rates for colorectal neuroendocrine neoplasms, 2009-2021, Germany**.**

Legend:

NET: Well-differentiated Neuroendocrine Tumor

NEC: Poorly differentiated Neuroendocrine Carcinoma

MiNEN: Mixed neuroendocrine-non-neuroendocrine Neoplasm

Supplement Table 1 Distribution of morphologies and grading of neuroendocrine neoplasms (NENs) with colorectal primary site according to ICD-O-3, 2009-2021, Germany.

NEN	Code and term	n (%)	Grading, %		
			G1	G2	G3
NET	8152/3 - L-cell tumor	2 (0)	50	50	0
NET	8240/3 - Neuroendocrine tumor, NOS	7241 (57.5)	92.6	5.2	2.2
NET	8241/3 - Enterochromaffin cell carcinoid	28 (0.2)	88.5	0	11.5
NET	8249/3 - Neuroendocrine tumor, grade 2	1047 (8.3)	3.9	91.2	4.9
NEC	8013/3 - Large cell neuroendocrine carcinoma	584 (4.6)	1	2.9	96.2
NEC	8041/3 - Small cell carcinoma, NOS	529 (4.2)	1	6.9	92.1
NEC	8246/3 - Neuroendocrine carcinoma, NOS[a,b]	2423 (19.2)	0	0	100
MiNEN	8244/3 - Mixed adenoneuroendocrine carcinoma	684 (5.4)	1.9	12	86.1
MiNEN	8245/3 - Adenocarcinoid tumor	8 (0.1)	42.9	42.9	14.3
MiNEN	8154/3 - Mixed neuroendocrine non-neuroendocrine neoplasm (MiNEN)	56 (0.4)	1.9	9.6	88.5

[a]950 cases originally coded as 8246 with grade 1 had been recoded as 8240

[b]295 cases originally coded as 8246 with grade 2 had been recoded as 8249

Supplement Table 2 Age-standardized incidence rates per million person-years (world standard population) for colorectal neuroendocrine neoplasms, 2019-2021, Germany.

	Sex	Well-differentiated Neuroendocrine Tumors (NETs)		Poorly differentiated Neuroendocrine Carcinomas (NECs)		Mixed neuroendocrine-non-neuroendocrine Neoplasm (MiNENs)	
	Sex	Rate	95%-CI	Rate	95%-CI	Rate	95%-CI
Colon							
Overall	Males	1.36	1.19; 1.52	0.95	0.83; 1.08	0.25	0.19; 0.31
	Females	1.20	1.04; 1.36	0.68	0.58; 0.78	0.25	0.19; 0.31
< 55 Years	Males	0.95	0.78; 1.13	0.36	0.25; 0.47	0.15	0.09; 0.22
	Females	1.01	0.81; 1.2	0.29	0.2; 0.39	0.11	0.05; 0.18
≥ 55 Years	Males	5.47	4.74; 6.21	4.59	3.93; 5.24	1.38	1.01; 1.74
	Females	4.55	3.9; 5.19	3.56	3.02; 4.1	1.29	0.96; 1.61
UICC							
I/II	Both	0.59	0.51; 0.68	0.10	0.07; 0.13	0.03	0.02; 0.04
III	Both	0.35	0.28; 0.42	0.16	0.12; 0.2	0.08	0.05; 0.1
IV	Both	0.33	0.27; 0.39	0.56	0.49; 0.63	0.14	0.11; 0.18
Rectum							
Overall	Males	4.71	4.39; 5.02	0.68	0.57; 0.79	0.09	0.05; 0.13
	Females	3.73	3.44; 4.02	0.44	0.35; 0.53	0.07	0.03; 0.11
< 55 Years	Males	3.94	3.56; 4.31	0.32	0.22; 0.42	0.05	0.01; 0.09
	Females	3.83	3.46; 4.2	0.29	0.19; 0.39	0.07	0.02; 0.12
≥ 55 Years	Males	17.33	15.99; 18.67	3.20	2.65; 3.75	0.50	0.28; 0.72
	Females	11.19	10.12; 12.25	1.85	1.44; 2.25	0.19	0.06; 0.32
UICC							
I/II	Both	3.69	3.48; 3.9	0.11	0.07; 0.15	0.02	0.007; 0.04
III	Both	0.29	0.22; 0.37	0.13	0.09; 0.17	0.02	0.002; 0.03
IV	Both	0.22	0.15; 0.28	0.31	0.25; 0.36	0.04	0.02; 0.06

Legend:

UICC: Stage according to Union for International Cancer Control

Supplement Table 3 Age-standardized incidence rates per million person-years (U.S. 2000 standard population) for colorectal neuroendocrine neoplasms, 2019-2021, Germany.

