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ORIGINAL ARTICLE

Phase angle, body mass index and KRAS status of metastatic colorectal cancer in response to chemotherapy with and without target therapy: clinical impact and survival

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Summary

Purpose: *KRAS mutations are associated with colorectal cancer survival whereas the role of body mass index (BMI) is less defined. Phase angle, which is more an indicator of cell integrity also has not been studied as prognostic and predictive factor. We evaluated the association between BMI, phase angle and colorectal cancer overall survival (OS), by KRAS mutation status and other prognostic for metastatic colorectal cancer.*

Methods: *This prospective study included 89 patients diagnosed with metastatic colorectal cancer in oncology and pathology departments. BMI and phase angle alpha were reported from the TANITA MC-780U mutifrequency segmental body composition analyzer at presentation at our department. KRAS mutation status was analyzed. Multivariate analysis was estimated from Cox proportional hazards models.*

Results: *High phase angle which indicated proper cell integrity was associated with good performance status, low T stage, low fat percent and high BMI. Overall response was statistically significant with left sided colon cancer and high BMI. On multivariate analysis, the factors maintaining statistical significance with OS were KRAS and overall response. High BMI was associated with higher OS in both mutated and wild groups without statistical significance. As regard progression-free survival (PFS), surgery, T stage, and lymphovascular invasion maintained statistical significance on multivariate analysis.*

Conclusion: *High phase angle was associated with improved performance status. High BMI was associated with improved OS in all KRAS subgroups.*

Key words: *phase angle, BIA, BMI, metastatic, colorectal cancer, KRAS*

Introduction

The third cause of cancer worldwide is colorectal cancer (CRC) [1]. The danger of colon malignancy increases up to 33% in subjects with high BMI in contrast to average as provided by many metanalysis data [2,3]. Obesity is a worldwide medical issue that has expanded in all age groups, and is defined risk factor for carcinogenesis [4,5].

One of the major risk factors for morbidity and mortality of advanced CRC is malnutrition [6,7].

Bioelectrical impedance is used for assessment of body composition as noninvasive, easily reproducible method in assessing the body composition. Phase angle reflects the changes of cellular membrane and integrity of cell. Lower phase angle means

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cell death and it has been studied in many diseases such as liver cirrhosis, diabetes and lung cancer [8,9].

A large meta-analysis in 2015 of 6128 metastatic CRC patients treated with bevacizumab and chemotherapy as first line showed that a lower median OS was reported in patients with low BMI (<25 kg/m2) [6]. Also high BMI was reported to be associated with better OS in CAIRO 1 but not in CAIRO 2 trial [7].

About 13-37% of CRC express oncogenic transformations of RAS and BRAF respectively, which initiate the MAPK flagging pathway [10]. In Brändstedt et al study KRAS mutation was associated with high BMI and high waist hip ratio [11] and with lower OS as reported by many authors [12,13].

The aim of the present study was to evaluate the phase angle, BMI, KRAS family and various prognostic factors with response, OS, and PFS.

Methods

This prospective study was conducted in Clinical Oncology and Anatomical Pathology departments, Tanta University hospitals, from January 2011 to December 2018. Eighty nine histologically confirmed stage IV CRC patients, either operated with metastases discovered immediately after operation or not operated due to metastases were included in this study. Written informed consent was taken from all patients.

Bioelectric impedance analyzer (BIA) was performed in our nutritional clinics at baseline and thereafter every month using a TANITA MC-780U multifrequency segmental body composition analyzer. BIA was conducted while the patients were standing by using the tetra polar electrode on the hands and feet. From BIA we get the phase angle which is more informative than BMI in the evaluation of cell health status [13,14]. The median phase angle was calculated. Phase angle more than or equal to 4.1 meant the integrity of cell membrane.

Table 1. Correlation of different patient clinicopathologic characteristics with phase angle

	Phase angle < 4.1 *n (%)*	*Phase angle >4.1* *n (%)*	*p value*
Sex			0.245
Female	19 (42.2)	24 (54.5)	
Male	26 (57.8)	20 (45.5)	
Age, years			0.530
<40	6 (13.3)	8 (18.2)	
≥40	39 (86.7)	36 (81.8)	
Performance status			0.000
0	10 (22.2)	24 (54.5)	
1	20 (44.4)	20 (45.5)	
2	15 (33.3)	0 (0)	
Weight, kg			0.000
<59	43 (95.6)	7 (15.9)	
≥59	2 (4.4)	37 (84.1)	
BMI			0.000
<25	44 (97.8)	0 (0)	
≥25	1 (2.2)	44 (100)	
Fat			0.002
<25	15 (33.3)	29 (65.9)	
≥25	30 (66.7)	15 (34.1)	0.046
Muscle, kg			
<31.5	1 (2.2)	6 (13.6)	
≥31.5	44 (97.8)	38 (86.4)	
Tumor markers			0.078
Normal CEA& CA19.9	21 (46.7)	17 (38.6)	
High CEA and normal CA19.9	4 (8.9)	7 (15.9)	
Normal CEA and high CA19.9	10 (22.2)	3 (6.8)	
High both	10 (22.2)	17 (38.6)	
Surgery			0.534
Yes	30 (66.7)	32 (72.7)	
No	15 (33.3)	12 (27.3)	

