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Excess of weight: is it a modifiable predictive and prognostic factor in locally advanced rectal cancer?

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Abstract. – OBJECTIVE: To evaluate the relationship between body mass index (BMI) and rates of treatment tolerance and clinical outcomes in patients with locally advanced rectal cancer treated with a multimodality approach.

PATIENTS AND METHODS: This study was conducted on 56 patients with histologically proven rectal adenocarcinoma, staged T3-4, and/or node-positive tumor, which underwent intensified radiochemotherapy (RT-CHT) treatment before surgery. We calculated adiposity indices and analyzed their influence on treatment tolerance and clinical outcomes.

RESULTS: Distribution of the 56 patients according to BMI was BMI < 25 kg/m² (n = 19; 33.9%), BMI 25-29 kg/m² (n = 29; 51.8%) and BMI ≥ 30 kg/m² (n = 8; 14.3%). BMI had no significant influence on neo-adjuvant treatment-related toxicity. With a median follow-up of 23 months (range 11-47), the 2-year survival was 85.7%. We did not observe any significant difference among the three BMI categories for any of the outcomes.

CONCLUSIONS: This study suggested no evident links between overweight and survival in patients with locally advanced rectal carcinoma treated with neo-adjuvant RT-CHT. Overweight patients tolerate treatment as normal-weight patients.

Key Words
Rectal cancer, BMI, Obesity, Radiotherapy, Chemotherapy, Surgery.

Introduction

Overweight and obesity are a growing public health problem in industrialized countries, as a result of a total change in lifestyle based on physical inactivity and increased fat-rich dietary intake. They are typically defined by a high body mass index (BMI) and associated with cardiovascular and metabolic diseases[1]. However, epidemiological analysis has demonstrated that in 15-45% of cases, excess of weight is linked to cancerogenesis process in certain cancer types, including rectal carcinoma[1,2]. The mechanism is still unknown, but it seems related to the distribution of body fat, particularly in the visceral compartment[3,4]. In fact it has been suggested a relationship between visceral adiposity and worst oncologic outcome for rectal cancer, especially for males[5-7]. However, there are different studies that have not demonstrated any predictive value on overall mortality in overweight and obese patients[8,9]. Therefore, at present, the impact of adiposity remains controversial. The aim of this study is to determine if the excess of weight, as measured by conventional adiposity indices, can be defined a risk factor for post multimodality treatment outcome in locally advanced rectal cancer.

Patients and Methods

Patient Selection

Data of all patients who received intensified neo-adjuvant treatment for locally advanced rectal carcinoma were abstracted from a prospectively maintained rectal database after Institutional Review Board Approval. We enrolled patients once an informed consent was signed. All patients had histologically proven rectal adenocarcinoma, clinically staged IIa-IIIc disease (according to the 7th American Joint Committee on Cancer Staging System[10]). Patients were excluded from the study in case of synchronous tumors, cardiovascular disease, history of neurological or psychiatric disorders, or previous radiation therapy or chemotherapy.

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Adiposity Indices

The measure of excess of weight used was the BMI, calculated as weight divided by height squared (kg/m^2). Pre-treatment BMI was obtained for all patients. According to the WHO guidelines[11], patients were classified as normal weight (BMI < 25 kg/m^2), overweight (BMI 25-29 kg/m^2) and obese (BMI ≥ 30 kg/m^2). Considering that BMI does not differentiate between lean mass and adipose tissue, we have calculated other quantitative measure of abdominal fat compartments to define the obesity in term of visceral fat. Validating quantitative radiologic measures of subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) volumes were assessed using pre-treatment CT scan[12,13]. A single axial slice at the level of L4-L5 intervertebral space was used to measure SAT and VAT. CT image was set between -195 to -45 Hounsfield units. The areas of adipose tissue were delineated by a physician. SAT was defined as the extra-peritoneal fat between the skin and muscles, and VAT as the intra-peritoneal fat. SAT and VAT areas were automatically calculated by CT software. Visceral fat to subcutaneous fat ratio (V/S) was obtained to achieve an additional parameter. A ratio of 0.4 was considered the cut-off line to define visceral obesity (V/S ≥ 0.4) and subcutaneous adiposity (V/S < 0.4)[14].

