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Impact of Nutrition Intervention on Body Weight, Outcomes and Toxicities in Patients with Metastatic Colorectal Cancer in 1st Line Treatment with Chemotherapy and Target Therapy

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Abstract: Colorectal cancer is the 2nd most common cancer in Europe. First line treatment in metastatic colorectal cancer (mCRC) is based on chemotherapy (ChT) combined with target therapy according to molecular analysis. Malnutrition is common in these patients. The aim of this study is to understand the role of nutrition intervention (NI) in body weight (BW), outcomes and toxicities in mCRC patients under first line metastatic treatment. This retrospective cohort study analyzed mCRC patients treated with ChT in combination with panitumumab (ChT-Pan) or bevacizumab (ChT-Bev), at two hospital units in Portugal, between January 2015 and December 2018. A total of 178 patients were evaluated, 65 were treated with ChT-Pan and 113 with ChT-Bev. Unresectable mCRC patients with higher BMI experienced increased survival (p=0.01). Lower BMI was associated with severe toxicities (p=0.024; OR 1.08; CI95% [1.01-1.17]). Mean Δ BW was negative, with a mean loss of 3.68 kg (SD ± 4.10) and 2.61 kg (SD ± 4.10) in ChT-Pan and ChT-Bev groups, respectively. BW loss did not influence OS in unresectable mCRC, although in ChT-Pan group an association with severe cutaneous toxicity (p=0.01) and in ChT-Bev group an association with severe toxicities (p= 0.011; OR 0.92; CI 95% [0.86-0.98]) and DLT (p=0.06; OR 0.91; CI 95% [0.85-0.97]) was present. NI was associated with reduction of BW loss (p=0.021), although no association with outcomes was observed. NI appears to be associated with reduced severe cutaneous toxicities (p=0.033) and DLT (p=0.022) in ChT-Pan group and severe toxicities (p=0.005) in unresectable mCRC treated with ChT-Bev. Patients with lower BMI appear to have reduced OS and increased severe toxicities. NI does not seem to increase survival as a unimodal approach in unresectable mCRC, however it is an effective strategy reducing BW loss and possibly decreasing treatment severe toxicities, although this data should be prospectively confirmed in a randomized clinical trial.

Keywords: malnutrition; body weight; body mass index; nutrition intervention; metastatic colorectal cancer; chemotherapy toxicities; dose limiting toxicities

1. Introduction

Colorectal cancer is the second most diagnosed cancer in Europe with 499.000 new cases in 2018 and the second with highest mortality with 242.000 deaths[1]. In the last two decades the incidence

has been increasing, meanwhile patients with metastatic colorectal cancer (mCRC) experienced some improvement in survival outcomes, with the introduction of multidisciplinary cancer treatment committees, as well as development of local treatment directed to oligometastatic disease and new systemic target therapies[2].

Some degree of malnutrition in present in mCRC patients and it is defined as a state resulting from the lack of intake or uptake of nutrients that lead to altered body composition and body cell mass. It can result from starvation, disease or aging. In disease malnutrition, in this case, cancer malnutrition (CM), there is a chronic inflammatory state, which may lead to anorexia, cachexia and sarcopenia[3,4,5]. Cancer treatment complications, such as loss of appetite and gastrointestinal toxicity may also contribute to reduced caloric intake. Depletion of muscle and fat mass is usually present, causing a decrease in functional performance and quality of life and an increase in mortality, chemotherapy toxicity, hospital admissions and costs to public health system[6,7,8,9]. CM prevalence ranges from 25% to over 70% based on nutritional assessments, and besides its serious negative consequences it is still taken too lightly by medical oncology units. According to literature only 1/3 of patients at risk of malnutrition receives nutrition support.[10,11] Nutrition intervention (NI) strategies are ineffective in states of refractory cachexia, however this approach may be efficient in early phases of the disease. Patients may experience some degree of dysgeusia and loss of appetite which may contribute to body weight (BW) loss and an individualized nutrition intervention could optimize their caloric input and improve their quality of life, therefore it is imperative to stratify patients according to their nutritional risk[6,12,13]. While the negative impact of malnutrition, cachexia and sarcopenia is striking, the effect of nutrition in patient´s overall prognosis is weak or inconsistent. Several studies attempted to understand if individualized nutrition have impact on BW, outcomes and toxicities in cancer, although many studies include different cancer pathologies, different stages and different treatment approaches. This heterogeneity in the data produces conflicting results and impairs the production of significant systematic revisions and metanalysis[13,14,15]. The aim of the study is to understand if NI referral has influence in BW changes, outcomes and toxicities in patients with metastatic colorectal cancer (mCRC) under first line treatment with chemotherapy (ChT) associated with target therapy.