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	Phase angle < 4.1 *n (%)*	*Phase angle >4.1* *n (%)*	*p value*
Pathology			0.134
	25 (55.6)	32 (72.7)	
Signet ring adenocarcinoma	13 (25.9)	10 (27.7)	
Mucoid adenocarcinoma	7 (15.6)	2 (4.5)	
Grade			0.030
1	3 (6.7)	0 (0)	
2	17 (37.8)	29 (65.9)	
3	16 (35.6)	11 (25)	
4	9 (20)	4 (9.1)	
Gross appearance			0.823
Cauliflower	17 (37.8)	14 (31.8)	
Napkin ring	11 (24.4)	11 (25)	
Ulcerating	17 (37.8)	19 (43.2)	
Site			0.389
Rectum	17 (37.8)	17 (37.8)	
Right side colon	11 (24.4)	10 (22.7)	
Transverse colon	12 (26.7)	7 (15.9)	
Left side colon	5 (11.1)	10 (22.7)	
T stage			0.004
T2	0 (0)	10 (22.7)	
T3	25 (59.5)	22 (50)	
T4	17 (40.5)	12 (27.3)	
N stage			0.836
NX	17 (40.5)	18 (40.9)	
N0	11 (26.2)	11 (25)	
N1	6 (14.3)	4 (9.1)	
N2	8 (19)	11 (25)	
LVI			0.128
Yes	19 (42.2)	21 (47.7)	
No	4 (8.9)	0 (0)	
Unknown	22 (48.9)	23 (52.3)	
PNI			0.865
Yes	6 (15.6)	7 (15.9)	
No	8 (17.8)	6 (13.6)	
Unknown	30 (66.7)	31 (70.5)	
Surgery (at presentation)			0.348
Yes	30 (66.7)	32 (72.7)	
No	15 (33.3)	12 (27.3)	
KRAS			0.463
Mutated	28 (62.2)	24 (54.5)	
Wild	17 (37.8)	20 (45.5)	
Chemotherapy			0.551
FOLFOX	27 (60)	30 (68.2)	
XELOX	12 (27.7)	11 (25)	
FOLFIRI	6 (13..3)	3 (6.8)	
Type of target therapy			0.438
No	13 (26.7)	11 (25)	
Bevazuicmab	7 (15.6)	11 (2)	
Pantimumab	12 (26.7)	14 (31.8)	
Cetixumab	14 (31.1)	8 (18.2)	

Height and weight were measured without shoes. BMI is calculated from weight in kg over height squared in meter [15-17].

Tumor tissue analysis

In the Department of Clinical Pathology, Tanta University Hospital, QiagenQIAamp DNA FFPE Tissue Kit was used for DNA extraction. DNA amplification was performed by PCR using specific primers, kits (Viennalab). KRAS was analyzed by sequencing the activating mutations in codon 12 and 13. Twenty nine mutations in KRAS (CD12, CD13, CD59, CD0, CD117, CD146) and 22 mutations in N-Ras (CD12, CD13, CD59, CD60, CD61, CD146) were assessed.

KRAS expression by immunohistochemistry

Immunohistochemistry for KRAS [18] was performed on formalin-fixed, paraffin embedded 4 μm thick tumor tissue sections. The sections were stained according to manufacturer's protocol. The primary antibody used was KRAS mouse monoclonal (Clone-F234, Santa Cruz Biotechnology dilution: 1:10). Prior to application of the primary antibody, antigen retrieval was performed for 20 min in a pressure cooker. All sections were scored in a blinded fashion by two independent observers familiar with immunohistopathology, unaware of the clinical outcome of the patient. A semiquantitative score ranging from negative (no staining or, 10% of cells stained) to 3+ (1+ staining in 11-30% of the cells: weak, 2+ staining in 31-50% of cells: moderate, and 3+ staining in >50% of cells: intense) was used.

Treatment received

Patients were administered modified FOLFOX 6, XELOX, or FOLFIRI. In case of target therapy given it was given in combination of chemotherapy in the form of bevacizumab, cetuximab or panitumumab.

