



The association between body mass index and postoperative complications, 30-day mortality and long-term survival in Dutch patients with colorectal cancer



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ABSTRACT

Introduction: This retrospective study aims to examine the association between body mass index (BMI) and serious postoperative complications, 30-day mortality and overall survival in colorectal cancer (CRC) patients.

Materials and methods: All CRC patients diagnosed between 2008 and 2013 in the south-eastern part of the Netherlands were included. Patients were categorized into four BMI groups: underweight (<18.5), normal weight (18.5 ≤ BMI < 25), overweight (25 ≤ BMI < 30), and obese (≥ 30).

Results: A total of 7371 CRC patients were included (underweight 133 (1.8%); normal weight 2054 (41.4%); overweight 2955 (40.1%); obesity 1229 (16.7%)). Underweight patients were more likely to have postoperative complications (18.8% vs. 11.7%, adjusted OR 1.95, 95% CI 1.08–3.49) and had a worse 30-day mortality (9.8% vs. 3.3%, adjusted OR 4.37, 95% CI 2.03–9.42) compared to normal weight patients. After stratification for stage (stage I–III and stage IV), underweight was associated with a worse overall survival in both groups compared to normal weight (stage I–III: HR 2.06, 95% CI 1.51–2.80; stage IV: HR 1.65, 95% CI 1.11–2.45). Overweight was associated with an improved overall survival compared to normal weight in both stage groups. Only in stage IV patients obesity was associated with a significant better overall survival compared to stage IV normal weight patients.

Conclusion: Underweight CRC patients were more likely to have postoperative complications and a worse 30-day mortality compared to patients in other BMI categories. The underweight population also has a worse long-term survival while overweight CRC patients and obese stage IV CRC patients were associated with an improved survival compared to normal weight patients.

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Introduction

Colorectal cancer (CRC) is the most common cancer in the Netherlands with approximately 15,000 newly diagnosed patients in 2015 [1]. Although long term results are continuously improving in CRC, still approximately 4900 patients die each year as a result of metastasized CRC [2,3]. Treatment for CRC is mainly based on stage

and localization of the tumour. Surgical resection is indicated for the vast majority of newly diagnosed patients. Preoperative or postoperative treatment (i.e. radiotherapy and chemotherapy) is given according to international guidelines [4].

Several studies have investigated the influence of body mass index (BMI) on morbidity rates after surgery. Most studies suggest obesity (BMI ≥ 30 kg/m²) as a risk factor for morbidity after colorectal as well as non-colorectal surgical procedures [5–10]. A multicentre prospective cohort study showed that overweight and obese patients undergoing surgery for gastrointestinal malignancy are at increased risk of major postoperative complications [11].

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Patients who are underweight (BMI ≤ 18.5) also experience higher postoperative morbidity when compared with normal BMI [5,12,13]. Being underweight is associated with more cases of respiratory complications, urinary tract infections, sepsis and coma in general intra-abdominal surgery [13]. Morbidity rates found in underweight patients can be up to three times higher than morbidity rates in normal weight or even obese patients after surgery for rectal cancer [5]. A recently published population based study described the influence of obesity on perioperative and short-term postoperative outcome of colorectal surgery in Dutch CRC patients. Obesity (BMI ≥ 30) was identified as independent predictor of a complicated postoperative course in CRC surgery [14].

Only few studies examined the association between BMI and 30-day mortality. These studies showed that underweight is associated with lower 30-day survival rates [5,8]. A retrospective study in a large group of patients undergoing elective proctectomy showed that mortality rates can be up to three times higher in underweight patients (BMI < 18.5) compared to normal weight patients (3.9% vs. 1.3%) [15]. On the other hand, obesity (BMI > 30) also seems to be a risk factor for increased 30-day mortality [16,17]. Some studies suggest that the relationship between BMI and postoperative survival is U-shaped in CRC patients, with the highest risk of death observed among the lowest (BMI < 18.5) and highest (BMI > 35) BMI categories [13].

Not only early postoperative outcome seems influenced by patients' BMI, but also long-term risk on CRC recurrence and survival is suggested to be influenced. A study with 634 CRC patients showed that severely obese patients experienced worse survival outcomes independent of many other factors [18]. The U-shaped pattern for mortality and BMI also seems to apply for long-term overall survival, with increased risk of all-cause and cancer-specific mortality in both obese and underweight patients, with the highest risk in the underweight group [13,19]. The aim of the current study was, to determine the association between BMI and short and long-term outcomes in patients with CRC. Since postoperative outcome and long term survival in stage IV patients is significantly worse compared to curatively treated stage I-III patients, we separated these groups in the various analyses.

