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Predictive value of mucinous histology in colon cancer: a population-based, propensity score matched analysis

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Background: This investigation aimed to assess whether mucinous histology impacts overall (OS) and cancer-specific survival (CSS) in colon cancer.

Methods: Colon cancer patients who underwent surgery between 2004 and 2011 were identified in the Surveillance, Epidemiology, and End Results database. OS and CSS were assessed using Cox regression and propensity score methods.

Results: Out of 121 628 patients, 12 863 (10.6%) had a mucinous histology. Five-year OS and CSS for mucinous adenocarcinoma were 54.4% (95% CI: 53.4–55.5%) and 66.5% (95% CI: 65.5–67.5%) compared with 60.2% (95% CI: 59.8–60.5%) and 71.9% (95% CI: 71.5–72.2%) for non-mucinous adenocarcinoma ($P<0.001$). This survival disadvantage disappeared in multivariable analyses (hazard ratio (HR) = 1.02, 95% CI: 0.99–1.05, $P=0.269$ and HR = 1.03, 95% CI: 0.99–1.06, $P=0.169$), and after propensity score matching (OS: HR = 0.99, 95% CI: 0.93–1.04, $P=0.606$ and CSS: HR = 0.99, 95% CI:0.92–1.06, $P=0.783$).

Conclusions: In this population-based investigation, a mucinous histology did not negatively impact survival. Hence, the present study does not provide evidence to change treatment strategies in patients with mucinous adenocarcinoma of the colon.

Among patients with colon cancer, ~10–20% present with a mucinous adenocarcinoma (MAC) (Kang *et al*, 2005; Catalano *et al*, 2012; Hyngstrom *et al*, 2012; Benedix *et al*, 2013) defined as a tumour composed of more than 50% extracellular mucin (Jass and Sobin, 1989). Whereas some studies report a worse prognosis of colorectal MAC compared with non-mucinous adenocarcinoma (NMAC) (Verhulst *et al*, 2012; Kim *et al*, 2013; Vigano *et al*, 2014), others have not found a worse prognosis (Kang *et al*, 2005; Catalano *et al*, 2012; Gao *et al*, 2013; Hugen *et al*, 2013; Hogan *et al*, 2014). We have previously analysed the impact of a mucinous histology on the prognosis of rectal cancer and did not find an impact of MAC *vs* NMAC on survival (Tarantino *et al*, 2015). Two studies demonstrated worse outcomes for mucinous rectal cancer but not for MAC of the colon (Du *et al*, 2004; Hyngstrom *et al*, 2012). Some authors have suggested a more aggressive surgical treatment, an increased use of systemic chemotherapy, and a more stringent follow-up for patients with MAC (Benedix *et al*, 2013; Kim *et al*, 2013; Lee *et al*, 2013). The objective of the present population-based analysis was to evaluate in a cohort of exclusively colon cancer patients whether mucinous histology represents an independent prognostic factor using Cox regression and propensity score matching for optimal adjustment.

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METHODS

The colorectal cancer part ($N = 866\,626$) of the November 2013 ASCI text data-version of the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute, covering ~28% of cancer cases in the United States, was the source of present analysis (National Cancer Institute, 2014). Of 220 269 colon cancer patients diagnosed between 2004 and 2011, 121 628 met the inclusion criteria for the present study presented in Figure 1. These patients were grouped according to histology into patients with MAC and NMAC. NMAC were defined based on the third edition of the International Classification of Diseases for Oncology (ICD-O-3) histology codes 8140, 8144, 8210, 8211, 8221, 8261, 8262, 8263 and MAC by the codes 8480 and 8481.

The main outcomes were overall (OS) and cancer-specific survival (CSS) defined as time to event data as days from the diagnosis. For OS, patients alive at the end of follow-up were censored. For CSS, patients alive or dead due to other than cancer-specific causes were censored.