Modified FOLFOX consisted of oxaliplatin 85 mgm/m2 iv over 2 h on days 1 and 15, leucovorin 400 mg/m2 over 2 h on days 1 and 15, and fluorouracil 400 mg/m2 iv

Table 2. Correlation of clinicopathologic factors with body mass index

Clinicopathologic factors	*BMI<25 n (%)*	*BM≥25 n (%)*	*p value*
Sex			0.338
Female	19 (43.2)	24 (53.3)	
Male	25 (56.8)	21 (46.7)	
Age, years			0.592
<40	6 (13.6)	8 (17.8)	
>40	38 (86.4)	37 (82.2)	
Performance status			0.000
0	9 (20.5)	25 (55.6)	
1	20 (45.5)	20 (44.4)	
2	15 (34.1)	0 (0)	
Weight, kg			0.000
<59	43 (97.7)	7 (15.6)	
≥59	1 (2.3)	38 (84.4)	
Angle alpha			0.000
<4.1	44 (97.8)	0 (0)	
≥4.1	1 (2.2)	44 (100)	
Fat			0.002
<25	14 (31.8)	30 (66.7)	
≥25	30 (68.2)	15 (33.3)	
Muscle , kg			0.053
<31.5	1 (2.2)	6 (13.6)	
≥31.5	44 (97.8)	38 (86.4)	
Tumor markers			0.081
Normal CEA& CA19.9	21 (47.7)	17 (37.8)	
High CEA and normal CA19.9	5 (11.4)	7 (15.6)	
Normal CEA and high CA19.9	9 (20.5)	3 (6.7)	
High both	9 (20.5)	18 (40)	
Surgery			0.534
Yes	30 (68.2)	32 (71.1)	
No	14 (31.8)	12 (28.9)	

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Clinicopathologic factors	*BMI<25* *n (%)*	*BM≥25* *n (%)*	*p value*
Pathology			0.326
	25 (56.8)	32 (71.7)	
Signet ring adenocarcinoma	13 (29.5)	10 (22.2)	
Mucoid adenocarcinoma	6 (13.6)	3 (6.7)	
Grade			0.018
1	3 (6.8)	0 (0)	
2	16 (36.4)	30 (66.7)	
3	16 (36.4)	11 (24.4)	
4	9 (20.5)	4 (14.6)	
Gross appearance			0.696
Cauliflower	17 (38.6)	14 (31.1)	
Napkin ring	11 (25)	11 (24.4)	
Ulcerating	18 (36.4)	20 (44.4)	
Site			0.389
Rectum	17 (37.8)	17 (37.8)	
Right side colon	10 (22.7)	11 (24.4)	
Transverse colon	12 (27.3)	7 (15.6)	
Left side colon	5 (11.4)	10 (22.2)	
T stage			0.006
T2	0 (0)	10 (22.2)	
T3	25 (61)	22 (48.9)	
T4	16 (39)	13 (28.9)	
N stage			0.836
NX	16 (39)	19 (42.2)	
N0	11 (26.8)	11 (24.4)	
N1	6 (14.6)	4 (8.9)	
N2	8 (19.5)	11 (24.4)	
LVI			0.117
Yes	19 (43.2)	21 (47.7)	
No	4 (9.1)	0 (0)	
Unknown	21 (47.7)	23 (52.3)	
PNI			0.810
Yes	7 (15.9)	7 (15.6)	
No	8 (18.2)	6 (13.3)	
Unknown	29 (65.9)	32 (68.5)	
KRAS			0.578
Mutated	27 (61.4)	25 (55.6)	
Wild	17 (38.6)	20 (44.4)	
Tumor marker (post treatment)			0.002
Normalized	16 (36.4)	31 (68.9)	
Elevated	28 (63.6	14 (31.1)	
Chemotherapy			0.479
FOLFOX	26 (59.1)	31 (68.9)	
XELOX	12 (27.3)	11 (24.4)	
FOLFIRI	6 (13..6)	3 (6.7)	
Type of target therapy			0.366
No	12 (27.3)	11 (24.4)	
Bevazuicmab	7 (15.9)	11 (24.4)	
Pantimumab	11 (25)	15 (33.3)	
Cetixumab	14 (31.8)	8 (17.8)	

bolus on days 1 and 15, followed by 5 fluorouracil 2,400 mg/m2 continuous infusion over 46 h on days 1-3 and 15-17.

FOLFIRI consisted of irinotecan 180 mg/m2 iv over 2 h on days 1 and 15, leucovorin 400 mg/m2 iv over 2 h on days 1 and 15, and fluorouracil 400 mg/m2 iv bolus on days 1 and 15, followed by fluorouracil 2,400 mg/m2 continuous infusion over 46 h on days 1-3 and 15-17.

Bevacizumab 5 mg/kg iv was administered over 30-90 min on day 1,14 with either FOLFOX or FOLFIRI.

XELOX with or without bevacizumab: Oxaliplatin 130 mg/m2 iv over 2 h on day 1 plus capecitabine 1000 mg/m2 per os twice for 14 days; repeat every 3 weeks with or without bevacizumab 7.5 mg/kg IV every 3 weeks.