Treatment Plan

All patients were treated with a long course of radiochemotherapy (RT-CHT). Radiation therapy (RT) was delivered with a 3D-conformational multiple field technique at a dose of 45 Gy (in 25 daily fractions of 1,8 Gy given in 5 weeks) to the whole pelvis, plus a 5,4-9 Gy (in 3-5 daily fractions of 1,8 Gy) to the tumor volume, with 6-15 MV energy photons. Chemotherapy (CHT) consisted of 2 h oxaliplatin infusion 50 mg/m^2 on the first day of each week of radiotherapy and 5 daily continuous infusion of 5-FU 200 mg/m^2/die[15]. The choice of adding oxaliplatin to the standard schedule of 5-FU was dictated by our previous experience, in which the addition of oxaliplatin has resulted in a high rate of pathological complete response (pCR) with acceptable toxicity, although in literature its real benefit remains unclear[16,17]. Treatment-related toxicity was recorded by grade according to the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 4.03[18].

Surgery was planned 7-9 weeks after the end of RT-CHT treatment. The type of surgery was left to the surgeon's discretion. The type of adjuvant chemotherapy was chosen by the oncologist. After surgery, all patients were monitored at 3-month intervals for the first year and at 6-month intervals for the subsequent years.

Statistical Analysis

Baseline characteristics were summarized with descriptive statistics. Fisher's exact tests were used to compare discrete variables between groups. Statistical tests were two-sided. A p-value < 0.05 was considered statistically significant in the tests.

Overall survival (OS) and disease-free survival (DFS) were measured in months from the end of the neo-adjuvant treatment to the date of death or last follow-up. To determine the influence on survival, the variable BMI and V/S were considered. The Kaplan-Meier method was used to estimate the survival distribution and comparisons of survival between subgroups were made using the long-rank test. The relationship between predictive factors and survival was assessed using a logistic model in multivariate analysis. Statistical analysis was performed using R statistical package.

Results

Between January 2010 and December 2013, 56 patients underwent intensified neo-adjuvant RT-CHT and met the inclusion criteria. The cohort included 37 male and 19 female patients with a median age of 63.28 years (range 38-76). Patients characteristics and adiposity measurements are shown in Table I. Distribution of the 56 pa-

Table I. Patient characteristics and adiposity measurement.

Characteristics	N patients (%)
Age, years	
Median (range)	63.28 (38-76)
Sex	
Male	37 (66.1)
Female	19 (33.9)
BMI, kg/m^2	
Median (range)	26.35 (14.84-34.94)
< 25	19 (33.9)
25-29	29 (51.8)
≥ 30	8 (14.3)
VAT, cm^2	
Median (range)	74.66 (5.20-164.04)
SAT, cm^2	
Median (range)	125.425 (16.95-229.26)
V/S	
< 0.4	7 (12.5)
≥ 0.4	49 (87.5)

BMI: body mass index; VAT: visceral adipose tissue; SAT: subcutaneous adipose tissue; V/S: visceral fat to subcutaneous fat ratio

Table II. Acute toxicity.

Toxicity	% patients (n)			
	Total	BMI < 25	BMI ≥ 25	*p*-value
Neutrophils-granulocytes				
≤ G2	1.9 (1)	5.3 (1)	0 (0)	0.169
> G2	.	.	.	.
Fatigue				
≤ G2	19.6 (11)	21.1 (4)	18.9 (7)	0.866
> G2	.	.	.	.
Radiation-dermatitis				
≤ G2	33.9 (19)	36.8 (7)	32.4 (12)	0.662
> G2	5.4 (3)	5.3 (1)	5.4 (2)	0.771
Constipation				
≤ G2	21.4 (12)	21.1 (4)	21.6 (8)	0.866
> G2	.	.	.	.
Diarrhea				
≤ G2	30.4 (17)	26.3 (5)	32.4 (12)	0.653
> G2	3.5 (2)	10.5 (2)	0 (0)	0.055
Nausea				
≤ G2	14.3 (8)	15.7 (3)	13.5 (5)	0.851
> G2	.	.	.	.
Proctitis				
≤ G2	69.6 (39)	73.7 (14)	67.6 (25)	0.763
> G2	3.6 (2)	5.3 (1)	2.7 (1)	0.771
Vomiting				
≤ G2	7.1 (4)	15.7 (3)	2.7 (1)	0.059
> G2	.	.	.	.
Neuropathy: sensory				
≤ G2	16.1 (9)	15.7 (3)	16.2 (6)	0.851
> G2	1.8 (1)	0 (0)	2.7 (1)	0.669
Abdominal pain or cramping				
≤ G2	10.7 (6)	10.5 (2)	10.8 (4)	0.826
> G2	1.8 (1)	0 (0)	2.7 (1)	0.669
Dysuria-painful urination				
≤ G2	16.1 (9)	21.1 (4)	13.5 (5)	0.358
> G2	.	.	.	.