2. Materials and Methods

Retrospective analysis of data collected in medical records of 178 patients with histologically confirmed colorectal cancer adenocarcinoma, stage IV, that underwent first line metastatic ChT associated with target therapy (epidermal growth factor receptor inhibitor [EGFRi] panitumumab or vascular endothelial growth factor inhibitor [VEGFi] bevacizumab). Patients were identified from regional oncological registry (ROR), at two hospital units in Centro Hospitalar Universitário do Algarve (CHUA), in Portugal, between January 2015 and December 2018. Information was gathered on a wide range of variables including demographic (age, sex, comorbidities, performance status), tumor related (colon or rectal cancer, side, RAS mutational status, metastasis location), treatment related (treatment protocol, metastasectomy, nutrition intervention support), anthropometric measurements (weight and height), toxicities (graded according to common terminology criteria for adverse events – CTCEA v5.0) and outcomes (date of the prescription of treatment and date of disease progression in tomography scan).

Statistical Analysis:

For the purpose of this analysis, continuous variables are presented as mean and standard deviation and categorical variables as percentages. The assumption of normality was verified with the Kolmogorov-Smirnov test. Association between two categorical variables was assessed with chi square or Fisher´s exact test. Association between a categorical variable and a quantitative variable was assessed with Student's T-test or Mann–Whitney U-test, as appropriate. ANOVA F-test was performed to determine the variability between groups of initial BMI according to outcomes. Survival analysis were performed with the Kaplan-Meier method using the log-rank test. Statistical

significance was set at a *P* value <0.05. Missing data was treated using listwise deletion method. All data were analyzed using IBM SPSS Statistics v25.

3. Results

3.1. Basal Characteristics

A total of 178 patients were analyzed, 65 underwent treatment with ChT plus panitumumab (ChT-Pan) and 113 with ChT plus bevacizumab (ChT-Bev). 117 were male (65.7%) and the mean age was 62 years old (SD ± 10.57). 112 (62.9%) presented ECOG performance status of 0. 51 (28.7%) patients had rectal cancer and 127 (71.3%) colon cancer, more commonly affecting the left side (53,5%). Ras mutation was present in 55.8% of patients that had ChT-Bev. The most common site of metastasis was the liver (77.5%). Metastasectomy was performed in 21 patients (11.8%). Basal characteristics of the population can be seen in greater detail in *table 1*.

Table 1. Basal characteristics.

Variable	ChT + Panitumumab N=65	ChT + Bevacizumab N=113	Total N=178	p-value
Age	64.22 ± 11.71	61.25 ± 9.75	62.33 ± 10.57	NS - p=0.071
Gender				
Male	42 – 56.9%	75 – 66.4%	117 - 65.7%	NS - p=0.813
Female	23 – 35.4%	38 – 33.6%	61 - 34.3%	
ECOG PS				
0	37 – 56.9%	75 - 66.4%	112 – 62.9%	NS - p=0.392
1	17 – 26.2%	24 – 21.2%	41 -23.0%	
≥2	11 – 16.9%	14 -12.4%	25 – 14.1%	
Smoker				NS - p=0.984
0	53 – 81.5%	92 – 81.4%	145 – 81.5%	
1	12 – 18.5%	21 – 18.6%	33 – 18.5%	
Diabetes mellitus				
0	57 – 87.7%	99 – 87.6%	156 – 87.6%	NS - p=0.987
1	8 – 12.3%	14 – 12.4%	22 – 12.4%	
Histology				NS - p=0.366
Colon cancer	49 – 74.4%	78 – 66.4%	127 – 71.3%	
Rectal cancer	16 – 24.6%	38 – 33.6%	51 – 28.7%	
Laterality				
Left colon	28 – 57.1%	40 – 51.3%	68 – 53.5%	NS - p=0.587
Right colon	21 - 42.9%	38 – 48.7%	59 – 46.5%	
Ras mutation				
Ras *wild-type*	65 -100%	38 – 33.6%	103– 57.9%	*p <0.001
Ras mutated	0 – 0%	63 – 55.8%	63 – 35.4%	
Unknown	0 - 0%	12 – 10.6%	12– 6.7%	
Nº Metastasis sites				
1	43 – 66.2%	69 – 61.1%	112 – 62.9%	NS - p=0.498
≥1	22 – 33.8%	44 – 38.9%	66 – 37.1%	
Metastasis				NS
Liver	46 - 70.8%	92 -81.4%	138 -77.5%	p=0.101
Lung	21 – 32.3%	30 – 26.5%	51 – 28.7%	p=0.413
Peritoneum	12 – 18.5%	23 – 20.4%	35 -19.7%	p=0.760
Treatment				
F + O + TT	30 – 46.2%	67 – 59.3%	97 – 54.5%	
F + I + TT	33 – 50.8%	34 - 30.1%	67 – 37.6%	NS - p=0.853
F + TT	2 – 3.1%	8 – 7.1%	10 – 5.6%	
F + O + I + TT	0 – 0%	4 -3.5%	4 – 2.2%	
Metastasectomy				
0	58 – 89.2%	99 – 87.6%	157 – 88.2%	NS - p=0.747
1	7 – 10.8%	14 – 12.4%	21 – 11.8%	
Nutrition Intervention				
0	54 – 83.1%	92 -81.4%	146 – 82%	NS - p=0.783
1	11 – 16.9%	21 – 18.6%	32 -18.0%	