In case of Pan KRAS wild type, before chemotherapy, cetuximab 400 mg/m2 loading dose was administered over 2 h on day 1, then cetuximab 250 mg/m2 over 1 h weekly, and panitumumab 6 mg/kg iv infusion over 1 h on day 1 were administered.

Abdominopelvic CT or MRI examinations were done every 6-10 weeks for follow up. Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 were used to evaluate the tumor response [19]. In case of complete response, partial response or stable disease after 3 cycles the patients continued the same line of treatment for 3 cycles. In case of progressive disease after first or second evaluation second line of treatment was given.

Statistics

Overall survival (OS) was calculated from the beginning of palliative chemotherapy until death or last patient contact. Progression free survival (PFS) was defined as the date from definitive diagnosis to the date of progression.

Univariate and multivariate Cox regression analyses were performed to determine survival trends adjusted for clinicopathologic factors, The Kaplan-Meier method was used to estimate OS and DFS, and the log-rank test was used to make comparisons. Statistical analyses were performed using SPSS 23.0 software (SPSS, Chicago, IL), and p value <0.05 was considered statistically significant [20].

Table 3. Correlation of overall response with different prognostic factors

Prognostic factors	*Response*		*p value*
	OAR *n (%)*	*Nonresponsive* *n (%)*	
Sex			0.706
Female	26 (50.0)	43 (48.3)	
Male	26 (50.0)	46 (51.7)	
Age, years			0.096
<40	11 (21.2)	3 (8.1)	
≥40	41 (78.8)	34 (91.9)	
Performance status			0.073
0	20 (38.5)	14 (37.8)	
1	27 (51.9)	13 (35.1)	
2	5 (9.6)	10 (27.0)	
Weight			0000
<59kg	21 (40.4)	29 (78.4)	
≥59kg	31 (59.6)	8 (21.6)	
BMI			0.000
<25	16 (30.8)	36 (69.2)	
≥25	28 (75.7)	9 (24.3)	
Fat			0.578
<25	27 (51.9)	17 (45.9)	
≥25	25 (48.1)	20 (54.1)	
Muscle, kg			0.1126
<31.5	6 (11.5)	1 (2.7)	
≥31.5	46 (88.5)	36 (97.3)	
Angle			0.000
<4.1	16 (30.8)	28 (75.7)	
≥4.1	36 (69.2)	9 (24.3)	
Gross appearance			0.001
Cauliflower	11 (21.2)	20 (54.1)	
Napkin ring	12 (23.1)	10 (27.0)	
Ulcerating	29 (55.8)	7 (18.9)	

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Prognostic factors	*Response*		*p value*
	OAR *n (%)*	*Nonresponsive* *n (%)*	
Surgery at presentation			0.002
Yes	43 (82.7)	19 (51.4)	
No	9 (17.3)	18 (48.6)	
Pathology			0.578
Adenocarcinoma	35 (67.3)	22 (59.5)	
Signet ring appearance	13 (25.0)	10 (27.0)	
Mucoid adenocarcinoma	4 (7.7)	5 (13.5)	
Grade			0.132
1	0 (0.0)	3 (8.1)	
2	30 (57.7)	16 (43.2)	
3	14 (26.9)	13 (35.1)	
4	8 (15.4)	5 (13.5)	
LVI			0.034
Yes	29 (55.8)	11 (29.7)	
No	1 (1.9)	9 (8.1)	
Unknown	22 (42.3)	23 (62.2)	
PNI			0.889
Yes	8 (15.4)	6 (16.2)	
No	9 (17.3)	5 (13.5)	
Unknown	35 (67.3)	26 (70.3)	
T stage			0.022
T2	10 (19.2)	0 (0.0)	
T3	27 (51.9)	20 (58.8)	
T4	15 (28.8)	14 (41.2)	
N stage			0.278
Nx	18 (34.6)	17 (50.0)	
N0	17 (32.7)	5 (14.7)	
N1	6 (11.5)	4 (11.8)	
N2	11 (21.2)	8 (23.5)	
KRAS mutation			0.651
Wild	32 (61.5)	21 (56.8)	
Mutated	20 (38.5)	16 (43.2)	
Chemotherapy regimen			0.246
FOLFOX	34 (65.4)	23 (62.2)	
XELOX	15 (28.8)	8 (21.6)	
FOLFIRI	3 (5.8)	6 (16.2)	
Type of target therapy			0.650
No	11 (21.2)	12 (32.4)	
Bevazucimab	11 (21.2)	7 (18.9)	
Panitumumab	17 (32.7)	9 (24.3)	
Cetuximab	13 (25.0)	9 (24.3)	
Pre treatment tumor markers			0.205
Normal CEA& CA19.9	26 (50.0)	12 (32)	
High CEA and normal CA19.9	4 (7.7)	7 (18.9)	
Normal CEA and high CA19.9	6 (11.5)	7 (18.9)	
High both	16 (30.8)	11 (29.7)	
Post treatment tumor marke			0.000
Normalized	43 (82.7)	4 (10.8)	
High	9 (17.3)	33 (89.2)	