Statistical analyses were performed using the R software (www.r-project.org). MAC *vs* NMAC was assessed as a prognostic factor for OS and CCS in univariate Cox regression and with risk-adjustment for baseline confounding variables (tumour location, tumour stage, T-stage, retrieved regional lymph nodes, grading, preoperative carcinoembryonic antigen, year, age, gender, ethnicity, and marital status) in a full Cox model. In addition, an exact weighted-propensity score matching analysis using the MatchIt R package was performed for optimal adjustment for the baseline confounding variables (Ho *et al*, 2011). Each patient in the two groups was matched to all possible patients in the other group with exactly the same values of all the covariates. MAC patients that did not have a counterpart among the NMAC patients and vice versa were excluded from this analysis. The prognostic value of

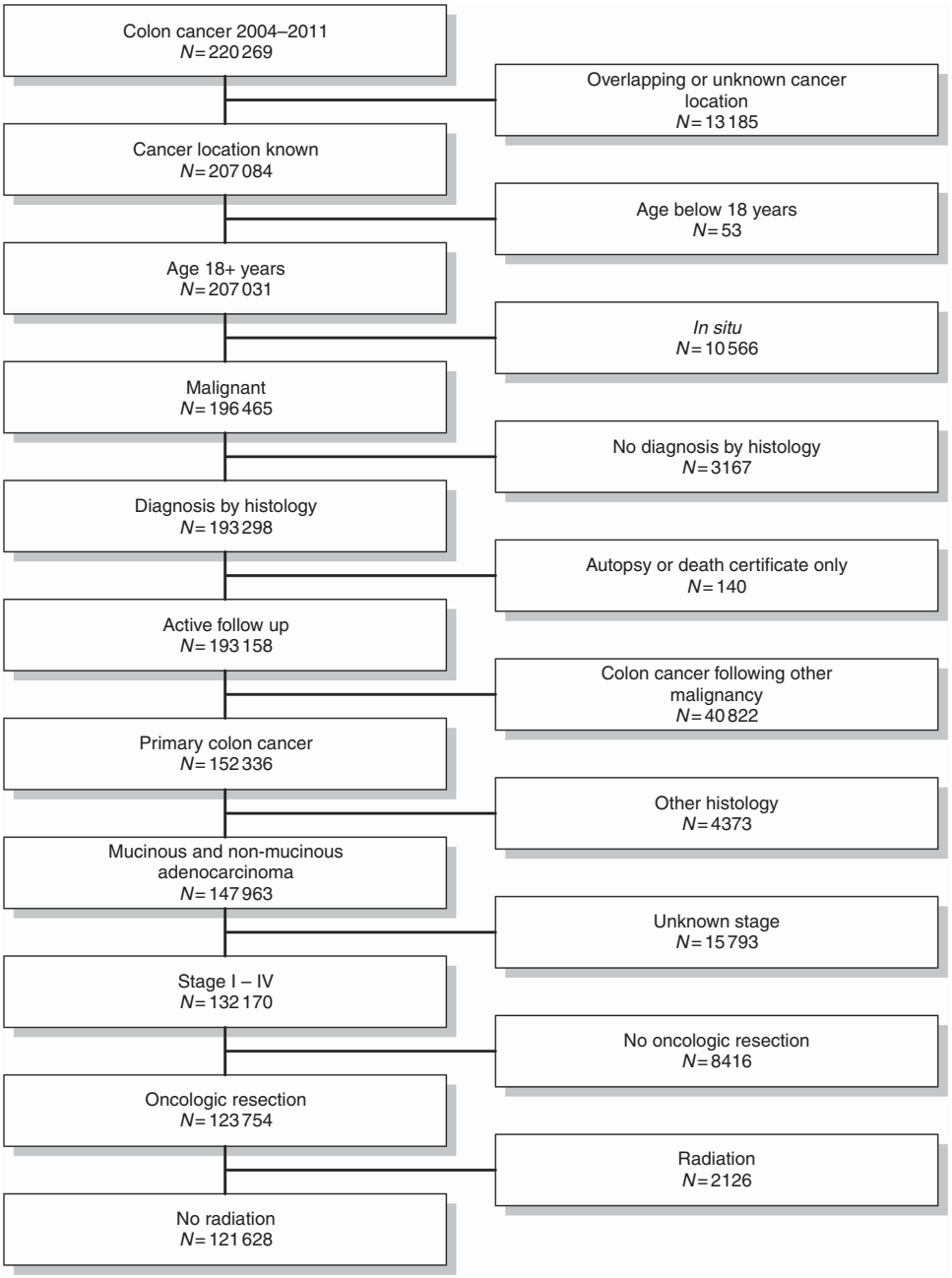

Figure 1. Flow chart of the patient cohort selection.