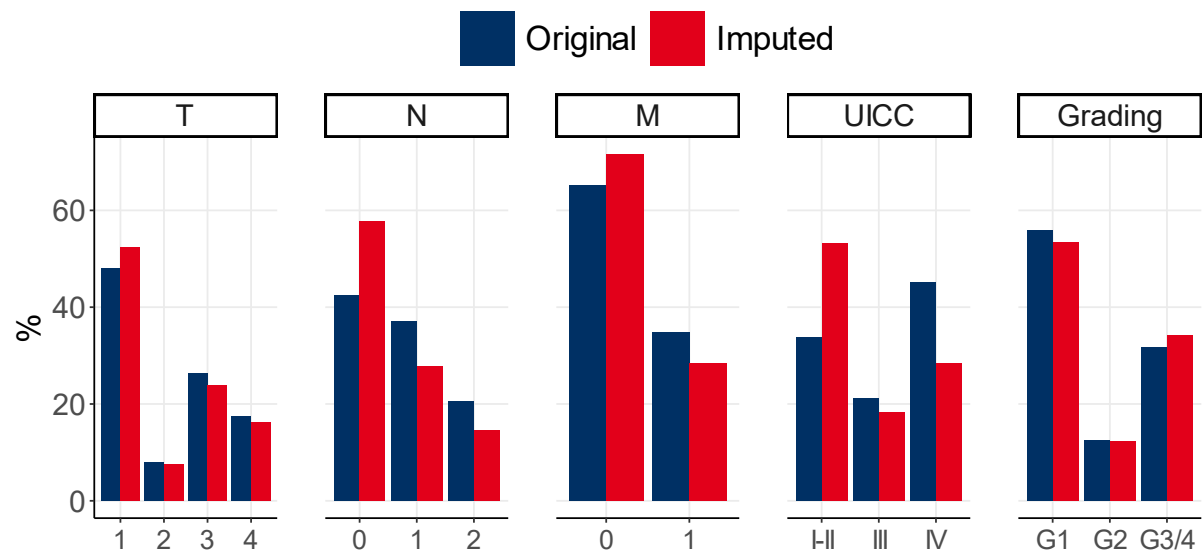|	Sex	Well-differentiated Neuroendocrine Tumors (NETs)		Poorly differentiated Neuroendocrine Carcinomas (NECs)		Mixed neuroendocrine-non-neuroendocrine Neoplasm (MiNENs)	
		Rate	95%-CI	Rate	95%-CI	Rate	95%-CI
Colon							
Overall	Males	1.85	1.64; 2.07	1.46	1.28; 1.65	0.38	0.29; 0.47
	Females	1.62	1.42; 1.82	1.11	0.96; 1.25	0.40	0.31; 0.48
< 55 Years	Males	0.76	0.58; 0.95	0.38	0.25; 0.51	0.07	0.02; 0.12
	Females	0.74	0.56; 0.92	0.21	0.11; 0.31	0.08	0.02; 0.14
≥ 55 Years	Males	5.62	4.9; 6.34	5.26	4.56; 5.96	1.53	1.15; 1.91
	Females	4.72	4.11; 5.33	4.32	3.75; 4.9	1.53	1.18; 1.87
UICC							
I/II	Both	0.76	0.66; 0.87	0.17	0.12; 0.21	0.05	0.03; 0.07
III	Both	0.49	0.41; 0.58	0.25	0.2; 0.31	0.13	0.09; 0.17
IV	Both	0.47	0.39; 0.55	0.86	0.76; 0.96	0.21	0.16; 0.26
Rectum							
Overall	Males	5.91	5.53; 6.3	1.01	0.86; 1.16	0.14	0.09; 0.2
	Females	4.58	4.23; 4.93	0.61	0.49; 0.73	0.10	0.05; 0.16
< 55 Years	Males	2.96	2.61; 3.32	0.27	0.16; 0.38	0.03	0; 0.06
	Females	2.95	2.59; 3.31	0.23	0.13; 0.33	0.08	0.01; 0.14
≥ 55 Years	Males	15.95	14.75; 17.15	3.54	2.97; 4.12	0.56	0.33; 0.79
	Females	9.80	8.9; 10.7	1.95	1.56; 2.33	0.20	0.07; 0.32
UICC							
I/II	Both	4.57	4.32; 4.82	0.15	0.1; 0.2	0.04	0.01; 0.06
III	Both	0.37	0.28; 0.46	0.19	0.14; 0.24	0.03	0.007; 0.05
IV	Both	0.27	0.2; 0.35	0.45	0.38; 0.52	0.05	0.03; 0.08

Legend:

UICC: Stage according to Union for International Cancer Control

Supplement Table 4 Absolute 5-year survival probability in percent for colorectal neuroendocrine neoplasms, period 2017 to 2021, Germany.