Table 4. Univariate and multivariate analysis of different prognostic factors with overall free survival

Parameters	*Univariate analysis Sig*	*Multivariate analysis Sig*
Age	0.000	0.963
Sex	0.890	
PS	0.015	0.552
BMI	0.042	0.495
Phase angle	0.032	0.357
Pretreatment tumor marker	0.007	0.651
Site	0,000	0.073
Surgery	0.000	0.338
Gross	0.526	
Pathology	0.436	
T stage	0.029	0.758
N stage	0.002	0.228
Grade	0.243	
LVSI	0.000	0.146
PNI	0,041	0.387
KRAS	0.003	0.013
Post treatment tumor marker	0.003	0714
Regimen of chemotherapy	0.008	0.124
Target therapy	0.051	
OAR	0.000	0.002

Table 5. Univariate and multivariate analysis of different prognostic factors with progression free survival

Parameters	*Univariate analysis Sig*	*Multivariate analysis Sig*
Age	0.001	0.966
Sex	0.337	
PS	0.215	
BMI	0.106	
Phase angle	0.110	
Pretreatment tumor markers	0.267	
Site	0.009	0.176
Surgery	0.005	0.017
Gross	0.292	
Pathology	0.681	
T stage	0.022	0.033
N stage	0.005	0.127
Grade	0.952	
LVSI	0.000	0.013
PNI	0.001	0.058
KRAS	0.085	
Post treatment tumor markers	0.012	0.073
Regimen of chemotherapy	0.068	
Target therapy	0.438	
Response	0.087	

Results

A total of 89 patients met the eligibility criteria and were included in this prospective study. Sixty two patients had been operated before presentation to the oncology department, and 27 patients were metastatic, so no operation was done in them.

Patient baseline clinicopathologic characteristics are presented in Table 1. More than half of patients were male, with a median age of 40 years (range 30-75).

KRAS wild type was detected in 41.6% of CRC (Figure 1). In correlation of phase angle with different clinicopathologic factors, good performance