mucinous *vs* non-mucinous histology for survival was then assessed in an additional Cox regression, incorporating the weights and strata obtained by the propensity score analysis.

RESULTS

Among 121 628 patients diagnosed with stage I–IV adenocarcinoma, 12 863 patients (10.6%) had a MAC. Their histology was coded as mucinous adenocarcinoma ($N=10.492$) and mucin-producing adenocarcinoma ($N=2.371$) in the Surveillance, Epidemiology, and End Results database. The histology of the 108 765 NMAC were coded as adenocarcinoma, not otherwise stated ($N=88.328$), adenocarcinoma in tubulovillous adenoma ($N=9.213$, adenocarcinoma in adenomatous polyp ($N=7.853$), adenocarcinoma in villous adenoma ($N=3.194$), villous adenocarcinoma ($N=96$), tubular adenocarcinoma ($N=64$), and adenocarcinoma of intestinal type ($N=17$). The mean follow-up was 35.4 ± 27.1 months. At the end of follow-up, 81 692 patients (67.2%) were alive, 26 452 patients (21.7%) died from cancer and 13 484 (11.1%) died of other causes.

MAC were associated with older age, right-sided location, more advanced stages, T4 tumours, resection of 12 or more lymph nodes, poor differentiation (G3 and G4), elevated carcinoembryonic antigen, female gender, and Caucasian ethnicity (Table 1). In univariate Cox regression, the overall mortality risk in patients with MAC was increased by 21% (hazard ratio (HR) = 1.21, 95% CI: 1.18–1.25, $P<0.001$), and the risk for cancer-specific mortality by 26% (HR = 1.26, 95% CI: 1.22–1.31, $P<0.001$). The 5-year OS in patients with MAC was 54.4% (95% CI: 53.4–55.5%) compared with 60.2% (95% CI: 59.8–60.5%) in patients with a NMAC ($P<0.001$). The 5-year CSS in patients with a MAC was 66.5% (95% CI: 65.5–67.5%) compared with 71.9% (95% CI: 71.5–72.2%) in patients with a NMAC ($P<0.001$). In multivariable Cox regression, mucinous histology was not confirmed to have a significant negative effect on OS (HR = 1.02, 95% CI: 0.99–1.05, $P=0.269$) and CCS (HR = 1.03, 95% CI: 0.99–1.06, $P=0.169$) (Table 2).

In the propensity score-based analysis, 6294 patients with a MAC were compared with 18 350 patients with a NMAC without any significant differences in the baseline confounding variables persisting after propensity score matching ($P=1.000$ for all covariates). After propensity score matching, mucinous histology had no prognostic value for OS (HR = 0.99, 95% CI: 0.93–1.04, $P=0.606$) and CSS (HR = 0.99, 95% CI: 0.92–1.06, $P=0.783$). The 5-year OS in patients with a MAC was 59.8% (95% CI: 58.4–61.1%) compared with 59.3% (95% CI: 58.5–60.2%) in patients with a NMAC. The 5-year CCS in patients with MAC was 73.4% (95% CI: 72.2–74.7%) compared with 73.2% (95% CI: 72.4–74.0%) in patients with a NMAC.