Material and methods

Design

This retrospective cohort study was conducted using population-based data from the Netherlands Cancer Registry (NCR). The NCR records data of all patients newly diagnosed with cancer in the Netherlands. The quality of the data is high, due to thorough training of the registration team and computerized consistency checks at regional and national levels. Completeness is estimated to be at least 95% [20]. No approval from a Medical Ethical Committee or Institutional Board was needed for this study, since anonymized and de-identified data were used from the NCR.

Comorbidity at diagnosis was registered according to a modified version of the Charlson comorbidity index, which included among others cardiovascular disease, pulmonary disease and diabetes mellitus. Socioeconomic status (SES: low, intermediate, high) was determined by postal code, combining mean household income and mean value of residence. Patients living in an institution, such as nursing homes, were assigned to a separate category. The NCR uses the International Classification of Disease-Oncology (ICD-O-3) to code tumour localization and morphology. Stage of disease was determined using the TNM (tumour-node-metastasis) classification of the World Health Organization (WHO) according to the edition valid at the time of diagnosis. For the present study, we combined the pathological stage (pTNM) with the clinical stage

(cTNM) in case (parts of) the pTNM were unknown or missing.

Primary outcome variables included serious postoperative complications, 30-day mortality and overall survival. Serious postoperative complications were defined as abscess and/or anastomotic leakage and were only registered when re-operation or re-hospitalization was needed. 30-day mortality was defined as occurrence of death within 30 days after surgery. Overall survival was determined using the time interval between the incidence date and the date of death or last follow-up. Data were censored at January 1st, 2015.

Patient selection

For this study, data from all patients diagnosed between 2008 until 2013 with stage I-IV CRC in the south-eastern part of the Netherlands were included ($n = 10,621$). This area consists of 2.4 million inhabitants (~15% of the Dutch population) and 10 peripheral hospitals including 2 radio therapeutic institutes spread over four locations. In all hospitals colorectal surgery is performed, however, surgery for locally advanced rectal cancer and colorectal cancer with operable liver metastases is centralized. Patients with other morphology than adenocarcinoma (e.g. carcinoids) were excluded ($n = 47$). BMI was defined as body weight (in kg) divided by square height in meter (kg/m^2). Patients were categorized in four BMI groups according to the BMI classifications of the World Health Organization: underweight (BMI $< 18.5 \text{ kg}/\text{m}^2$), normal weight ($18.5 \geq \text{BMI} < 25 \text{ kg}/\text{m}^2$), overweight ($25 \geq \text{BMI} < 30 \text{ kg}/\text{m}^2$), and obesity (BMI $\geq 30 \text{ kg}/\text{m}^2$) [21]. Patients with unknown BMI ($n = 3203$) were excluded resulting in 7371 patients available for analysis. There were no significant differences between the group with known BMI and the group with missing BMI (data not shown) with regard to patient, tumour and treatment characteristics. Data from all patients who underwent surgery, excluding polypectomy and TEM, were used to analyse the association between BMI and postoperative complications and 30-day mortality. Data from all patients were used to analyse the association between BMI and overall mortality.

Statistical analysis

Statistical analysis was performed using the chi-square test for categorical variables and the one-way ANOVA (with Bonferroni correction) for continuous variables.

The association between BMI and postoperative complications and 30-day mortality, was assessed by means of logistic regression. Overall survival plots were constructed using the Kaplan-Meier method. Hazard ratios of overall survival in CRC patients per BMI category were calculated using a Cox proportional hazard model. Both logistic regression and Cox regression analyses were adjusted for age, gender, SES, comorbidity, morphology, localization (colon versus rectum) and complications. In all analyses, normal weight was chosen as reference category.

All statistical analyses were performed using SPSS version 22.0 for Windows (SPSS, Inc., Chicago, IL). All tests were two-tailed and a p -value < 0.05 was considered statistically significant.

Results

Patient characteristics

The total number of patients diagnosed with CRC between 1 January 2008 and 31 December 2013 in the south-eastern part of the Netherlands was 10,621. The 7371 included patients were categorized in four BMI groups. 1.8% of these patients were underweight (BMI $< 18.5 \text{ kg}/\text{m}^2$), 41.4% had a normal weight range

($18.5 \geq \text{BMI} < 25 \text{ kg/m}^2$), 40.1% were overweight ($25 \geq \text{BMI} < 30 \text{ kg/m}^2$), and 16.7% were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$).

Patient and tumour characteristics stratified according to BMI category are presented in Table 1. The median age of the entire study population was 69 years [range: 20–96]. The ratio between males and females was 43:57. Differences between the BMI categories were observed for SES, comorbidity, stage, use of neo-adjuvant radiotherapy and neo-adjuvant chemoradiation, surgery,

surgical approach and emergency procedures ($p < 0.001$ for all). The groups were similar according to tumour localization, differentiation grade, morphology and systemic treatment.

Morbidity

The postoperative morbidity data is shown in Tables 2 and 3. The rate of serious postoperative complications differed significantly

Table 1
Characteristics of patients diagnosed with colorectal cancer.