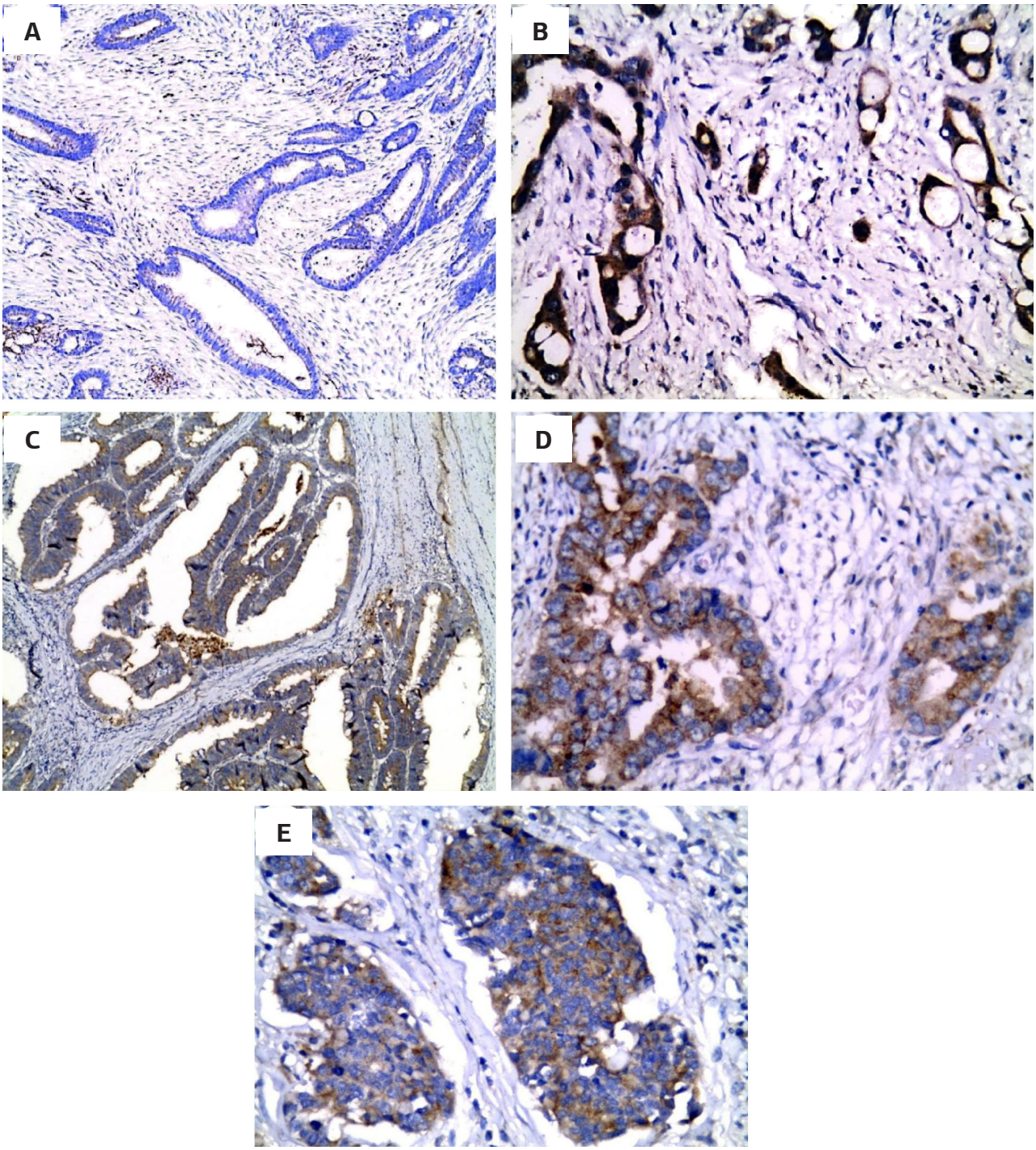

Figure 1. A: Negative KRAS immunostaining in well differentiated colorectal adenocarcinoma (×100). **B:** Positive KRAS immunostaining in a case of well differentiated colorectal adenocarcinoma with lymph node metastases (×400). **C:** Positive KRAS immunostaining in moderate differentiated colorectal adenocarcinoma (×100). **D:** Positive KRAS immunostaining in a case of moderate differentiated colorectal adenocarcinoma with perineural invasion (×400). **E:** Positive KRAS immunostaining in a case of poorly differentiated colorectal adenocarcinoma with vascular invasion (×400).

status 0-1, weight ≥59kg, BMI ≥25, fat <25%, low grade, low T stage were correlated with phase angle ≥4.1 (Table 1).

BMI higher than or equal to 25 was statically correlated with good performance status, weight ≥59 kg, low fat <25%, phase angle ≥4.1, low T stage, low grade, and normalized tumor marker post treatment (Table 2).

The overall response rate was 52%. The factors associated with statistical significant with overall response were weight >59kg, BMI >25, rectum, left sided colon, ulcerating lesion, surgical intervention at the time of diagnosis, lymphovascular space invasion, and T2 and T3 lesions (Table 3).

Median survival was 36 months (range 6-96). The 5-year survival was 37.6%. In univariate analysis the factors with statistical significance were age, performance status, phase angle, pretreatment tumor markers, site, surgery, T stage, N stage, LVI, post treatment tumor markers, KRAS, regimen of chemotherapy and overall response (Table 4 & Figure 2).

On multivariate analysis, the factors maintaining statistical significance with OS were KRAS and overall response.

According to BMI, high BMI was associated with higher OS in both mutated and wild groups but without statistical significance (Figure 3).

Median PFS was 48 months (range 20-96). Five-year PFS was 48.4% in univariate analysis, and the factors with statistical significance were age, site, surgery, T stage, N stage, LVI, perineural invasion, and post treatment markers (CEA-CA19.9). Surgery, T stage, and lymphovascular invasion maintained statistical significance on multivariate analysis (Table 5).

The changes in phase angle during treatment with nutritional counseling and addition of omega 3 are shown in Figure 4.

Discussion

The risk of CRC is associated with increased body weight. Moreover, genetic alterations includ-

