Appendix to Ane Sørlie Kværner, Helene Harnæs, Dena Helene Alavi, Linnea Bärebring, Hege Berg Henriksen, Marianne Grønlie Guren, Peter Mæhre Lauritzen, Heidi Beate Eggesbø, Gro Wiedswang, Sigbjørn Smeland, Rune Blomhoff. Should calculation of chemotherapy dosage for bowel cancer be based on body composition? Tidsskr Nor Legeforen 2020; 140. doi: 10.4045/tidsskr.19.0769.

This appendix is a supplement to the article and has not undergone editorial revision.

Appendix 2: Overview of studies that have investigated the relationship between clinical signs of disease-related malnutrition and chemotherapy toxicity in patients with localised colorectal cancer.

Author, year (journal)	**Study design (country)**	**Patient population, stage (number)**	**Chemotherapy regimen**	**Measuring tool**	**Parameters**	**Exposure variables**	**Endpoints**	**Adjusted for covariate variables**	**Main findings**
Cespedes Feliciano et al., 2017 (Cancer)	Historical cohort (USA)	Colorectal cancer, stages II–III (n=533)	FOLFOX	CT, Slice-O-Matic, v.5.0 (L3, one slice)	Skeletal muscle mass (cm^2) L3[1]	Skeletal muscle mass (cm^2) L3, gender-specific tertiles	Early discontinued course (<6 courses), postponed course (>3 days deviation from schedule ≥3 times) and/or dose reduction (relative dose intensity <0.70). Dose-limiting toxicity from first to last course (NCI-CTC v.3), specifically neutropenia, thrombocytopenia and neuropathy	Age, sex, cancer stage, BMI[2]	Low versus high skeletal muscle mass (cm^2) in L3 area associated with early discontinued course (OR: 2.34 (95% CI: 1.04-5.24, p for trend=0.03), postponed course (OR: 2:24 (95% CI: 1.37-3.66, p for trend=0.002), dose reduction (OR: 2.28 (95 CI: 1.19-4.36, p for trend=0.01). Neutropenia and thrombocytopenia, but not neuropathy, significantly more common in those with low compared to medium and high skeletal muscle mass.
Jung et al., 2015 (Support Care Cancer)	Historical cohort (South Korea)	Colon cancer, stage III (n=229)	FOLFOX	CT (Brilliance iCT) (L4)	Skeletal muscle mass (cm^2) L4, PI (mm^2/m^2)	PI (mm^2/m^2), continuous variable and sex-adjusted quartiles	Grade 3-4 dose-limiting toxicity (NCI-CTC v.3), specifically neuropathy, neutropenia, anaemia, thrombocytopenia, nausea, vomiting, diarrhoea, mucositis and liver function abnormalities	Age, sex, haemoglobin, GFR, ECOG status and Charlson score	Significant difference in incidence of grades 3–4 neutropenia and total dose-limiting toxicity between the different PI groups (p=0.009 and p= 0.001, respectively). 1 SD reduction in PI associated with increased odds of both grades 3–4 neutropenia (adjusted OR: 1.36, 95% CI: 0.93-1.98) and total dose-limiting toxicity (adjusted OR: 1.67, 95% CI: 1.13-2.46).

Prado et al., 2007 (Clin Cancer Res)	Historical cohort (Canada)	Colon cancer, stages II–III (n=62)	5-FU monotherapy	CT, Slice-O-Matic, v.4.3 (L3, four slices)	Skeletal muscle mass (cm^2) L3, FFM total body (kg)[3]	5-FU/FFM total body (mg/kg), continuous and categorical variable	Grade 3-4 dose-limiting toxicity (NCI-CTC v. 2) after 1st cycle (mucositis, diarrhoea, neutropenia, other grade 3-4 toxicity), postponed course, dose reduction and combination of all three	Unadjusted	Presence of dose-limiting toxicity (grade 3-4 toxicity, postponed course or dose reduction) associated with higher levels of 5-FU/kg FFM (18 vs 16 mg/kg, p=0.036), not 5-FU/BSA or 5-FU/kg body weight. A value of 20 mg/kg FFM identified as threshold value for developing toxicity (OR = 16.75, p= 0.013). Women had a particularly low FFM relative to their BSA.