DISCUSSION

To our knowledge, this is the first population-based analysis investigating the prognostic relevance of a mucinous histology in a large cohort of exclusively colon cancer patients adjusting with propensity score matching and multivariate analysis. The present investigation yields two main findings. First, MAC is associated with a variety of factors, such as a younger age of onset, location in the proximal colon, more advanced stage at presentation and poor grade of differentiation. Hence, the patient characteristics are strongly biased when comparing MAC *vs* NMAC. Second, after optimal adjustment for this bias, mucinous histology did not impact OS or CSS neither in multivariable Cox regression nor in propensity score-adjusted analyses. In consequence, the observed association between mucinous histology and worse OS and CSS in the univariate analysis is caused by differences in other clinical characteristics, such as tumour stage, grade, and localisation of the carcinoma, rather than the mucinous histology itself.

These findings are supported by several previous studies (Kang *et al*, 2005; Catalano *et al*, 2012; Hyngstrom *et al*, 2012; Hugen *et al*, 2013). One possible explanation for a worse prognosis of colorectal MAC in other studies (Verhulst *et al*, 2012; Kim *et al*, 2013; Vigano *et al*, 2014) might be an inadequate differentiation between signet ring carcinoma and MAC (Benedix *et al*, 2013). The inclusion of rectal and colon cancer patients into the same analysis might have contributed to the controversy, as some recent investigations have demonstrated a worse outcome for MAC of the rectum but not for MAC of the colon (Du *et al*, 2004; Hyngstrom *et al*, 2012). However, in an analogous analysis of rectal instead of colon cancer by our research group similar results were obtained (Tarantino *et al*, 2015). Mucinous histology was associated with unfavourable tumour characteristics. When optimally adjusting for confounding variables, mucinous histology had no impact on OS and CSS. OS and CSS of colon *vs* rectal cancer was worse for both NMAC (HR = 1.31, $P<0.001$ and HR = 1.22, $P<0.001$) and MAC (HR = 1.17, $P<0.001$ and HR = 1.09, $P=0.040$) in Cox regression analyses.

Moreover, the incidence of MAC differs substantially among different geographical regions (Du *et al*, 2004; Catalano *et al*, 2012). In addition, based on molecular analysis and clinical behaviour, two subtypes of MAC (microsatellite stable *vs* microsatellite instable) have been postulated and lead to the hypothesis that a different distribution of these two subtypes might have influenced the results especially in smaller series (Kondo *et al*, 2002; Liu *et al*, 2004; Leopoldo *et al*, 2008; Catalano *et al*, 2012).

The clinical relevance of identifying risk factors associated with an adverse outcome in patients with colorectal cancer is highlighted by patients diagnosed with stage II disease. Whereas, the survival benefit of adjuvant chemotherapy in stage III colon cancer has been well established, the value of such treatment for stage II colon cancer remains controversial (Haller *et al*, 2005; Twelves *et al*, 2005; Quasar Collaborative Group *et al*, 2007; Andre *et al*, 2009). In this regard, it is of utmost importance to identify those patients who will most likely benefit from adjuvant treatment. Based on previous studies demonstrating a worse prognosis of colorectal MAC, a more aggressive oncological treatment has been suggested, especially for patients with stage II disease (Lee *et al*, 2013). In contrast, a mucinous histology is not included in the list of risk factors on which to base adjuvant treatment (Benson *et al*, 2004). The present investigation, in which a mucinous histology *per se* was not identified as an independent negative prognostic factor, supports the existing guidelines. Furthermore, recent studies showed no differences in the efficacy of adjuvant chemotherapy between patients with MAC and NMAC (Catalano *et al*, 2012; Hugen *et al*, 2013). Hence, current adjuvant treatment recommendations should be applied regardless of a mucinous histology in colon cancer.