BMI category		Underweight n (%)	Normal weight n (%)	Overweight n (%)	Obesity n (%)	Total n (%)	p ^{A,B}
Patients per group		133 (1.8)	3054 (41.4)	2955 (40.1)	1229 (16.7)	7371	
Patient characteristics							
Gender	female	88 (66.2)	1440 (47.2)	1088 (36.8)	573 (46.6)	3189 (43.3)	<0.001
	male	45 (33.8)	1614 (52.8)	1867 (63.2)	656 (53.4)	4182 (56.7)	
Age (years) mean \pm SD		68 \pm 12	69 \pm 12	70 \pm 10	68 \pm 11	69 \pm 11	<0.001 ^C
SES	low	44 (33.1)	642 (21.0)	628 (21.3)	338 (27.5)	1652 (22.4)	<0.001
	average	42 (31.6)	1143 (37.4)	1114 (37.7)	503 (40.9)	2802 (38.0)	
	high	39 (29.3)	1006 (32.9)	956 (32.4)	301 (24.5)	2302 (31.2)	
	institutionalized	3 (2.3)	112 (3.7)	103 (3.5)	35 (2.8)	253 (3.4)	
	unknown	5 (3.8)	151 (4.9)	154 (5.2)	52 (4.2)	362 (4.9)	
Comorbidity	no comorbidity	48 (36.1)	1105 (36.2)	789 (26.7)	210 (17.1)	2152 (29.2)	<0.001
	1 comorbidity	32 (24.1)	777 (25.4)	876 (29.6)	333 (27.1)	2018 (27.4)	
	≥ 2 comorbidities	53 (39.8)	1138 (37.3)	1269 (42.9)	681 (55.4)	3141 (42.6)	
	unknown	0 (0)	34 (1.1)	21 (0.7)	5 (0.4)	60 (0.8)	
Tumour characteristics							
Localization	colon	82 (61.7)	2083 (68.2)	1996 (67.5)	868 (70.6)	5029 (68.2)	0.09
	rectosigmoid/rectum	51 (38.3)	971 (31.8)	959 (32.5)	361 (29.4)	2342 (31.8)	
Differentiation	grade 1	8 (6.0)	192 (6.3)	168 (5.7)	78 (6.3)	446 (6.1)	0.12
	grade 2	59 (44.4)	1631 (53.4)	1612 (54.6)	680 (55.3)	3982 (54.0)	
	grade 3	20 (15.0)	426 (13.9)	362 (12.3)	174 (14.2)	982 (13.3)	
	grade 4	0 (0.0)	7 (0.2)	3 (0.1)	3 (0.2)	13 (0.2)	
	unknown	46 (34.6)	798 (26.1)	810 (27.4)	294 (23.9)	1948 (26.4)	
Morphology	adenocarcinoma	120 (90.2)	2703 (88.5)	2604 (88.1)	1067 (86.8)	6494 (88.1)	0.77
	mucinous	12 (9.0)	288 (9.4)	297 (10.1)	135 (11.0)	732 (9.9)	
	signet ring cell	1 (0.8)	41 (1.3)	32 (1.1)	19 (1.5)	93 (1.3)	
	other	0 (0.0)	22 (0.7)	22 (0.7)	8 (0.7)	52 (0.7)	
Stage	1	25 (18.8)	506 (16.6)	625 (21.2)	274 (22.3)	1430 (19.4)	<0.001
	2	44 (33.1)	832 (27.2)	835 (28.3)	329 (26.8)	2040 (27.7)	
	3	34 (25.6)	923 (30.2)	866 (29.3)	381 (31.0)	2204 (29.9)	
	4	30 (22.6)	793 (26.0)	629 (21.3)	245 (19.9)	1697 (23.0)	
Treatment data							
Neo-adjuvant RT	yes	14 (10.5)	460 (15.1)	480 (16.2)	165 (13.4)	1119 (15.2)	<0.001
	no	81 (60.9)	2132 (69.8)	2078 (70.3)	910 (74.0)	5201 (70.6)	
	no surgery	38 (28.6)	462 (15.1)	397 (13.4)	154 (12.5)	1051 (14.3)	
Neo-adjuvant CR	yes	17 (12.8)	289 (9.5)	251 (8.5)	102 (8.3)	659 (8.9)	<0.001
	no	78 (58.6)	2303 (75.4)	2307 (78.1)	973 (79.2)	5661 (76.8)	
	no surgery	38 (28.6)	462 (15.1)	397 (13.4)	154 (12.5)	1051 (14.3)	
Chemotherapy	yes	41 (30.8)	1146 (37.5)	1081 (36.6)	413 (33.6)	2681 (36.4)	0.05
	no	92 (69.2)	1908 (62.5)	1874 (63.4)	816 (66.4)	4690 (63.6)	
Surgery	yes ^D	92 (69.2)	2517 (82.4)	2459 (83.2)	1038 (84.5)	6106 (82.8)	<0.001
	no	41 (30.8)	537 (17.6)	496 (16.8)	191 (15.5)	1265 (17.2)	
Procedure	elective	57 (42.9)	1562 (51.1)	1584 (53.6)	713 (58.0)	3916 (53.1)	<0.001
	emergency	7 (5.3)	186 (6.1)	112 (3.8)	35 (2.8)	340 (4.6)	
	stent/stoma ^E	3 (2.3)	24 (0.8)	13 (0.4)	7 (0.6)	47 (0.6)	
	no	66 (49.6)	1266 (41.5)	1233 (41.7)	467 (38.0)	3032 (41.1)	
	unknown	0 (0)	16 (0.5)	13 (0.4)	7 (0.6)	36 (0.5)	
Tumour approach	endoscopic	1 (0.8)	51 (1.7)	80 (2.7)	31 (2.5)	163 (2.2)	<0.001
	laparoscopic	23 (17.7)	871 (28.5)	900 (30.5)	329 (26.8)	2123 (28.8)	
	lap + conversion	3 (2.3)	137 (4.5)	167 (5.7)	112 (9.1)	419 (5.7)	
	open	65 (48.9)	1490 (48.8)	1382 (46.8)	590 (48.0)	3527 (47.8)	
	no surgery	38 (28.6)	462 (15.1)	397 (13.4)	154 (12.5)	1051 (14.3)	
	unknown	3 (2.3)	43 (1.4)	29 (1.0)	13 (1.1)	88 (1.2)	