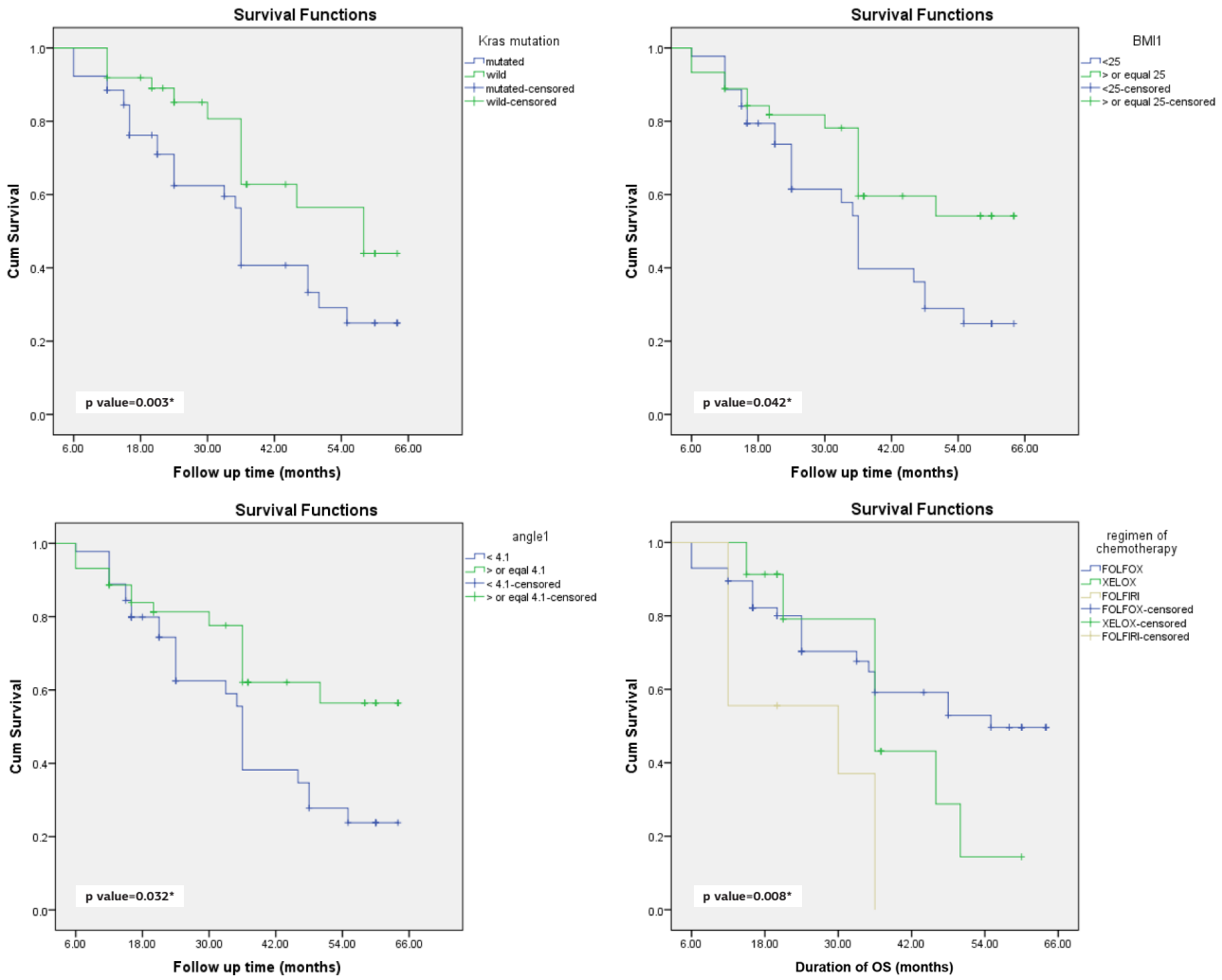

Figure 2. Overall survival in relation to prognostic factors.

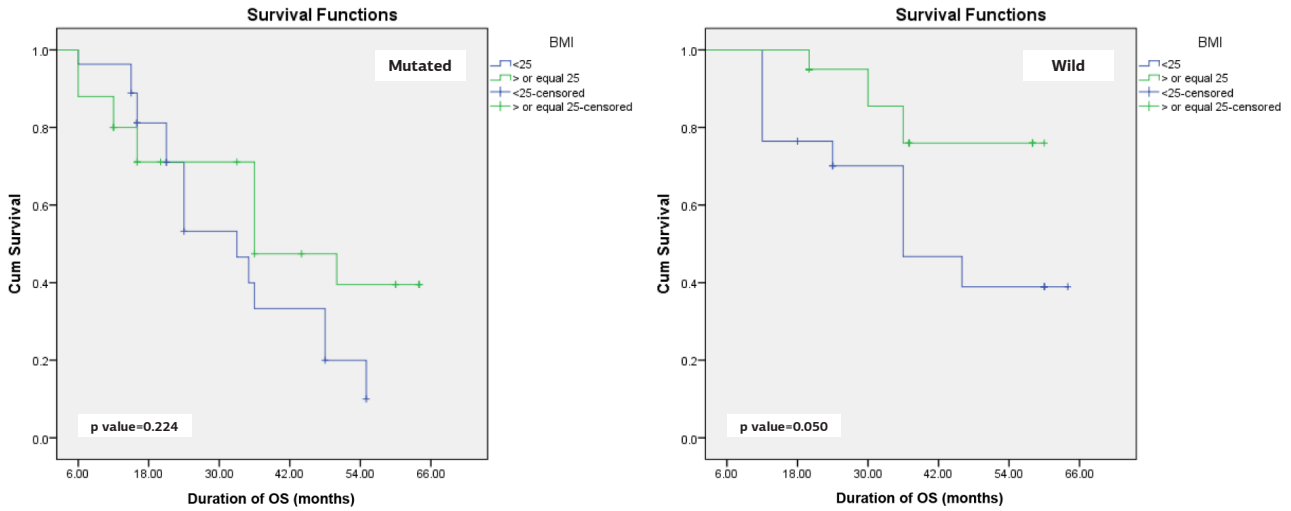

Figure 3. Overall survival in mutated and wild groups according to BMI.