Ilich et al., 2016 (J Oncol Pharm Practice)	Historical cohort (Canada)	Colorectal cancer, stages 0–III (n=299)[4]	Capecitabine	Demography	Sex (indirect measure of FFM)	Sex, categorical variable	Dose-limiting toxicity defined as postponed dose (≥3 days postponement), dose reduction (>10% reduction in mg/m^2) or discontinued course on 2nd or 3rd cycle	Age, creatinine secretion, ECOG score, cancer type, stage, empirical dose reduction on 1st cycle	Significant difference in incidence of dose-limiting toxicity between women and men (68 vs 52%, p=0.007, adjusted OR: 2.04; 95% CI: 1.23-3.36).
Williams et al., 2018 (Cancer Chemother Pharmacol)	Historical cohort (USA)	Colorectal cancer, stages II–IV (n=25)[5]	FOLFOX	CT, Slice-O-Matic, v.4.3 (L3)	Skeletal muscle mass (cm^2) L3, skeletal muscle mass index (cm^2/m^2) L3, FFM total body (kg)[6]	Sarcopenia as a categorical variable (sex- and BMI-specific cut-off values for skeletal muscle mass index (cm^2/m^2), 5-FU/FFM total body (mg/kg) as continuous variable)	5-FU pharmacokinetics 2–44 h after 1st 5-FU infusion (AUC, mg x t/L) and dose-limiting toxicity (NCI-CTC v.3) in the course of 1-4 courses	Unadjusted	No significant difference in 5-FU pharmacokinetics between those with and without sarcopenia (17 vs 19 AUC, p=0.43). A non-significant difference in the presence of dose-limiting toxicity among those with and without sarcopenia (50 vs 39%, p= 0.7). Trend towards those experiencing dose-limiting toxicity having higher 5-FU/kg FFM than those who did not experience it (105 vs 93 mg/kg, p=0.058). The findings were particularly pronounced for haematological toxicity (110 vs 94 mg/kg, p=0.002). No difference in 5-FU/kg FFM between the different AUC groups.