BMI: body mass index.

SES: social economic status.

RT: radiotherapy.

CR: chemoradiation.

P: p-value.

^A The mean difference is significant at the 0.05 level.

^B Pearson chi-square test.

^C One-way ANOVA.

^D Polypectomy and TEM are excluded.

^E Followed by elective surgery.

Table 2
Univariable analyses of morbidity and mortality of surgically treated colorectal cancer patients.

		Underweight n (%)	Normal weight n (%)	Overweight n (%)	Obesity n (%)	P ^A
Total of patients who underwent surgery ^B		n = 92	n = 2517	n = 2459	n = 1038	
Total of patients who underwent surgery and received anastomosis		n = 80	n = 2264	n = 2226	n = 941	
Morbidity ^C	no anastomotic leakage or abscess	64 (80.0)	1982 (87.5)	1948 (87.5)	808 (85.9)	0.001
	anastomotic leakage	7 (8.8)	104 (4.6)	130 (5.8)	42 (4.5)	
	abscess	6 (7.5)	108 (4.8)	98 (4.4)	58 (6.2)	
	abscess and anastomotic leakage	2 (2.5)	53 (2.3)	43 (1.9)	25 (2.7)	
	unknown	1 (1.2)	17 (0.8)	7 (0.4)	8 (0.8)	
30-day postoperative mortality	died ≤ 30 days postoperative	9 (9.8)	83 (3.3)	84 (3.4)	28 (2.7)	0.005

P: P-value.

^A Pearson Chi-square test.

^B Polypectomy and TEM are excluded.

^C Which required readmission or surgery.

Table 3
Multivariable analyses of morbidity and mortality of surgically treated colorectal cancer patients.

		Unadjusted			Adjusted ^A		
		OR ^{B,C}	95% CI	P	OR ^{B,C}	95% CI	P
Morbidity	Underweight	1.75	0.99–3.12	0.06	1.95	1.08–3.49	0.03
	Normal weight	1.00	Reference				
	Overweight	1.04	0.87–1.25	0.67	1.00	0.83–1.20	0.98
	Obesity	1.16	0.92–1.45	0.21	1.16	0.92–1.46	0.22
30-day mortality	Underweight	3.14	1.53–6.46	0.002	4.37	2.03–9.42	<0.001
	Normal weight	1.00	Reference				
	Overweight	1.03	0.76–1.41	0.84	1.10	0.80–1.52	0.54
	Obesity	0.81	0.53–1.25	0.34	0.98	0.62–1.52	0.91

OR: Odds ratio.

CI: Confidence interval.

^A Adjusted for: gender, age, SES, comorbidity, stage, localization and morphology.

^B Compared to normal weight.

^C Calculated by means of logistic regression.

between underweight (18.8%), normal weight (11.7%), overweight (12.2%) and obese patients (13.3%; P = 0.001). Anastomotic leakage was observed more frequently in the underweight group (underweight 7 (8.8%); normal weight 104 (4.6%); overweight 130 (5.8%); obese 42 (4.5%), P = 0.001). Intra-abdominal abscesses were observed more frequently in the underweight and obese population (underweight 6 (7.5%); normal weight 108 (4.8%); overweight 98 (4.4%); obese 58 (6.2%); p = 0.001).