We would like to acknowledge the limitations of the present investigation: data on chemotherapeutic treatments, family history, comorbidities, performance status and molecular data such as microsatellite instability are not available in the Surveillance, Epidemiology, and End Results database. In addition, although definitions of mucinous and signet ring cell histology have been standardised, variation in interpretation may have resulted in misclassification. Despite these limitations, the present study has a variety of strengths. First, the population-based nature of the registry is associated with a high degree of generalisability. Second, this study reports data over an 8-year period and includes 121 628 patients with stage I–IV colon cancer, of whom 12 863 (10.6%) patients had a MAC. The large sample size is associated with a high degree of power. Third, the results of multivariable analysis were

Table 1. Patient characteristics

	Patient characteristics			
	Total $N = 121\,628$	Mucinous carcinoma $N = 12\,863$	Non-mucinous carcinoma $N = 108\,765$	P^a
Location				
Caecum	29 987 (24.7%)	4053 (31.5%)	25 934 (23.8%)	<0.001
Ascending colon	25 240 (20.8%)	3371 (26.2%)	21 869 (20.1%)	
Hepatic flexure	6471 (5.3%)	876 (6.8%)	5595 (5.1%)	
Transverse colon	11 826 (9.7%)	1375 (10.7%)	10 451 (9.6%)	
Splenic flexure	4695 (3.9%)	485 (3.8%)	4210 (3.9%)	
Descending colon	7642 (6.3%)	657 (5.1%)	6985 (6.4%)	
Sigmoid colon	35 767 (29.4%)	2046 (15.9%)	33 721 (31.0%)	
Tumour stage (AJCC 6th ed.)				
I	28 541 (23.5%)	1628 (12.7%)	26 913 (24.7%)	<0.001
IIA	33 934 (27.9%)	4074 (31.7%)	29 860 (27.5%)	
IIB	4895 (4.0%)	812 (6.3%)	4083 (3.8%)	
IIIA	3999 (3.3%)	304 (2.4%)	3695 (3.4%)	
IIIB	20 396 (16.8%)	2320 (18.0%)	18 076 (16.6%)	
IIIC	12 291 (10.1%)	1641 (12.8%)	10 650 (9.8%)	
IV	17 572 (14.4%)	2084 (16.2%)	15 488 (14.2%)	
T-stage				
T1	15 992 (13.1%)	501 (3.9%)	15 491 (14.2%)	<0.001
T2	17 833 (14.7%)	1555 (12.1%)	16 278 (15.0%)	
T3	70 060 (57.6%)	8005 (62.2%)	62 055 (57.1%)	
T4	17 743 (14.6%)	2802 (21.8%)	14 941 (13.7%)	
Retrieved regional lymph nodes				
<12	36 965 (30.4%)	3584 (27.9%)	33 381 (30.7%)	<0.001
12+	84 663 (69.6%)	9279 (72.1%)	75 384 (69.3%)	
Grade				
G1	10 522 (8.7%)	1338 (10.4%)	9184 (8.4%)	<0.001
G2	83 425 (68.6%)	7887 (61.3%)	75 538 (69.5%)	
G3	21 647 (17.8%)	2533 (19.7%)	19 114 (17.6%)	
G4	2098 (1.7%)	304 (2.4%)	1794 (1.6%)	
Unknown	3936 (3.2%)	801 (6.2%)	3135 (2.9%)	
Carcinoembryonic antigen				
Normal	39 907 (32.8%)	3823 (29.7%)	36 084 (33.2%)	<0.001
Elevated	29 035 (23.9%)	3674 (28.6%)	25 361 (23.3%)	
Unknown/borderline	52 686 (43.3%)	5366 (41.7%)	47 320 (43.5%)	
Year of diagnosis				
2004–2005	31 935 (26.3%)	4028 (31.3%)	27 907 (25.7%)	<0.001
2006–2008	46 578 (38.3%)	4807 (37.4%)	41 771 (38.4%)	
2009–2011	43 115 (35.4%)	4028 (31.3%)	39 087 (35.9%)	
Age (years)				
<50	11 503 (9.5%)	1360 (10.6%)	10 143 (9.3%)	<0.001
50–64	35 540 (29.2%)	3203 (24.9%)	32 337 (29.7%)	
65–79	47 118 (38.7%)	4998 (38.9%)	42 120 (38.7%)	
80+	27 467 (22.6%)	3302 (25.7%)	24 165 (22.2%)	
Gender				
Male	59 065 (48.6%)	5915 (46.0%)	53 150 (48.9%)	<0.001
Female	62 563 (51.4%)	6948 (54.0%)	55 615 (51.1%)	
Ethnicity				
Caucasian	96 594 (79.4%)	10 566 (82.1%)	86 028 (79.1%)	<0.001
African-American	14 773 (12.1%)	1511 (11.7%)	13 262 (12.2%)	
Other/unknown	10 261 (8.4%)	786 (6.1%)	9475 (8.7%)	
Marital status				
Married	66 463 (54.6%)	6702 (52.1%)	59 761 (54.9%)	<0.001
Single	15 581 (12.8%)	1662 (12.9%)	13 919 (12.8%)	
Widowed	23 446 (19.3%)	2894 (22.5%)	20 552 (18.9%)	
Other/unknown	16 138 (13.3%)	1605 (12.5%)	14 533 (13.4%)	