Ali et al., 2016 (Cancer Medicine)	Historical cohort (Canada)	Colon cancer, stages I– IV (n=80)[7]	FOLFOX	CT, Slice-O-Matic, v.4.3 (L3, two slices)	Skeletal muscle mass (cm^2) L3, skeletal muscle mass index (cm^2/m^2) L3, FFM total body (kg)[6]	Oxaliplatin/FFM total body (mg/kg), continuous and categorical variable	Dose reduction or postponed course in the course of 1–4 courses, dose-limiting toxicity (NCi-CTC v.2 or v.3, specifically mucositis, diarrhoea, neuropathy, neutropenia, anaemia, nausea/vomiting, anorexia, other toxicity	Unadjusted	Threshold value for developing dose-limiting toxicity identified as 3.55 mg oxaliplatin/kg FFM. At this threshold value, 38% and 14%, respectively, of those with high and low oxaliplatin dose/kg FFM developed dose-limiting toxicity (p=0.024). Significant difference in incidence of early peripheral neuropathy among those with low (0%) and high (15%) oxaliplatin dose/kg FFM (15%) (p=0.046).
Suga et al., 2018 (J Pharm Health Care Sci)	Historical cohort[8] (Japan)	Colorectal cancer, stages I–IV (n=190)[9]	Oxaliplatin	Anthropometry	BMI (kg/m^2)	BMI, categorical variable (≤22 and >22 kg/m^2)	Vascular pain	Stage, earlier use of chemotherapy, oxaliplatin dose	Higher odds of vascular pain for those with low compared with normal/high BMI (72 vs 58%, adjusted OR: 0.48, 95% CI: 0.26-0.91, p=0.025).
Park et al., 2018 (Ann Surg Res)	Historical cohort[8] (South Korea)	Colorectal cancer, stages II– III (n=611)	FOLFOX	Anthropometry	BMI (kg/m^2)	BMI, continuous variable	Dose reduction (<60% vs ≥60% of planned dose)	Unadjusted	Dose reduction associated with significantly lower BMI compared with no/less pronounced dose reduction (23 vs 24 kg/m^2, p=0.005).
Shahriari-Ahmadi et al., 2015 (Asian Pac J Cancer Prev)	Historical cohort[8] (Iran)	Colorectal cancer, unspecified stage (n=130)	FOLFOX, XELOX	Anthropometry	BMI (kg/m^2)	BMI, categorical variable (< 20, 2025 and≥ 25 kg/m^2)	Chronic peripheral neuropathy (NCI-CTC v. 3)	Unadjusted	Significant difference in proportion of low, normal and high BMI among those with and without neuropathy (p=0.003). The presence of neuropathy appears to be associated with normal to high BMI (42% vs 87% for those with low and normal to high BMI).
Aprile et al., 2008 (Cancer)	Historical cohort[8] (USA)	Colorectal cancer, stages II–IV (n=300)[10]	FOLFOX, FOLFIRI, 5FU monotherapy	Anthropometry	Weight change (kg)	Weight loss and gain, categorical variables (cut-off values not defined)	Toxicity ≥ grade 1 (NCICTC v.2 or 3) at any time during the course	Unadjusted (network analysis)	Weight loss strongly correlated with fatigue and anorexia, moderately correlated with fever and dehydration and to a lesser extent chills, neuropathy and anxiety. Weight gain only observed in one individual.

Abbreviations: 5-FU: 5-fluorouracil, AUC: Area under curve, BSA: Body surface area, CT: computed tomography, DXA: dual-energy X-ray, ECOG: Eastern Cooperative Oncology Group, FFM: fat-free mass, FOLFIRI: (5-fluorouracil, irinotecan, calcium folinate), FOLFOX: (5-fluorouracil, oxaliplatin, calcium folinate), GFR: Glomerular filtration rate, CI: confidence interval, BMI: body mass index, MR: magnetic resonance tomography, NCI-CTC: National Cancer Institute Common Toxicity Criteria, OR: Odds ratio, PI: Psoas index, RR: Relative risk, SD: standard deviation, SMI: skeletal muscle mass index, XELOX; (capecitabine, oxaliplatin).

[1]The authors refer to close correlation (R^2=0.85) between muscle mass area at L3 and total body muscle mass: Total body skeletal muscle mass (volume)=(Muscle mass area 5 cm above L4-5 measured as MRx0.166)+2.142 (Shen et al., 2004).

[2]Analyses performed with and without adjustment for BMI. Presented endpoints represent non-BMI-adjusted endpoints.

[3]FFM total body calculated using the following formula developed by Mourtzakis et al. (submitted manuscript) with DXA as reference method: FFM total body (kg)=(Musculoskeletal mass L3 (cm^2)3.2459)/3.0583.

[4]*Represents the total number in the cohort, 49 had stage II-III cancer.*
[5]*Represents the total number in the cohort, 13 had stage II-III cancer.*
[6]*FFM total body calculated using the following formula developed by Mourtzakis et al. 2008 with DXA as reference method: FFM total body (kg)=(Musculoskeletal mass L3 (cm^2)x0.3) +6.06 (R2=0.88).*
[7]*Represents the total number in the Canadian cohort (only 21 adjuvant patients)*
[8]*Not clear whether exposure variable was measured before outcome variable*
.[9]*Represents the total number in the cohort, 173 had stage II-III cancer.*
[10]*Represents the total number in the cohort, 103 had stage II-III cancer.*