Logistic regression showed that underweight patients were more likely to have postoperative complications compared to normal weight patients (18.8% vs. 11.7%, OR 1.955, 95% CI 0.99–3.12). There was no significant difference in morbidity for overweight (OR 0.997, 95% CI 0.83–1.20) or obese patients (OR 1.15, 95% CI 0.91–1.45) versus normal weight patients.

30-day mortality

The 30-day mortality (shown in Tables 2 and 3) differed significantly between the four BMI groups. Underweight was associated with a higher 30-day mortality rate compared to the other BMI categories (underweight 9.8%; normal weight 3.3%; overweight 3.4%; obese 2.7%, p = 0.005).

Also, in multivariable analyses, underweight patients have a significant worse 30-day mortality (OR 4.37, 95% CI 2.03–9.42) compared to normal weight patients. There was no significant difference for overweight (OR 1.10, 95% CI 0.80–1.52) or obese (OR 0.98, 95% CI 0.62–1.52) patients compared to normal weight patients.

Table 4
Overall survival in colorectal cancer patients per BMI category and stage of disease.

		5-year overall survival	Unadjusted			Adjusted ^A		
			HR ^B	95% CI	P	HR ^B	95%CI	P
Stage I-III	Underweight	57%	1.95	1.44–2.65	<0.001	2.06	1.51–2.80	<0.001
	Normal weight	66%	1.00	Reference		1.00	Reference	
	Overweight	70%	0.88	0.78–0.99	0.03	0.86	0.76–0.97	0.01
	Obesity	65%	1.00	0.86–1.16	0.99	1.01	0.87–1.17	0.88
Stage IV	Underweight	6%	1.58	1.07–2.34	0.02	1.65	1.11–2.45	0.01
	Normal weight	12%	1.00	Reference		1.00	Reference	
	Overweight	10%	0.96	0.85–1.08	0.46	0.85	0.75–0.95	0.007
	Obesity	12%	0.86	0.73–1.02	0.08	0.76	0.64–0.91	0.002

HR: Hazard ratio.

CI: Confidence interval.

P: P-value.

^A Adjusted for: comorbidity, SES, gender, age, morphology, localization and complications (anastomotic leakage/abscess).

^B Compared to normal weight.

Overall survival

Median follow-up time was 42 months. In the total study population, underweight patients had a significantly worse overall survival, when compared with normal weight patients (five-year overall survival 45% vs. 52% ($p < 0.001$), adjusted HR 1.53, 95% CI 1.20–1.95). Overweight and obese patients had a significantly better overall survival compared to normal weight patients (overweight vs. normal weight: five-year overall survival 57% vs. 52% ($p < 0.001$), adjusted HR 0.83, 95% CI 0.76–0.90; obese vs. normal weight: five-year overall survival 55% vs. 52% ($p < 0.001$), adjusted HR 0.84, 95% CI 0.75–0.94).

After stratification (see Table 4), multivariable analyses showed that underweight was again associated with a worse overall survival compared to normal weight patients for both stages I–III and stage IV patients (stage I–III: HR 2.06, 95%CI 1.51–2.80; stage IV: HR 1.65, 95% CI 1.11–2.45). In both stage groups, overweight patients were associated with an improved overall survival. In the group of obese patients, only in stage IV patients obesity was associated with a statistically significant better overall survival compared to stage IV normal weight patients. Fig. 1 demonstrates these differences in survival for both curatively treated patients (stage I–III) and often palliatively treated patients (stage IV).

Discussion

The role of BMI as a risk factor for postoperative morbidity and mortality and long-term survival in CRC patients is a matter of debate in the literature. In this large population based study, underweight CRC patients had a significantly higher postoperative

complication risk and 30-day mortality compared to patients in the other weight categories. Long-term survival was significantly worse in underweight patients in all stages, while overweight and stage IV obese patients were associated with improved survival compared to normal weight patients.

The present large database of more than 7300 CRC patients demonstrated, that underweight patients (BMI <18.5) were more likely to have postoperative complications after colorectal surgery. This result is similar to previously published studies [8,16]. In a retrospective analysis of an electronic database with a total of 414 patients, underweight (BMI <20) was associated with a higher incidence of major complications and sepsis rate [8]. A retrospective study comparing the outcomes of rectal cancer surgery showed higher postoperative sepsis rates in underweight patients (BMI <20) [5].

The adjusted OR for 30-day mortality in the present study was 4.39 in underweight patients, which is comparable to the 2–3 fold increased likelihood of 30-day mortality reported in recent literature [5,15]. However, we found no statistical significant association between overweight and obesity and 30-day survival. Previous studies showed similar results without differences in short-term survival between normal weight and obese patients [8,16]. Whereas others suggest that obesity is a risk factor for postoperative death [5].