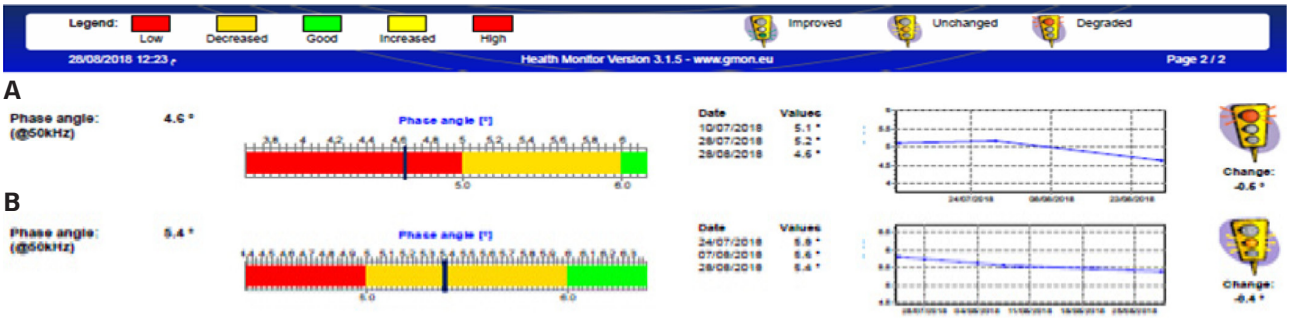

Figure 4. Changes of phase angle during treatment: **A:** decreasing phase angle; **B:** decreased phase angle at first, later on stable.

ing genetic mutations lead to colorectal carcinogenesis [21]. Correlation of body weight and BMI with different molecular subtypes has not been studied.

Thirty to 40% of CRC express mutation in KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogenic homolog) [22]. Mutated KRAS is predictive of non-response to epidermal growth factor but its prognostic value was not studied [23].

KRAS wild type was detected in our series in 41.6% of CRC patients, similar to other studies [21-23].

In our study, high BMI was found to be associated with risk of KRAS-mutated tumors but without statistical significance, a fact reported by other authors as well [9, 24].

Overall response was higher in patients with high BMI and left sided colon cancer in our study. Toiyama et al have reported in 2016 that low BMI less than I0 is associated with poor OS and DFS and bad prognosis [25]. Superior OS and PFS were in left sided colon cancer versus right sided cancer colon as proven by multivariate analysis of PROVETTA study [26].

High phase angle is positively correlated with BMI in the study by Siddiquiet et al in 2016 [27] and this was similar to the study reported by us where the phase angle which indicated cell integrity was associated with good performance status, low T stage, low fat and high BMI.

Adam and colleagues reported that stage IV CRC treated with oxaliplatin-based chemotherapy achieved a 5-year survival rate of 33% [28]. This was in concordance with our data about OS (37.6%).

In univariate analysis the factors with statistical significance were age, performance status, phase angle, pretreatment tumor markers, site, surgery, T stage, N stage, LVI, post treatment tumor markers, KRAS, regimen of chemotherapy and overall response. Tumor site, palliative surgery, T and N stage were predictive of OS in many trials [29,30].

In multivariate analysis, the factors that maintained statistical significance with OS were KRAS and overall response. The first to identify a link between KRAS and lack of response of epidermal growth receptor targeted therapy were Lièvre et al [31] who reported that OS was significantly higher

in KRAS wild type versus mutated one (median OS: 16.3 mo vs 6.9 mo, respectively, p=0.016).

Positive effect of high BMI was detected with OS in all gastrointestinal malignancies except pancreas [32]. In our series, high BMI was associated with higher OS in both mutated and wild groups but it was statistically insignificant.

Median PFS was 48 months. Five-year PFS was 48.4%. In univariate analysis, the factors with statistical significance were age, site, surgery, T stage, N stage, LVI, perineural invasion, and post treatment markers (CEA-CA19.9). Surgery, T stage, and lymphovascular invasion maintained statistical significance on multivariate analysis similar to that reported by Jang et al in 2016 [33].

In conclusion, high phase angle was associated with improved performance status, low T stage, low fat and high BMI. High BMI was associated with improved OS in all KRAS subgroups but without statistical siginficance.

Conflict of interests

The authors declare no conflict of interests.

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