BMI: body mass index.

tients according to BMI was BMI < 25 kg/m^2 (n = 19; 33.9%), BMI 25-29 kg/m^2 (n = 29; 51.8%) and BMI ≥ 30 kg/m^2 (n = 8; 14.3%). The median BMI, VAT and SAT were 26.35 kg/m^2, 74.66 cm^2 and 125.425 cm^2, respectively.

Excess of Weight and Toxicity

We analyzed the influence of excess of weight on the rates of the major RT-CHT adverse effects. The occurrence of acute toxicity is summarized in Table II. Due to the low number of obese patient (n = 8), we combined patients with BMI 25-29 kg/m^2 and BMI ≥ 30 kg/m^2 and compared them to normal weight in the data analyses. Proctitis, grade ≤ G2, was the most common symptom (69.6%). The occurrence of fatigue (*p*-value = 0.866), neutrophils-granulocytes alteration (p = 0.169) and radiation-dermatitis (p = 0.662) did not differ between overweight and normal weight patients. Similarly, the occurrence of gastrointestinal symptoms was comparable. We observed a higher prevalence of vomiting in normal weight patients, but the proportion was not significantly different in the two groups (p = 0.059). Overweight patients were less subject to diarrhea grade > 2, but this relationship was not significantly (p = 0.055). Briefly, BMI had no significant influence on neo-adjuvant treatment-related toxicity.

Excess of Weight and Sex

In terms of BMI only 14.3% of patients were classified as obese. Alternatively, considering the

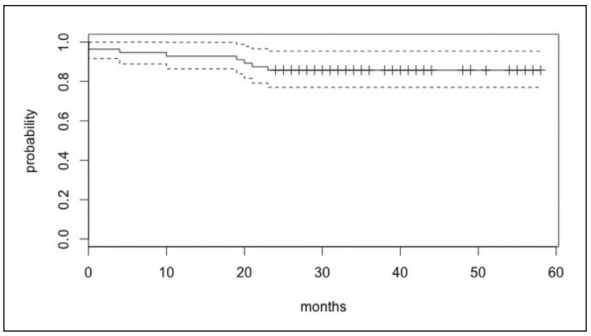

Figure 1. Overall survival of patients undergoing radiochemotherapy followed by surgery for locally advanced rectal cancer.

classification of visceral obesity, 87.5% of patients had a V/S ≥ 0.4. There was a statistically significant higher proportion of patients classified as obese when using V/S *vs.* BMI ($p \leq 0.001$). There was no difference by sex in overweight patients ($p = 0.06$). Any significant survival probability was observed when combining sex and visceral adiposity ($p = 0.884$).

Excess of Weight and Outcomes

With a median follow-up of 23 months (range 11-47) the 2-year survival was 85.7% (Figure 1). We did not observe any significant differences among the three BMI categories for any of the outcomes. Figure 2 shows comparisons of OS (Figure 2a) and DFS (Figure 2b) of the patients stratified by BMI < 25 kg/m^2, 25-29 kg/m^2 and BMI ≥ 30 kg/m^2. There was no statistically significant difference in OS or DFS in patients stratified by BMI ($p = 0.792$ and 0.807, respectively). Figure 3 illustrates the comparisons of OS and DFS between patients stratified by BMI < 25 *vs.* BMI ≥ 25 (Figure 3a-b) and BMI < 30 *vs.* BMI ≥ 30 (Figure 3c-d). Again, there was no statistically significant difference in OS and DFS between patients with BMI < 25 *vs.* BMI ≥ 25 ($p = 0.582$ and 0.571, respectively) or BMI < 30 *vs.* ≥ 30 ($p = 0.829$ and 0.882, respectively). OS and DFS did not differ by obesity when defined by V/S measure ($p = 0.235$ and 0.185, respectively) (Figure 3).