In addition, our study showed that being underweight was associated with a lower overall survival in both stage I–III and stage IV CRC patients. This finding was previously reported in a clinical trial with early-stage CRC patients in which underweight patients (BMI <18.5) had a 50% (95% CI 43–56) increased risk of death and 27% (20–34) increased risk of disease progression compared to obese patients [22]. Furthermore, a low BMI has also been shown to be a prognostic factor for disease progression and survival time in metastatic CRC patients. In these patients, underweight in cancer is often a sign of more advanced disease and as such, the lower survival in metastatic patients with underweight might be the result of the advanced character of the disease and not of the low BMI itself [23].

Recently published studies demonstrated that overweight and obesity were risk factors for major postoperative complications in patients undergoing surgery for gastrointestinal malignancy [11,14]. In the present study, obesity and overweight did not result in different postoperative complications or mortality in multivariable analyses. Surprisingly, long term overall survival was suggested to be better in overweight CRC patients. More and more evidence is available to suggest that overweight and obesity is, surprisingly, associated with better prognosis in cancer patients [24]. This is referred to as the “obesity paradox”, in which overweight or mild obesity is associated with improved outcomes [13]. However, the exact mechanisms underlying the obesity paradox have not been clearly explained. It might be possible that patients with overweight develop less aggressive tumours or respond better to cancer treatment.

However, recent cardiovascular studies, suggests that methodological biases might also be involved as information on body composition or location of adipose tissue (visceral or subcutaneous) is often not taken into account [25]. Moreover, it is suggested that the obesity paradox might be biased by a specific form of selection bias, the so called “collider stratification bias” [25]. This occurs when two variables share a common effect (pre-diagnostic obesity is independently associated with both CRC and mortality, and at the same time CRC is associated with mortality) and stratification on the variable representing that effect induces a false, strengthened, or reversed association between otherwise independent factors.

The present study found no association between obesity and

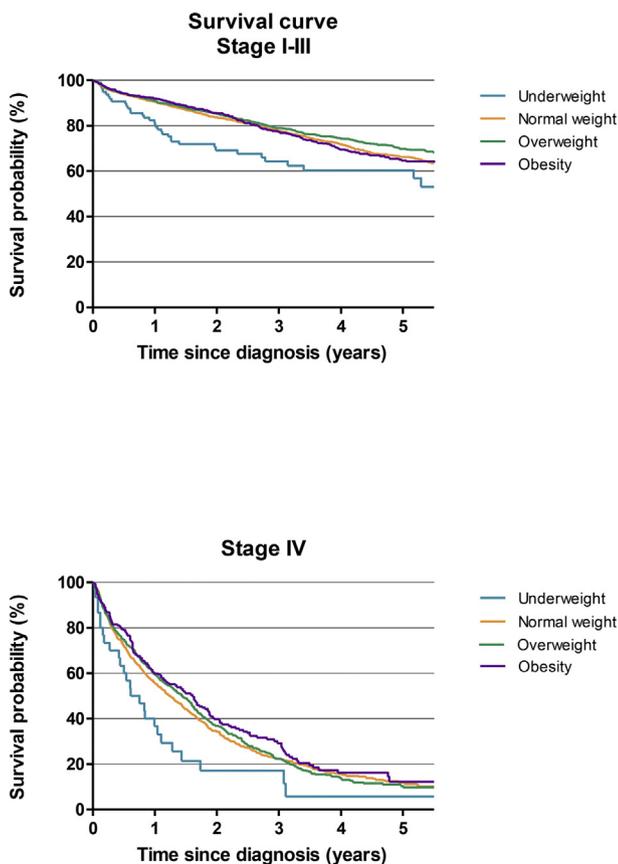


Fig. 1. Survival in stage I–III and stage IV patients with colorectal cancer.

overall survival, except for stage IV CRC in which obesity was associated with a better overall survival compared to normal weight patients. This finding is confirmed by a study in 2249 CRC patients from 6 prospective epidemiologic cohort studies. This study found an association between BMI and CRC survival varying according to cancer stage at diagnosis. In this study a higher BMI was associated with higher mortality in early-stage CRC patients (overweight stage I, obese stages I–II) while higher BMI was associated with lower mortality in advanced-stage CRC patients (overweight stages II–IV, obese stages III–IV) [26]. Hines et al. also described that being overweight or obese was associated with a decreased risk of death for patients with stage IV CRC [27]. A possible explanation might be that BMI reflects the body's energy and protein reserves. The survival advantage in obese patients might be due to the larger energy reserve of obese persons [28]. A larger energy reserve is especially important in stage IV CRC patients because of the incurable character of the disease with expected progressive weight loss. However, in a prospective American cohort study, severely obese CRC stage I–III patients (BMI >30) experienced worse survival outcomes independent of many other factors [18]. However, American populations have different BMI distributions which might be responsible for the difference in results.

