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Does nutritional status affect treatment tolarability, response and survival in metastatic colorectal cancer patients? Results of a prospective multicenter study

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Abstract

Background: The efficacy and tolerability of modern cytotoxic chemotherapy regimens used in malnourished metastatic colorectal cancer (mCRC) patients is uncertain. The aim of this study was to investigate the effect of malnutrition on efficacy and tolerability of cytotoxic chemotherapy and overall survival in mCRC patients.

Methods: In this multicenter study, demographic, oncologic and nutritional data were collected prospectively from mCRC patients. Nutritional status of the patients were evaluated on the basis of NRI (Nutritional Risk Assessment), BMI (Body Mass Index) and WL (Weight Loss) before the first chemotherapy, after the first and second chemotherapy during 2 cycles of chemotherapy every 15 days. To determine the inter-treatment weight loss toxicity assessment was included to theese parameters after each chemotherapy. NRI calculation was performed as [1.51xserum albumin level (g/L)+41.7xcurrent weight/basic weight]. NRIs were examined in 3 categories as 'no malnutrition' (NRI $>$97.5), 'moderate malnutrition' (97.5 $\geq$NRI $\geq$83.5) or 'severe malnutrition' (NRI $<$83.5). Response to treatment and drug-induced toxicities were assessed based on Criteria in Solid Tumors (RECIST) 1.1 and National Cancer Institute CTCAE version 4.0 respectively.

Results: One-hundred and thirty-seven mCRC patients were prospectively included. Median age was 48 (range 18-83). Primary location was colon in 66% of patients and 84% of their primary source was left colon. Malnutrition was detected in 39% of the cases. Response rate to treatment was twenty four percent. While there was no significant relationship between chemotherapy response and moderate/severe malnutrition ($p = 0.24$), moderate/severe malnutrition was associated with multipl site of metastases, WHO PS (World Health Organization Performance Status) of 1, over the median value of CEA/CA 19-9 (carcinoembryonic antigen/carbohydate antigen 19-9) levels ($p = 0.003$, $p = 0.03$, $p < 0.001$, and $p = 0.02$; respectively). Hypoalbuminemia and moderate/severe malnutrition were associated with all types of toxicity ($p < 0.001$ and $p < 0.001$). Moderate/severe malnutrition was associated with thrombocytopenia, and diarrhea following chemotherapy predominately, ($p = 0.02$ and $p = 0.04$; respectively). In moderate/severe malnutrition group median overall survival was prominently shorter than those with no malnutrition [6.6 moths (95%CI, 5.6-7.6) vs 11.9 moths (95% CI, 11.1-12.7) respectively, $p < 0.001$].

Conclusions: Our study showed that moderate/severe malnutrition in mCRC patients was associated with decreased overall survival and increased chemotherapy toxicity.

Keywords

Colorectal cancer, malnutrition, toxicity, survival

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Introduction

Colorectal cancer (CRC) is a common and lethal disease.[1] Although CRC mortality has been progressively declining since 1990, at a current rate of approximately 1.7 to 1.9 percent per year,[2] it still remains the third most common cause of cancer death in the United States in women, and the second leading cause of death in men. Current literature suggests that over 86 percent of those diagnosed under the age of 50 are symptomatic at diagnosis, and this is associated with more advanced stage at diagnosis and poorer outcomes.[3]

In patients with gastrointestinal malignancies, i.e. cancers of the stomach, colon, liver, biliary tract or pancreas, progressive malnutrition can be regularly observed during the course of illness and it significantly affects the patients' quality of life, morbidity and survival.[4,5] The impact of body mass index (BMI) on the survival of patients with CRC is controversial. Increased BMI has been associated by some authors with short survival in CRC.[6] In contrast, other studies have shown lower mortality among overweight or moderately obese patients with CRC.[7,8] However, the combination of several nutritional scores, such as the use of BMI, bioelectrical impedance analysis, Nutritional Risk Assessment (NRI), and the subjective Patient-Produced Subjective Nutritional Assessment (PG-SGA), have demonstrated more conclusive responses in predicting survival in patients with CRC.[7–9] Clear evidence suggests that the nutritional status in peri- and postdiagnosis periods of CRC patients also influences the prognosis related to the disease.[10]