Multivariate Analysis

Multivariate analysis was performed to identify independent prognostic factors for OS and DFS. The variables entered into the equation were age, gender, BMI, clinical stage, tumor localization and pCR. None were associated with OS or DFS ($p \geq 0.05$).

Discussion

In the last few years, the impact of the excess of weight on cancer-related outcomes has become a critical issue. The current analysis represents an initial attempt to examine the effect of adiposity indices on toxicity occurrence and OS and DFS in rectal cancer patients treated with a long course of intensified RT-CHT followed by surgery. Whereas the association between obesity and colon cancer has been well studied[19,20], only a few studies have evaluated the role that obesity plays in the outcomes of rectal cancer[8,21,22]. This is the first comparison of general and visceral obesity as predictors of pre-operative RT-CHT-related toxicity and survival outcomes in locally advanced rectal cancer. Our analysis indicates that treatment-related toxicity was not related to excess of weight. In general, gastrointestinal toxicity was the most common side effect and it was classified as grade > 2 in 4 patients only. No severe hematological and renal toxicity were seen. When comparing nor-

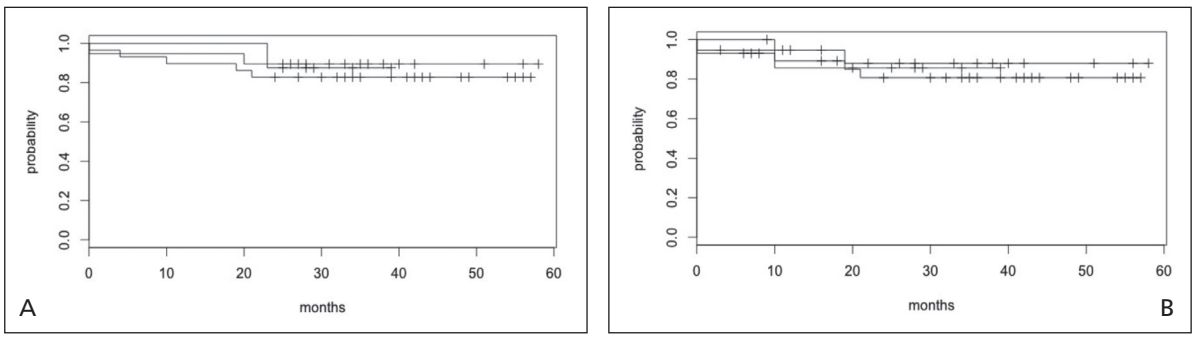

Figure 2. Overall survival (**A**) and disease free survival (**B**) in patients stratified by BMI < 25 kg/m^2, 25-29 kg/m^2 and BMI ≥ 30 kg/m^2.