F – Fluoropyrimidine; O – Oxaliplatin; I – Irinotecan; TT – Target therapy.

3.2. Outcomes and Toxicities

The outcomes varied in both treatment groups. In ChT-Pan group the overall response rate (ORR) was 64.6%, progression free survival (PFS) was 13 months and overall survival (OS) 21 months. In the ChT-Bev group the ORR was 59.3%, PFS 10 months and OS 19 months (*figure 1*).

Any grade toxicities in ChT-Pan treatment group were present in 58 (89,2%) patients, mainly cutaneous. Severe toxicities, described as grade 3 and 4 according to CTCEA v 5.0, were present in 26 (40%), mainly cutaneous in 14 (21.5%), hematological in 7 (10.8%), gastrointestinal in 4 (6.2%) and peripheral neuropathy in 3 (4.6%). Any grade toxicities in ChT-Bev treatment group were present in 87 patients (77%) and severe toxicities in 57 (50.4%), mainly hematological 27 (23.9%), gastrointestinal 15 (13,2%) and peripheral neuropathy 6 (5.3%). The incidence of higher severe hematological and gastrointestinal toxicities in ChT-Bev group compared to ChT-Pan group may be, in part, explained by the use of a triplet chemotherapy protocol in 4 patients. Dose limiting toxicities (DLT) characterized by severe toxicities, delay in treatment, dose reduction and treatment discontinuation, were present in 43 patients (66.2%) of ChT-Pan group and in 66 (58.4%) in ChT-Bev. Two toxic deaths were observed in ChT-Bev group due to febrile neutropenia and none in ChT-Bev treatment group.