Malnutrition has become more important as a prognostic indicator and it is predictive of CT toxicity. Although, survival and nutrition are matched together, there is limited data about the relationship of nutrition and chemotherapy. In a new study; malnutrition according to PG-SGA was significantly associated with chemotherapy-related grade $\geq$2 clinical toxicities in CRC patients.[5] Furthermore, malnutrition risk according to different nutritional assessment tools and whey protein intake were found to be significantly predictive of chemotherapy toxicity in patients with CRC receiving CT.[11] Even one course of CT worsens the nutritional status of the patients in geriatric GI malignancies.[12] Impact of nutritional status in the era of FOLFOX/FIRI-based chemotherapy was also studied and it was found that the well-nourished patients at first 6 months may predict a good response to therapy and fewer adverse events in FOLFOX/FIRI chemotherapy.[13]

In this study, we aimed to investigate the effect of malnutrition on efficacy and tolerability of cytotoxic chemotherapy and overall survival in mCRC patients.

Materials and methods

Patients' characteristics

Between February 2018 and March 2019, the nutritional status of patients receiving chemotherapy for their metastatic colorectal cancer were screened in outpatient services of three gastrointestinal medical oncology and surgery departments in Turkey. Nutritional status of the patients were evaluated on the basis of NRI, BMI and WL before the first chemotherapy, after the first and second chemotherapy during 2 cycles of chemotherapy every 15 days. Age >18 years, mCRC currently being treated with first line chemotherapy (Fluoropyrimidine derivate (5-FU or capecitabine) + oxaliplatin or irinotecan + targeted treatments) and not receiving nutritional support were determined as inclusion criteria. Patients with a follow-up of less than 2 months were excluded because of compromising the treatment tolerability assessment and insufficient data. The study was approved by our institutional ethics committee and also informed consent was obtained from each patient included. Nutritional and oncological data were recorded prospectively and anonymously on standardized and computerized case report forms.

Nutritional assessment and oncological data

Age, sex, overall weight (6 months before diagnosis) and current weight, height, WHO PS, biochemical parameters including albumin, carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA 19-9) levels were recorded to determine nutritional status.

BMI (weight/height^2), WL percentage [100-(current weight/basic weight x100)] and NRI [1.51xserum albumin level (g/L) + 41.7xcurrent weight/basic weight] were also calculated at each visit. NRIs were examined in 3 categories 'no malnutrition' (NRI >97.5), 'moderate malnutrition' (97.5 $\geq$NRI $\geq$83.5) or 'severe malnutrition' (NRI <83.5) in accordance with what was previously defined.[14]

Primary tumor location, number of metastases and sites, complete biochemistry including CA 19-9 and CEA levels and hemogram parameters were recorded as oncologic data. Complete biochemistry values were recorded after the first and second chemotherapy and toxicity was assessed by grading according to CTCAE 4.0.[15] In the event of grade 3 hematological toxicity, treatment was discontinued until either toxicity decreased to grade 2 or the blood count reached the lower limit of the laboratory and then the original dose of the drug was administered. In hematologic grade 4 and nonhematologic grade 3–4 toxicities, treatment was interrupted until ameliorated to grade 2 and

grade 1 respectively. Nutritional evaluation was carried out before treatment and after the completion of the second chemotherapy. Response to treatment was assessed together with recording all potentially chemotherapy-related adverse events after 2 months of the completion of first nutritional evaluation. Response assessment was evaluated based on Criteria in Solid Tumors (RECIST) 1.1 after two months of treatment.

Statistical analysis

SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL., USA) was used to calculate the data. Follow-up times were calculated by subtracting the date of the first chemotherapy from the date of death or last follow-up visit. The overall survival (OS) was defined as the time between the first treatment date and death or the last date the patient-patient relative was contacted. Quantitative datas were expressed with mean value, standard deviation, median value including minimum and maximum values. Qualitative analyzes were expressed as frequency and percentage. Pearson chi-square test was used to analyze the relationships and comparisons between clinical and laboratory variables. Fisher's exact test was used if Pearson chi-square test could not be performed. Kaplan-Meier method was used for the probability of survival function and the log-rank statistics was used in order to caculate the differences in OS. All statistical analyses

Table 1. Patients and laboratory characteristics & Mediastinal LAP, adnex, pancreas, spleen, adrenal gland.