The major strengths of this study are the large patient population included in the analyses and the population based character of the study. The major advantage of a population-based study is that patients are not excluded based on high age or bad condition so that results are generalizable to the whole population of Dutch CRC patients. A previous study using data of the NCR demonstrated no differences in long term survival between hospitals, which makes data from this region in the Netherlands reliable and applicable nationwide [29]. Furthermore, also stage IV CRC patients were included and overall survival analyses were separately performed for stage I–III and IV.

Limitations of the study are the lack of information on pre-diagnosis weight changes or other preoperative parameters for nutritional status, which are not registered in the NCR. Especially pre-diagnosis weight loss is known to be associated with shorter survival times, worsened performance status, and decreased response to chemotherapy [30].

A second limitation is the lack of information about cancer-specific mortality. Unfortunately, these data were not available in the NCR database. To exclude that the overall survival data are related to comorbidity and not to a more specific effect of BMI, we adjusted all analyses for comorbidity. The association between underweight and worse overall survival and overweight/obesity and better overall survival still remains significant.

Furthermore, other variables not available in this study might influence postoperative complications such as physical activity, amount of muscle mass and body fat distribution. A prospective study in patients with colon cancer after laparoscopic colectomy showed that the visceral fat area is a more powerful parameter than BMI. For future research, we therefore recommend to measure muscle mass, fat mass and body fat distribution for example by using abdominal CT scans. An easier way to estimate visceral obesity is to measure waist circumference [30,31].

In conclusion, this retrospective population-based cohort study of 7371 patients demonstrated that underweight CRC patients were more likely to have postoperative complications and a worse 30-day mortality compared to other BMI categories. The underweight population also has a worse long-term survival while overweight CRC patients and obese stage IV CRC patients were associated with an improved survival compared to normal weight patients. More research is required to determine the effects of contributing factors such as muscle mass and intra-abdominal fat

on postoperative complications, 30-day mortality and overall survival and whether interventions to improve BMI, muscle and fat mass can improve these outcome variables in CRC patients. Furthermore, research evaluating the effects of prehabilitation programmes aimed at improving preoperative nutritional status and condition need to be established.

Disclosure of commercial interest

None.

Conflict of interest statement

We have no conflict of interest to declare.

References

- [1] van der Geest LG, Lam-Boer J, Koopman M, Verhoef C, Elferink MA, de Wilt JH. Nationwide trends in incidence, treatment and survival of colorectal cancer patients with synchronous metastases. *Clin Exp Metastasis* 2015;32(5): 457–65.
- [2] Brouwer NPM, Tanis PJ, Hugen N, Nagtegaal ID, de Wilt JHW, Verhoeven RHA. Survival continuously improves during 25 years of treating colorectal cancer patients: results from the Dutch Cancer Registry. *Int J Canc* 2018. in press.
- [3] Netherlands Cancer Registry, accessed February 27, 2017. [Available from: <http://www.cijfersoverkanker.nl/>].
- [4] Labianca R, Nordlinger B, Beretta GD, Mosconi S, Mandala M, Cervantes A, et al. Early colon cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol: Off J Euro Soc Med Oncol* 2013;24(Suppl 6). vi64–72.
- [5] Smith RK, Broach RB, Hedrick TL, Mahmoud NN, Paulson EC. Impact of BMI on postoperative outcomes in patients undergoing proctectomy for rectal cancer: a national surgical quality improvement program analysis. *Dis Colon Rectum* 2014;57(6):687–93.
- [6] Merkow RP, Billimoria KY, McCarter MD, Bentrem DJ. Effect of body mass index on short-term outcomes after colectomy for cancer. *J Am Coll Surg* 2009;208(1):53–61.
- [7] Khoury W, Stocchi L, Geisler D. Outcomes after laparoscopic intestinal resection in obese versus non-obese patients. *Br J Surg* 2011;98(2):293–8.
- [8] Healy LA, Ryan AM, Sutton E, Younger K, Mehigan B, Stephens R, et al. Impact of obesity on surgical and oncological outcomes in the management of colorectal cancer. *Int J Colorectal Dis* 2010;25(11):1293–9.
- [9] DeMaria EJ, Carmody BJ. Perioperative management of special populations: obesity. *Surg Clin* 2005;85(6):1283–9 [xii].
- [10] Amri R, Bordeianou LG, Sylla P, Berger DL. Obesity, outcomes and quality of care: body mass index increases the risk of wound-related complications in colon cancer surgery. *Am J Surg* 2014;207(1):17–23.
- [11] STARSurg Collaborative. Multicentre prospective cohort study of body mass index and postoperative complications following gastrointestinal surgery. *Br J Surg* 2016;103(9):1157–72.
- [12] Pausch T, Hartwig W, Hinz U, Swolana T, Bundy BD, Hackert T, et al. Cachexia but not obesity worsens the postoperative outcome after pancreatoduodenectomy in pancreatic cancer. *Surgery* 2012;152(3 Suppl 1): S81–8.
- [13] Mullen JT, Moorman DW, Davenport DL. The obesity paradox: body mass index and outcomes in patients undergoing nonbariatric general surgery. *Ann Surg* 2009;250(1):166–72.
- [14] Poelmeijer YQM, Lijftogt N, Detering R, Fiocco M, Tollenaar RAEM, Wouters MWJM. Obesity as a determinant of perioperative and postoperative outcome in patients following colorectal cancer surgery: A population-based study (2009–2016). *Eur J Surg Oncol* 2018.
- [15] Hrabec JE, Sherman SK, Charlton ME, Cromwell JW, Byrn JC. Effect of BMI on outcomes in proctectomy. *Dis Colon Rectum* 2014;57(5):608–15.
- [16] Yasunaga H, Horiguchi H, Matsuda S, Fushimi K, Hashimoto H, Ayanian JZ. Body mass index and outcomes following gastrointestinal cancer surgery in Japan. *Br J Surg* 2013;100(10):1335–43.
- [17] Gendall KA, Raniga S, Kennedy R, Frizelle FA. The impact of obesity on outcome after major colorectal surgery. *Dis Colon Rectum* 2007;50(12): 2223–37.
- [18] Daniel CR, Shu X, Ye Y, Gu J, Raju GS, Kopetz S, et al. Severe obesity prior to diagnosis limits survival in colorectal cancer patients evaluated at a large cancer centre. *BJC (Br J Cancer)* 2016;114(1):103–9.
- [19] Doleman B, Mills KT, Lim S, Zelhart MD, Gagliardi G. Body mass index and colorectal cancer prognosis: a systematic review and meta-analysis. *Tech Coloproctol* 2016;20(8):517–35.
- [20] Schouten LJ, Jager JJ, van den Brandt PA. Quality of cancer registry data: a comparison of data provided by clinicians with those of registration personnel. *Br J Canc* 1993;68(5):974–7.
- [21] Organization WH. Global data on body mass index. BMI classification [Available from: <http://apps.who.int/bmi/index.jsp>].