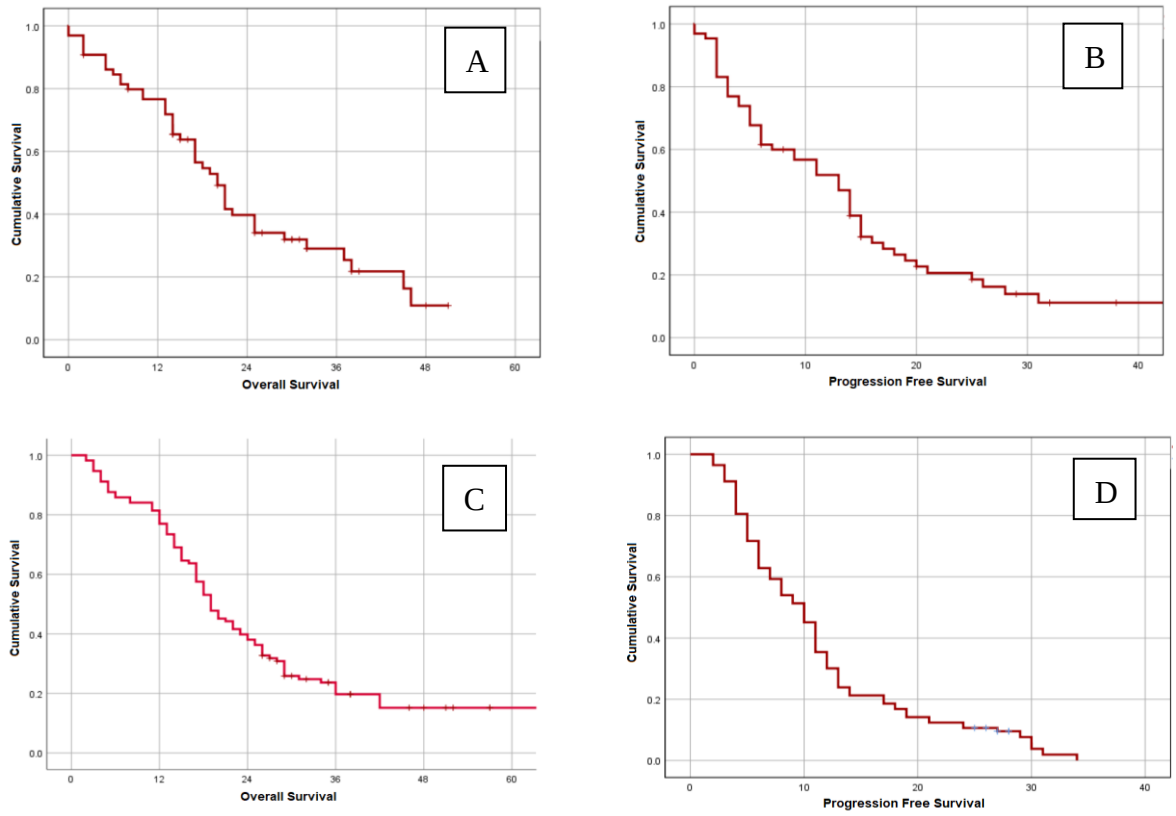

Figure 1. Outcomes.
A) OS of 21 months with Ch+ Panitumumab; B) PFS of 13 months with ChT + Panitumumab; C) OS of 19 months with ChT + Bevacizumab; D) PFS of 10 months with ChT + Bevacizumab.

3.3. Initial Body Weight and Δ in Body Weight along Treatment and It´s Association with Outcomes and Toxicities

Mean body weight (BW) at start of treatment was 71.12 kg (SD ± 15.9). BW variation (Δ BW) was described as the change in weight from treatment initiation to disease progression and was negative in both treatment groups. A mean loss of 3.68 kg (SD ± 4.10) was observed in patients who were treated with ChT-Pan and a mean loss of 2.61 kg (SD ± 4.10) when treated with ChT-Bev. BW differences in each group can be assessed in more detail in *Table 2*. When stratifying the initial body

mass index (BMI) in underweight (<18.5 kg/m²), normal weight (18.5 - 24.9 kg/m²), overweight (25 – 29.9 kg/m²) and obesity (>30 kg/m²) we can observe that obese patients with unresectable mCRC have higher OS and underweight patients appear to have lower OS (p=0.01) (*figure 2)*. Initial BMI seems to be associated with severe toxicities (p=0.024; OR 1.08; CI 95% [1.01-1.17]).

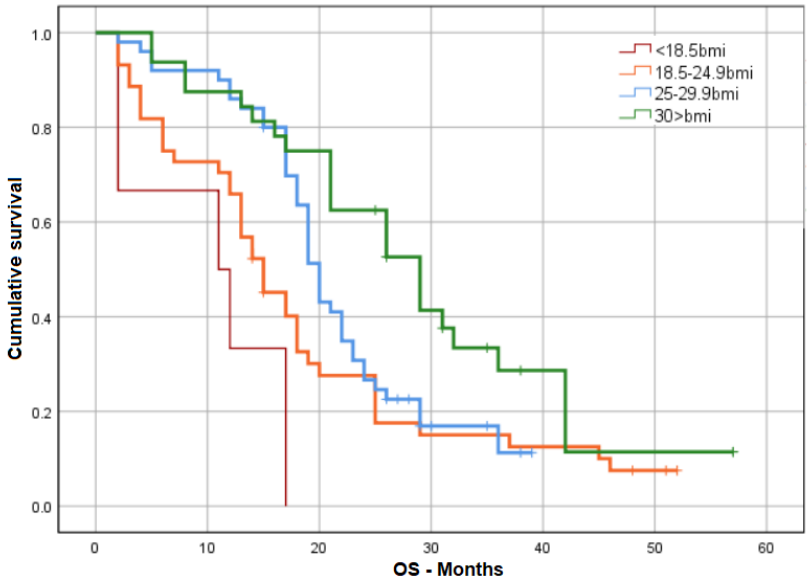

Figure 2. Initial BMI is associated with overall survival in patients with unresectable mCRC.