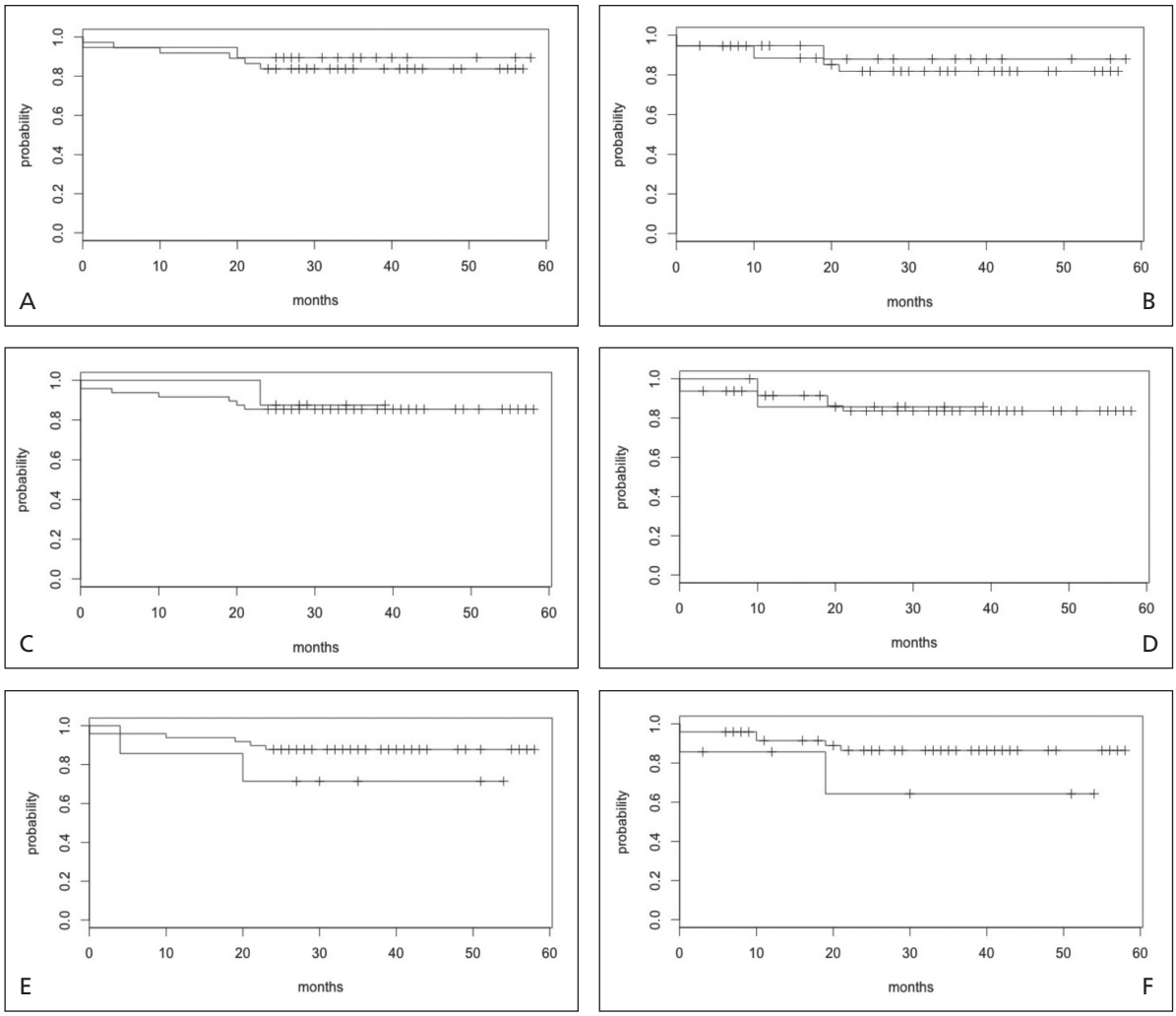

Figure 3. Comparisons of OS and DFS between patients stratified by BMI < 25 vs. BMI ≥ 25 (**A**-**B**) and BMI < 30 vs. BMI ≥ 30 (**C**-**D**) V/S measure (**E**-**F**).

mal-weight patients with overweight patients, we did not obtain any significant level of toxicity. Studies of rectal neo-adjuvant treatment have not analyzed RT-CHT complications in viscerally obese patients[21]. Meyerhardt et al[8], using data from a randomized trial of adjuvant RT-CHT in patients with stage II-III rectal cancer, found that obesity was associated with less treatment-related toxicity during RT-CHT. However, RT-CHT was performed after surgery, and we were unable to evaluate peri- and post- operative complications on the influence of adjuvant treatment toxicities. In literature, more data are available concerning the association between BMI and survival outcomes, but the results are often conflicting[5,8,19,21-24]; thus, it is difficult to compare them. In some publications of rectal surgery[8,19,24] no differences in OS were reached comparing survival between obese and non-obese groups; in others, high BMI and V/S values were associated with prolonged OS[22], whereas in others with poorer outcome[23]. This disparity in findings could be attributed to heterogeneity of samples (several studies reported colon and rectal cancer cases as a single cohort), as well as low statistical significant of studies and different measurable parameters using as surrogate of visceral adiposity. We also examined whether BMI and V/S were associated with survival. Independently of adiposity index given, overweight and obesity do not contribute to clinical outcomes. BMI and V/S were not demonstrated to be independent factors of decreased survival. Although statistical analysis failed to detect any differences, V/S was shown to have a less pronounced impact than BMI in both OS ($p = 0.235$ *vs.* 0.792) and DFS ($p = 0.185$