Variables	n (%)
Age, years	
Median (range) years	62 (18–83)
MedianMedian	66 (48)/71 (52)
Gender	
Male/Female	54 (39)/83 (61)
WHO performance status	
0/1	47 (34)/90 (64)
Primary tumor	
Right colon/left colon	22 (16)/115 (84)
Colon /rectum	91 (66)/46 (37)
Primary tumor resection	
Yes/No	58 (42)/79 (58)
Metastasis site	
Liver/lung	105 (77)/42 (31)
Abdominal implant-lymphadenopathy/bone	40 (29)/13 (1)
Others &	24 (18)
Number of metastases	
Single/multiple site	66 (48)/77 (52)
Chemotherapy	
1 line	93 (68)
2 lines	31 (23)
lines	13 (10)
Chemotherapy protocol	
FP+oxaliplatin /FP+İrinotecan	75 (58)/34 (26)
FP+oxaliplatin+irinotecan	13 (10)
FP alone	14 (10)
Targeted therapy	
Anti- VEGF monoclonal antibody	84 (61)
Anti- EGFR monoclonal antibody	38 (28)
Response to chemotherapy*	
Yes/No	33 (24)/74 (54)
CEA (ng/mL)	
Median (range)	23.12 (0.20–7966.00)
<Median />Median	61 (45)/59 (43)
CA-19-9 (U/mL)	
Median (range)	50.41 (0.60–14835.00)
<Median />Median	63 (46)/61 (45)

FP = Fluoropyrimidine.

*Stable disease wasn't accepted responsive.

were two-sided; comparisons were made as p value less than 0.05 was considered statistically significant.

Results

One-hundred and thirty-seven mCRC patients were prospectively included in the study from 3 Turkish hospitals. Median age was 48 (range 18-83) and sixty-one percent of the patients were men. Primary location was colon in 66% of patients, 84% of their primary source was left colon and 42% had primary tumor resection. WHO PS was 0 in 34% of patients and 52% had at least two metastatic sites. Liver and lung were the most common sites of metastasis. There were 68% of patients receiving first-line chemotherapy. While 10% of the patients received fluoropyrimidine chemotherapy alone, 61% received anti-VEGFR treatment. According to recicst 1.1 4 patients had complete response, 29 had partial response, 21 had stabil disease and 53 had progressive disease. When the treatment response was accepted as partial response and complete response %24 of patients were found to respond to treatment. The characteristics of the patients are summarized in Table 1.

Malnutrition was detected in 39% of the cases, of which 38% were moderate and 0.9% severe. WL $>10\%$ was seen in %25 of the patients however BMI <18.5 was detected in only 0.4% of the patients. Additionally, 49% of the patients were overweight/obese according to the BMI. Patients with moderate/severe malnutrition values did not decrease significantly after the second chemotherapy ($p=0.72$). Nutritional values are descripted in Table 2.

When the relationship between sex, age, primary location of tumor, resected primary tumor, WHO PS, number of metastatic sites, CEA, CA 19-9 and moderate/severe malnutrition was evaluated four clinic parameters were found associated with moderate/severe malnutrition; multipl sites of metastases, WHO PS of 1, over the median value of CEA/CA 19-9 levels ($p=0.003$, $p=0.03$, $p<0.001$, and $p=0.02$; respectively). There was no significant relationship between chemotherapy response and moderate/severe malnutrition. ($p=0.24$).

Chemotherapy-related adverse events are listed in Tables 3 and 4. Hypoalbuminemia and moderate/severe malnutrition were associated with all types of toxicity ($p<0.001$ and $p<0.001$). Moderate/severe malnutrition was associated with thrombocytopenia, nausea/vomiting, and diarrhea following chemotherapy predominately, ($p=0.02$, $p=0.05$, and $p=0.04$; respectively). Worser moderate/severe malnutrition values were found related to $\geq$grade 2 hematologic/non-hematological chemotherapy toxicities. ($p<0.001$ and $p=0.05$). Furthermore all hematological/non-hematological toxicity, anemia and grade 1 elevation of transaminases was also more frequent in patients with hypoalbuminemia, ($p<0.001$, $p<0.001$, $p=0.04$, and $p=0.03$; respectively). Both thrombocytopenia and all $\geq$grade 2 non-hematological toxicity were also more frequent in patients with BMI <25, ($p=0.02$ and $p=0.01$). $>10\%$ WL was significantly associated with $\geq$grade 2 leukopenia following chemotherapy, ($p=0.02$).

Median follow-up period from the date of nutritional evaluation was 4 months [95% confidence interval (CI), 1–13]. Forty of 137 patients died during study period. Median overall survival was 9.4 months (95% CI, 8.5–10.2). In moderate/severe malnutrition group median overall survival was prominently shorter than those with no malnutrition [6.6 months (95%CI,

Table 2. Nutritional characteristics of patients.