This study showed that 40.9% of patients in both treatment groups lost > 5% of BW during first line treatment. 16 patients (11.7%) presented an increase > 5% in BW and this appeared to be associated with increase OS (p=0.001), although a relevant number of patients in this subgroup had metastasectomy which influenced this result. Analyzing only patients with unresectable mCRC, Δ BW did not influence OS, however it seems to have some relation to severe toxicities. In ChT-Pan an association between BW loss and DLT and severe toxicities did not achieve statistical significance, although an association with increased severe cutaneous toxicities was found (p=0.01). In ChT-Bev treatment group an association between weight loss and severe toxicities (p= 0.011; OR 0.92; CI 95% [0.86-0.98]) and DLT (p=0.06; OR 0.91; CI 95% [0.85-0.97]) was observed.

Table 2. Body Weight changes.

Variable	ChT + Panitumumab N=65	ChT + Bevacizumab N=113	Total N=178	p-value
Initial BW (kg)	69.18 ± 14.02	72.22 ± 16.64	71.12 ± 15.9	NS P=0.230
Δ BW (kg)	-3.68 ± 4.10	-2.61 ± 7.27	-	-
Δ BW percentile				
Loss >5% BW	18 – 43.9%	38 – 39.6%	56 – 40.9%	
Normal range	20 – 48.8%	45 – 46.9%	65 – 47.4%	
Gain >5% BW	3 -7.3%	13 – 13.5%	16 – 11.7%	
Initial BMI (kg/m²)	24.94 ± 4.38	26.01 ± 4.82	25.71 ± 4.71	NS P=0.216
Δ BMI (kg/m²)	-1.36 ± 1.65	-0.94 ± 2.70	-	-

Body weight changes. Patients in both groups lose weight.

3.4. Impact of Nutrition Intervention on BW, Outcomes and Toxicities

A total of 32 patients (18%) received individualized nutrition intervention (NI). Referral to nutritional support team was performed based on physician´s clinical judgment and no malnutrition screening tool was used according to registry data. 11 patients (16.9%) in ChT-Pan group received NI. NI was associated with reduced BW loss (p=0.021), although no association with survival outcomes was found. Despite not achieving statistical significance in severe toxicities (p=0.078), NI appears to be associated with reduced severe cutaneous toxicities (p=0.033) and DLT (p=0.022). 21 patients (18.6%) in ChT-Bev treatment group received NI. Referral in this group was offered mainly to candidates to metastasectomy, which could explain the association with outcomes such as PFS (p=0.04). Analyzing only unresectable mCRC patients under ChT-Bev, NI did not influence OS nor PFS, however an association with reduction in BW loss (p=0.027) as well as a reduction of severe toxicities (p=0.005) was observed. A detailed analysis of NI impact can be seen in *Table 3*.

Table 3. Nutrition intervention on weight, outcomes and toxicities.

Group	Metastasectomy	OS	PFS	Initial BW	Initial BMI	Δ BW	Δ BMI	Toxicity	Severe Toxicity		DLT
ChT+Pan N=11	P=0.392	P=0.824	P=0.437	P=0.768	P=0.338	**P=0.021**	**P=0.011**	P=0.392	Toxicity G3-4 P=0.078	Rash G3-4 **P=0.033**	**P=0.022**
ChT+Bev N=21	**P <0.01**	P=0.080	**P=0.04**	**P=0.01**	**P=0.09**	**P=0.01**	**P=0.01**	P=0.932	**P=0.027**		P=0.110
	Unresectable	P=0.972	P=0.179	P=0.080	P=0.358	**P=0.027**	**P=0.049**	P=0.539	**P=0.005**		P=0.062

Impact of NI on BW, outcomes and toxicities.

4. Discussion

According to USA *National Cancer Institute,* the goal in patients with advanced cancer should be to give the best quality of life and control symptoms that cause distress. Based on *ESPEN guidelines on nutrition in cancer patients*, nutrition and metabolic interventions aim to maintain or improve food intake and mitigate metabolic derangements, maintain skeletal muscle mass and physical performance, reduce the risk of reductions or interruptions of scheduled anticancer treatments and improve quality of life[6]. NI represents an important strategy in selected patients with mCRC.