vs. 0.807). This means that V/S rather than whole body adipose tissue should be a risk factor for outcome after multimodality treatment in locally advanced rectal cancer. A similar trend towards worse OS and DFS among those patients with V/S $\geq$ 0.4 was also observed in Clark et al[21] analysis. In a population of 99 rectal cancer patients, they reported a shorter DFS ($p = 0.04$) and a worse OS ($p = 0.14$) in viscerally obese patients than those observed in patients with V/S < 0.4. This study is limited by its relatively small number of patients; therefore, the analysis of subgroup may prove not to be statistically significant simply because the study has insufficient ability to demonstrate real differences. However, well-defined inclusion criteria help to minimize bias. Follow-up time is relatively short to achieve safe conclusions about survival outcomes. The principal finding of this data analysis was that the majority of patients (66.1%) were overweight or obese. The absence of tumor-related cachexia could explain the lack of association between obesity and mortality. However, follow-up time is substantially adequate to detect differences in RT-CHT toxicity. Toxicity data were recorded at the time of patient presentation in a standardized manner to ensure quality and they were correlated with toxicity grading to reduce the rate of underreported events. Despite the reduced statistical power to examine the effect of intensified neo-adjuvant RT-CHT regime on outcome, our toxicity results suggest that the full-dose of CHT should be calculated on patient actual body weight, including overweight and obese. This study requires confirmation by larger cohort to account for his potential findings. V/S, rather than BMI, seems to be a possible prognostic factor. Considering that toxicity analysis has shown that intensified neo-adjuvant RT-CHT is well tolerated, overweight patients should be exposed to the same CHT dose calculation received by normal weight patients. Future studies on this topic may help to improve outcomes in overweight locally advanced rectal cancer patients.

Conclusions

Our data revealed no correlation between adiposity indices, both BMI and V/S, and oncologic outcomes in patients with locally advanced rectal carcinoma treated with neo-adjuvant RT-CHT. Patients with excess of weight well tolerate intensified pre-operative treatment as normal weight patients.

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Guido Tosi contributed to acquisition of data.

Conflict of Interest

The authors declare that they have no competing interests.

References

1) Pischon T, Nöthlings U, Boeing H. Obesity and cancer. Proc Nutr Soc 2008; 67: 128-145.
2) Bergström A, Pisani P, Tenet V, Wolk A, Adami HO. Overweight as an avoidable cause of cancer in Europe. Int J Cancer 2001; 91: 421-430.
3) Pou KM, Massaro JM, Hoffmann U, Lieb K, Vasan RS, O'Donnell CJ, Fox CS. Patterns of abdominal fat distribution: the Framingham Heart Study. Diabetes Care 2009; 32: 481-485.
4) Otake S, Takeda H, Suzuki Y, Fukui T, Watanabe S, Ishihama K, Saito T, Togashi H, Nakamura T, Matsuzawa Y, Kawata S. Association of visceral fat accumulation and plasma adiponectin with colorectal adenoma: evidence for participation of insulin resistance. Clin Cancer Res 2005; 11: 3642-3646.
5) Moon HG, Ju YT, Jeong CY, Jung EJ, Lee YJ, Hong SC, Ha WS, Park ST, Choi SK. Visceral obesity may affect oncologic outcome in patients with colorectal cancer. Ann Surg Oncol 2008; 15: 1918-1922.
6) Siegel EM, Ulrich CM, Poole EM, Holmes RS, Jacobsen PB, Shibata D. The effects of obesity and obesity-related conditions on colorectal cancer prognosis. Cancer Control 2010; 17: 52-57.
7) Haydon AM, Macinnis RJ, English DR, Giles GG. Effect of physical activity and body size on survival after diagnosis with colorectal cancer. Gut 2006; 55: 62-67.
8) Meyerhardt JA, Tepper JE, Niedzwiecki D, Hollis DR, McCollum AD, Brady D, O'Connell MJ, Mayer RJ, Cummings B, Willett C, Macdonald JS, Benson AB 3rd, Fuchs CS. Impact of body mass index on outcomes and treatment-related toxicity in patients with stage II and III rectal cancer: findings from Intergroup Trial 0114. J Clin Oncol 2004; 22: 648-657.
9) Morrison DS, Batty GD, Kivimaki M, Davey Smith G, Marmot M, Shipley M. Risk factors for colonic and rectal cancer mortality: evidence from 40 years' follow-up in the Whitehall I study. J Epidemiol Community Health 2011; 65: 1053-1058.
10) Edge S, Byrd D, Compton C, et al, Eds., AJCC Cancer Staging Manual, Springer, New York, NY, USA, 7th edition, 2009.
11) http://www.who.int/mediacentre/factsheets/fs311/en/index.html. Accessed 1 Nov 2009.
12) Balentine CJ, Marshall C, Robinson C, Wilks J, Anaya D, Albo D, Berger DH. Validating quantitative obesity measurements in colorectal cancer patients. J Surg Res 2010; 164: 18-22.
13) Florez H, Castillo-Florez S. Beyond the obesity paradox in diabetes: fitness, fatness, and mortality. JAMA 2012; 308: 619-620.