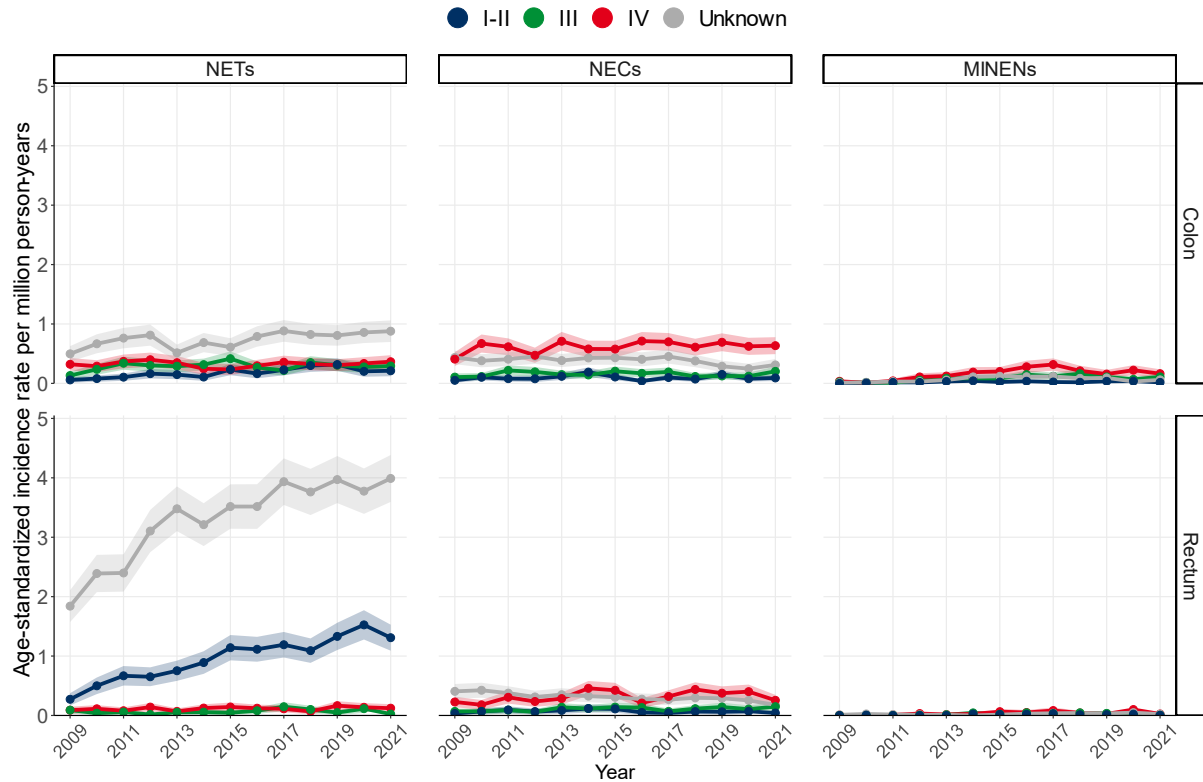|	Well-differentiated Neuroendocrine Tumors (NETs)		Poorly differentiated Neuroendocrine Carcinomas (NECs)		Mixed neuroendocrine-non-neuroendocrine Neoplasm (MiNENs)	
	Absolute 5-year survival probability	95%- Confidence interval	Absolute 5-year survival probability	95%- Confidence interval	Absolute 5-year survival probability	95%- Confidence interval
Colon						
Overall	73.2	70.4; 76	17.1	14.7; 19.5	21.6	17.2; 26
Overall Males	73.3	69.5; 77.2	14.5	11.3; 17.8	20.7	14.7; 26.7
Overall Females	73.1	69; 77.1	19.6	16; 23.2	22.3	15.9; 28.7
<55 Years	93.4	90.1; 96.8	20.7	12.1; 29.2	21	9; 33
>=55Years	67.4	64; 70.8	16.7	14.1; 19.2	21.6	16.9; 26.4
UICC						
I-II	86.2	82.2; 90.2	55.8	45.9; 65.7	70.2	54.9; 85.6
III	78.3	73.2; 83.3	27.8	20.7; 34.8	31.6	22.5; 40.7
IV	49.7	43.4; 56.1	6.6	4.4; 8.7	5.6	2.3; 9
Rectum						
Overall	89.6	88.4; 90.8	16.7	13.7; 19.8	23.4	14.5; 32.3
Overall Males	87.0	85.2; 88.7	13.3	9.8; 16.8	21.9	11; 32.8
Overall Females	92.8	91.3; 94.3	22.3	16.7; 27.8	24.8	9.6; 39.9
<55 Years	96.8	95.6; 98	33.0	23.4; 42.6	32.1	6.5; 57.7
>=55Years	86.0	84.4; 87.7	13.8	10.7; 16.8	21.4	12.1; 30.6
UICC						
I-II	92.7	91.5; 93.9	45.3	34.5; 56.1	51	25.8; 76.2
III	85.3	79.4; 91.1	23.3	15.5; 31.1	27.4	10.7; 44
IV	42.5	32.2; 52.9	5.3	2.9; 7.8	6.9	-1.7; 15.6

Legend:

UICC: Stage according to Union for International Cancer Control

Supplement Figure 2 Frequencies of imputed categorical variables in the original vs imputed datasets.

Legend:
UICC: Stage according to Union for International Cancer Control

Supplement Figure 3 Age-standardized incidence rates for colorectal neuroendocrine neoplasms stratified by UICC, 2009-2021, Germany.

Legend:
NET: Well-differentiated Neuroendocrine Tumors
NEC: Poorly differentiated Neuroendocrine Carcinomas
MiNEN: Mixed neuroendocrine-non-neuroendocrine Neoplasm
UICC: Stage according to Union for International Cancer Control

Supplementary references

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