In this retrospective cohort, patients with mCRC lost weight along 1st line ChT in combination with target therapy, which goes in accordance with other studies[16, 17]. Initial BMI is associated with OS in unresectable mCRC, especially overweight and obese patients appear to have increased survival. Similar results are reported in the literature[18,19]. Initial BMI appears to be associated with severe toxicities, although association with DLT did not present statistical significance in this study. There is contradiction in studies concerning initial BMI as a predictor for toxicities. In a study using 730 mCRC patients from phase III *CAIRO* trial, the median number of treatment cycles increased with increasing BMI, although it was not statistically significant (p=0.392)[20]. On a pool analysis of 3155 mCRC patients from 5 clinical trials, lower BMI was associated with higher probability of G3-4 anemia (p=0.03) and G3-4 neutropenia (p<0.001)[21].

Reduction of BW during treatment did not influence OS in this analysis. Patients that lost weight during treatment with ChT-Bev suffered from more severe toxicities and DLT. Patients who lost weight during treatment with ChT-Pan endured more cutaneous severe toxicities, yet no statistical significance was achieved on all severe toxicities nor DLT. According to a study using data from phase III *CAIRO 3* trial, in 182 patients treated with capecitabine in combination with bevacizumab initial BMI and Δ BMI were unrelated to severe toxicities and DLT, although in 232

patients treated with capecitabine, oxaliplatin and bevacizumab, Δ BMI was associated to severe toxicities (OR 1.08 [1.10-1.16]) but not DLT. Interesting fact in this study is that sarcopenia and loss of skeletal muscle mass >2%, detected by tomography scan, were associated with increased DLT, however BMI could not detect sarcopenia nor SMI loss, which raises the question if body composition evaluation should be introduced as standard clinical practice, as its prognostic and predictive value for toxicities seems to be superior to anthropometric measurements[17].

Nutrition intervention seems to be able to decrease BW loss in this study. Reduction of BW loss due to oral NI seems to be consistent across studies. A meta-analysis showed benefit of NI in patients under cancer treatment, especially when supplemented with high protein and n-3 polyunsaturated fatty acids[13]. In a randomized study with 95 colon cancer patients, NI with oral supplements slightly increased mean BMI in comparison with control group who lost weight. This intervention also increased *visual analog scale for appetite* and *subjective global assessment* scores[16].

NI does not seem to influence outcomes as a unimodal approach in unresectable mCRC[13,15]. Information regarding impact of NI on toxicities is scarce. In this study NI appears to reduce severe cutaneous toxicity and DLT in ChT-Pan treatment group and reduce severe toxicities but not DLT in ChT-Bev group. A systematic review does not support this findings[13]. In a randomized study with 90 mCRC comparing the efficacy of NI to *ad libitum*, no significant difference was observed on hematological toxicities nor vomiting or diarrhea, although a decreased in grade 2-3 mucositis was demonstrated (38% vs 62%)[22]. Several studies appear to associate NI with oral supplementation of n-3 polyunsaturated fatty acids to increase in lean body mass, decrease in fatigue and reduction of peripheric neuropathy secondary to platins [23,24].

As a retrospective study some limitations are present as it relies on data not primarily meant for research. Missing data was observed and was treated accordingly. Patient referral to NI was based on physician´s clinical judgement, without the support of any screening tool. The detailed NI strategy was not described. The number of patients that received NI was small and this data should be interpreted with caution.

Investigation involving NI in cancer care is changing to a multimodal approach in combination with physical exercise, supplementation and pharmacological therapies. Medical oncologists should be aware of malnutrition screening, as early identification of patients with malnutrition or in risk of malnutrition benefit from referral to nutritional support team. Body composition detected by computer tomography scan appears to be more relevant for prognosis and prediction of toxicities than anthropometric measurements in cancer patients, it´s use in clinical practice should be incentivized. Detailed guidelines for NI and multimodal approaches studies should be developed, according to cancer type and treatment strategy, to achieve reliable results and allow production of systematic reviews and meta-analysis with reduced heterogeneity.

5. Conclusion

Patients with low BMI appear to have reduced overall survival and increased severe toxicities. NI is an effective strategy to prevent body weight loss, although it does not seem to increase survival as a unimodal approach in unresectable mCRC. NI appears to reduce treatment severe toxicities, although this data should be prospectively confirmed in a randomized clinical trial.

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