Variables	n (%)
Weight loss (WL)	
Former body WL% median (range): 8.5 (1.3–27.7)	
>10% WL	34 (25)
<10% WL	55 (40)
Body mass index (BMI)	
Underweight (<18.5)	5 (0.4)
Normal weight (18.5–25)	60 (44)
Overweight (25–30)	36 (26)
Obesity (>30)	32 (23)
Albumin (g/L)	
Median (range): 37.5 (24–45)	
Nutritional status based on the NRI	
<83.5	12 (0.9)
83.5–97.5	52 (38)
>97.5	73 (53)

Table 3. Nutritional characteristics and chemotherapy-related hematologic toxicity (G1 vs $\geq$G2).

	Leucopenia	Anemia	Thrombocytopenia	All Toxicity
10% WL				
>10%	2/8	19/13	9/2	17/15
<10%	4/0	31/18	19/0	34/18
p	**0.02**	0.72	0.42	0.27
BMI				
<25	10/9	39/21	24/8	41/22
>25	12/5	44/19	15/0	41/24
p	0.36	0.57	**0.02**	0.81
Albumin				
<35	2/2	77/24	4/2	78/28
>35	21/12	10/16	35/2	8/18
p	0.69	**<0.001**	0.29	**<0.001**
NRI				
≤97.5	6/10	32/30	21/8	30/34
>97.5	17/4	55/10	18/0	56/11
p	0.36	0.57	**0.02**	**<0.001**

Thickened in $p \leq 0.05$.
Bold p values are significant ($p \leq 0.05$).

Table 4. Nutritional characteristics and chemotherapy-related non-hematologic toxicity (G1 vs ≥G2).

	Kreatin	Transam.	Nausea Vomiting	Mucosit	Diarrhea	Constipation	Neuropathy	All toxicity
10% WL								
>10%	6/4	10/4	1/5	0/6	0/0	2/0	5/5	16/18
<10%	1/0	24/3	4/3	1/6	3/9	2/0	11/3	26/18
p	0.73	0.38	0.23	0.73	NC	1.0	0.26	0.29
BMI								
<25	7/4	29/6	4/8	1/11	4/7	5/0	16/7	28/31
>25	3/0	21/1	5/1	1/4	2/2	3/0	11/2	36/15
p	0.37	0.16	0.10	0.72	0.75	1.0	0.47	**0.01**
Albumin								
<35	0/0	41/4	0/0	0/2	0/0	2/0	4/0	56/14
>35	10/4	10/3	10/9	6/7	10/9	6/0	23/9	8/33
p	NC	**0.03**	NC	0.84	0.38	1.0	0.39	**0.03**
NRI								
≤97.5	4/4	28/6	10/4	0/10	0/9	2/0	16/4	26/28
>97.5	6/0	23/1	0/5	2/6	0/3	6/0	11/5	38/6
p	0.14	0.12	**0.05**	0.41	**0.04**	1.0	0.58	**0.05**

Thickened in $p \leq 0.05$, NC= No istastistics are computed.
Bold p values are significant ($p \leq 0.05$).

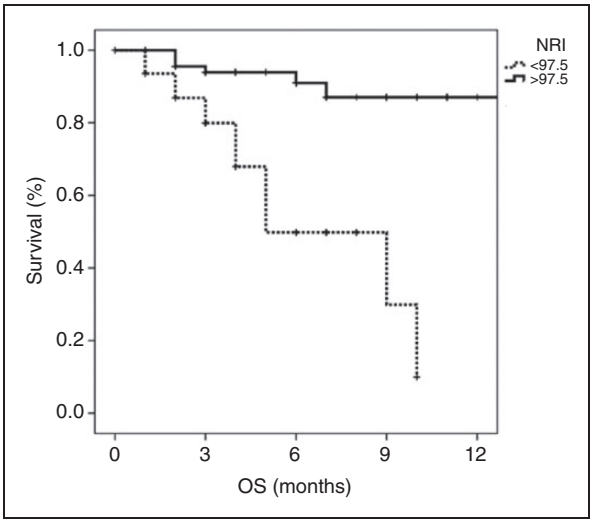

Figure 1. Overall survival and nutritional status in two patient groups (malnourished patients and non-malnourished patients) ($p < 0.001$).

5.6–7.6) vs 11.9 moths (95% CI, 11.1–12.7) respectively, $p < 0.001$] (Figure 1). Other clinicopathological parameters linked to overall survival are detailed in Table 5.