n (%).
[a]Chi-square test.

confirmed after propensity score matching. The importance in matching all patients' characteristics is highlighted when considering the difference in the grading of the MAC and NMAC, as patients with a MAC were more often diagnosed with a poor grade of differentiation. In this respect, previous studies accounted only for differences in tumour stage.

Table 2. Prognostic factors for overall and cancer-specific mortality

	Overall survival using Cox regression				Cancer-specific survival using Cox regression			
	Univariate[a]		Full model[b]		Univariate[a]		Full model[b]	
	HR (95% CI)	P[c]	HR (95% CI)	P[c]	HR (95% CI)	P[c]	HR (95% CI)	P[c]
Histology								
Non-mucinous	Reference	<0.001	Reference	0.269	Reference	<0.001	Reference	0.169
Mucinous	1.21 (1.18–1.25)		1.02 (0.99–1.05)		1.26 (1.22–1.31)		1.03 (0.99–1.06)	
Location								
Caecum	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Ascending colon	0.88 (0.86–0.91)		1.00 (0.97–1.03)		0.80 (0.77–0.83)		0.97 (0.94–1.00)	
Hepatic flexure	0.89 (0.85–0.93)		1.02 (0.97–1.07)		0.85 (0.80–0.89)		1.01 (0.96–1.07)	
Transverse colon	0.91 (0.88–0.95)		0.99 (0.95–1.02)		0.88 (0.84–0.92)		0.95 (0.91–1.00)	
Splenic flexure	0.89 (0.84–0.93)		0.92 (0.87–0.97)		0.91 (0.86–0.97)		0.89 (0.84–0.95)	
Descending colon	0.79 (0.75–0.82)		0.90 (0.86–0.94)		0.80 (0.76–0.85)		0.87 (0.83–0.92)	
Sigmoid colon	0.73 (0.71–0.75)		0.87 (0.84–0.89)		0.74 (0.72–0.77)		0.84 (0.81–0.87)	
Tumour stage (AJCC 6th ed.)								
I	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
IIA	1.55 (1.49–1.60)		0.98 (0.89–1.08)		2.47 (2.32–2.64)		1.45 (1.29–1.63)	
IIB	2.85 (2.70–3.01)		1.21 (1.09–1.34)		7.05 (6.51–7.63)		2.62 (2.31–2.97)	
IIIA	1.13 (1.05–1.22)		1.21 (1.12–1.31)		2.08 (1.85–2.34)		2.13 (1.89–2.39)	
IIIB	2.27 (2.19–2.36)		1.45 (1.32–1.59)		5.63 (5.29–5.99)		3.19 (2.85–3.59)	
IIIC	3.27 (3.15–3.41)		2.30 (2.10–2.52)		9.59 (9.00–10.2)		5.80 (5.18–6.49)	
IV	8.53 (8.24–8.82)		5.58 (5.10–6.10)		28.5 (26.9–30.2)		15.6 (14.0–17.5)	
T-stage								
T1	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
T2	1.51 (1.43–1.59)		1.29 (1.22–1.36)		1.87 (1.71–2.06)		1.44 (1.31–1.59)	
T3	2.80 (2.68–2.92)		1.67 (1.52–1.84)		6.24 (5.78–6.74)		1.96 (1.73–2.21)	
T4	6.06 (5.79–6.35)		2.43 (2.20–2.67)		16.7 (15.5–18.1)		2.95 (2.60–3.33)	
Retrieved regional lymph nodes								
<12	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
12+	0.78 (0.77–0.80)		0.74 (0.72–0.75)		0.80 (0.78–0.82)		0.72 (0.70–0.74)	
Grade								
G1	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
G2	1.36 (1.30–1.42)		1.07 (1.02–1.11)		1.67 (1.57–1.76)		1.11 (1.05–1.17)	