- [22] Renfro LA, Loupakis F, Adams RA, Seymour MT, Heinemann V, Schmoll HJ, et al. Body mass index is prognostic in metastatic colorectal cancer: pooled analysis of patients from first-line clinical trials in the ARCAD database. *J Clin Oncol: Off J Am Soc Clin Oncol* 2016;34(2):144–50.
- [23] Zacharakis M, Xynos ID, Lazaris A, Smaro T, Kosmas C, Dokou A, et al. Predictors of survival in stage IV metastatic colorectal cancer. *Anticancer Res* 2010;30(2):653–60.
- [24] Giles KA, Hamdan AD, Pomposelli FB, Wyers MC, Siracuse JJ, Schermerhorn ML. Body mass index: surgical site infections and mortality after lower extremity bypass from the National Surgical Quality Improvement Program 2005–2007. *Ann Vasc Surg* 2010;24(1):48–56.
- [25] Banack HR, Kaufman JS. The obesity paradox: understanding the effect of obesity on mortality among individuals with cardiovascular disease. *Prev Med* 2014;62:96–102.
- [26] Kocarnik JM, Chan AT, Slattery ML, Potter JD, Meyerhardt J, Phipps A, et al. Relationship of prediagnostic body mass index with survival after colorectal cancer: stage-specific associations. *Int J Canc* 2016;139(5):1065–72.
- [27] Hines RB, Shanmugam C, Waterbor JW, McGwin Jr G, Funkhouser E, Coffey CS, et al. Effect of comorbidity and body mass index on the survival of African-American and Caucasian patients with colon cancer. *Cancer* 2009;115(24):5798–806.
- [28] Li L, Kalantar-Zadeh K. Obesity that makes kidney cancer more likely but helps fight it more strongly. *J Natl Cancer Inst (Bethesda)* 2013;105(24):1848–9.
- [29] Bos AC, van Erning FN, Elferink MA, Rutten HJ, van Oijen MG, de Wilt JH, et al. No difference in overall survival between hospital volumes for patients with colorectal cancer in The Netherlands. *Dis Colon Rectum* 2016;59(10):943–52.
- [30] Cakir H, Heus C, Verduin WM, Lak A, Doodeman HJ, Bemelman WA, et al. Visceral obesity, body mass index and risk of complications after colon cancer resection: a retrospective cohort study. *Surgery* 2015;157(5):909–15.
- [31] Kartheuser AH, Leonard DF, Penninckx F, Paterson HM, Brandt D, Remue C, et al. Waist circumference and waist/hip ratio are better predictive risk factors for mortality and morbidity after colorectal surgery than body mass index and body surface area. *Ann Surg* 2013;258(5):722–30.