Discussion

Malnutrition is a serious problem in patients who receive anticancer therapy. Cancer-related malnutrition is multifactorial and reflects the balance between disease course and its treatment.[16–18]

In our study, hypoalbuminemia and moderate/severe malnutrition were associated with all types of toxicity and moderate/severe malnutrition was associated with thrombocytopenia, and diarrhea following chemotherapy predominately and median OS was prominently shorter in moderate/severe malnutrition group than those without malnutrition. Nutritional status might be very important to continue chemotherapy without severe adverse events. Therefore, maintaining patients well-nourished during chemotherapy might have a key role in the outcomes of treatment and it is crucial for survival benefit.

Four clinic parameters were found associated with moderate/severe malnutrition; multipl site of metastases, WHO PS of 1, over the median value of CEA and CA 19-9 levels. All these parameters are the predictors of survival, too.

Evaluation of the baseline nutritional status of patients with CRC should be a part of routine clinical practice because maintaining a well-nourished situation during CT might contribute to higher response to cancer and fewer adverse events for patients. A nutritional support should be one of the options for the patients in bad-nourished ones.[18,19]

Malnutrition and frailty were strongly associated with an increased mortality risk in patients who underwent palliative chemotherapy in older CRC patients receiving CT. Furthermore, a poor score on Mini Nutritional Assessment (MNA) was predictive for less tolerance of chemotherapy.[20] In our country; in

Table 5. Univariate analyses of overall survival.

Variables	Survival (months) Median (±SD)	p
Age, years	11.7 (0.4)/6.9 (0.5)	**<0.001**
Gender		
Male/Female	10.8 (0.7)/8.4 (0.5)	**0.05**
WHO performance status		
0/1	11.9 (0.5)/8.1 (0.5)	**0.002**
Primary tumor localization		
Colon/Rectum	9.5 (0.5)/8.1 (0.7)	**0.04**
Primary tumor localization		
Right colon/Left colon	8.8 (0.9)/9.3 (0.5)	0.31
Number of metastases		
Single/Multiple site	10.6 (0.6)/7.9 (0.6)	**0.03**
Response to chemotherapy*		
Yes /No	12.7 (0.3)/8.6 (0.5)	**<0.001**
CEA		
<Median/>Median	11.2 (0.4)/6.9 (0.6)	**<0.001**
CA-19-9		
<Median/>Median	10.5 (0.4)/7.1 (0.5)	**<0.001**
Albumin		
<35/>35	5.6 (0.6)/9.8 (0.5)	**0.004**
10% WL	8.4 (0.7)/9.0 (0.7)	0.83
>10%/<10%	8.4 (0.7)/9.0 (0.7)	0.83
BMI		
<25/>25	7.7 (0.5)/10.3 (0.6)	**0.04**
NRI		
>97.5/83.5–97.5/<83.5	11.9 (0.4)/6.4 (0.5)/5.3 (0.4)	**<0.001**
NRI		
≤97.5/>97.5	6.6 (0.5)/11.9 (0.4)	**<0.001**
NRI		
≤83.5/≥83.5	5.3 (0.4)/9.4 (0.5)	0.85

Thickened in $p \leq 0.05$.
Bold p values are significant ($p \leq 0.05$).
*Stable disease wasn't accepted responsive.

newly diagnosed cancer patients, 70% of the patients were found to be obese before the onset of CT and sarcopenia was present in only 15% of the CRC patients before CT. For obese/overweight patients the percentage of sarcopenia was found to be 8%.[21]

In the light of the literature; we can suggest that malnutrition is a prognostic tool for survival and it is also related with treatment toxicity.

Conclusion

Prospective documentation of the nutritional status of patients with GI cancer, especially for CRC patients, is essential for predicting toxicities and the survival of patients.

Author contributions

Conceptualization, SK and CUA; Methodology, CUA and SK; Software, MK and SK; Validation, FF; Formal Analysis, MK; Investigation, DT; Resources, ID; Data Curation, MK and FF; Writing—Original Draft Preparation, CUA; Writing—Review & Editing, CUA and SK; Visualization, FF; Supervision, DT; Project Administration, MK and ID; Funding Acquisition, SK.

Consent for publication

All authors consent the submission of the manuscript as it is.

Ethical approval and consent to participate

Ethical approval was taken before the study from Istanbul University Medical Faculty, Institute of Oncology's local ethical committee. Written informed consent was obtained from each participant.

Declaration of conflicting interests

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