G3	2.24 (2.15–2.34)		1.32 (1.26–1.38)		3.25 (3.06–3.44)		1.48 (1.39–1.57)	
G4	2.51 (2.32–2.71)		1.49 (1.38–1.61)		3.67 (3.34–4.02)		1.65 (1.51–1.82)	
Unknown	1.07 (0.99–1.15)		1.09 (1.01–1.17)		1.28 (1.17–1.41)		1.20 (1.09–1.32)	
Carcinoembryonic antigen								
Normal	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Elevated	2.59 (2.52–2.66)		1.54 (1.49–1.58)		3.40 (3.28–3.51)		1.61 (1.56–1.67)	
Unknown/borderline	1.53 (1.49–1.57)		1.38 (1.34–1.41)		1.65 (1.59–1.70)		1.44 (1.40–1.49)	
Year of diagnosis								
2004–2005	Reference	<0.001	Reference	0.004	Reference	<0.001	Reference	0.002
2006–2008	0.94 (0.92–0.96)		1.00 (0.98–1.02)		0.94 (0.91–0.96)		1.01 (0.98–1.03)	
2009–2011	0.86 (0.84–0.89)		0.96 (0.93–0.99)		0.86 (0.83–0.90)		0.95 (0.91–0.98)	
Age (years)								
<50	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
50–64	0.99 (0.95–1.03)		1.14 (1.09–1.19)		0.89 (0.84–0.93)		1.08 (1.03–1.13)	
65–79	1.44 (1.38–1.50)		1.88 (1.80–1.96)		1.04 (0.99–1.08)		1.52 (1.45–1.60)	
80+	2.84 (2.73–2.96)		3.87 (3.71–4.05)		1.67 (1.59–1.74)		2.71 (2.58–2.85)	
Gender								
Male	Reference	0.992	Reference	<0.001	Reference	0.011	Reference	<0.001
Female	1.00 (0.98–1.02)		0.81 (0.79–0.82)		1.03 (1.01–1.06)		0.89 (0.87–0.91)	
Ethnicity								
Caucasian	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
African-American	1.13 (1.09–1.16)		1.18 (1.14–1.21)		1.25 (1.21–1.29)		1.20 (1.16–1.24)	
Other/unknown	0.78 (0.75–0.81)		0.82 (0.79–0.86)		0.86 (0.82–0.90)		0.86 (0.82–0.90)	
Marital status								
Married	Reference	<0.001	Reference	<0.001	Reference	<0.001	Reference	<0.001
Single	1.32 (1.28–1.36)		1.34 (1.30–1.38)		1.34 (1.30–1.39)		1.26 (1.22–1.31)	
Widowed	1.85 (1.81–1.89)		1.35 (1.32–1.39)		1.54 (1.50–1.59)		1.27 (1.23–1.32)	
Other/unknown	1.20 (1.16–1.24)		1.22 (1.18–1.26)		1.16 (1.12–1.21)		1.15 (1.10–1.19)	

Hazard ratios (HR) with 95% confidence intervals (CI).
[a]Univariate Cox regression analysis.
[b]Multivariable Cox regression analysis, full model.
[c]Likelihood ratio tests.

In conclusion, the present population-based investigation on exclusively colon cancer patients did not provide evidence that a mucinous histology itself deteriorates OS or CSS. Therefore, a mucinous histology cannot be considered as an independent risk factor upon which the decision for or against chemotherapy should be based. Standard treatment strategies applied in patients with NMAC of the colon can also be applied in patients with MAC of the colon in accordance with recent guidelines.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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