14) Matsuzawa Y, Nakamura T, Shimomura I, Kotani K. Visceral fat accumulation and cardiovascular disease. Obes Res 1995; 3: 645S-647S.
15) Musio D, De Felice F, Magnante AL, Ciolina M, De Cecco CN, Rengo M, Redler A, Laghi A, Raffetto N, Tombolini V. Diffusion-weighted magnetic resonance application in response prediction before, during, and after neoadjuvant radiochemotherapy in primary rectal cancer carcinoma. Biomed Res Int 2013; 2013: 740195.
16) Musio D, De Felice F, Bulzonetti N, Guarnaccia R, Caiazzo R, Bangrazi C, Raffetto N, Tombolini V. Neoadjuvant intensified treatment for rectal cancer: time to change? World J Gastroenterol 2013; 19: 3052-3061.
17) De Felice F, Musio D, Izzo L, Tombolini V. Neoadjuvant chemoradiotherapy for locally advanced rectal cancer: The debate continues. World J Gastrointest Oncol 2014; 6: 438-440.
18) Cancer Therapy Evaluation Program. Common Terminology Criteria for Adverse Events, Version 3.03. 2010. Available from: URL: http://ctep.cancer.gov
19) Rickles AS, Iannuzzi JC, Mironov O, Deeb AP, Sharma A, Fleming FJ, Monson JR. Visceral obesity and colorectal cancer: are we missing the boat with BMI? J Gastrointest Surg 2013; 17: 133-143.
20) Garcia-Oria Serrano MJ, Armengol Carrasco M, Caballero Millán A, Ching CD, Codina Cazador A. Is body mass index a prognostic factor of survival in colonic cancer? A multivariate analysis. Cir Esp 2011; 89: 152-158.
21) Clark W, Siegel EM, Chen YA, Zhao X, Parsons CM, Hernandez JM, Weber J, Thareja S, Choi J, Shibata D. Quantitative measures of visceral adiposity and body mass index in predicting rectal cancer outcomes after neoadjuvant chemoradiation. J Am Coll Surg 2013; 216: 1070-1081.
23) Ballian N, Lubner MG, Munoz A, Harms BA, Heise CP, Foley EF, Kennedy GD. Visceral obesity is associated with outcomes of total mesorectal excision for rectal adenocarcinoma. J Surg Oncol 2012; 105: 365-370.
23) Guiu B, Petit JM, Bonnetain F, Ladoire S, Guiu S, Cercueil JP, Krausé D, Hillon P, Borg C, Chauffert B, Ghiringhelli F. Visceral fat area is an independent predictive biomarker of outcome after first-line bevacizumab-based treatment in metastatic colorectal cancer. Gut 2010; 59: 341-347.
24) Healy LA, Ryan AM, Sutton E, Younger K, Mehigan B, Stephens R, Reynolds JV. Impact of obesity on surgical and oncological outcomes in the management of colorectal cancer. Int J Colorectal Dis 2010; 25: 1293-1299.