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Research Article

Higher Value of Skeletal Muscle Index are Associated with Lower Neoadjuvant Rectal Score in Patients Treated with Concurrent Neoadjuvant Chemoradiotherapy

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Abstract

Background: Sarcopenia (low muscle mass) is an emerging syndrome associated with poor outcome in cancer patients. We investigated the relation between skeletal muscle index (SMI) and neoadjuvant rectal score (NAR) in a group of patients with locally advanced rectal adenocarcinoma, treated with neoadjuvant concurrent chemoradiotherapy (nCCRT) with Capecitabine and surgery.

Methods: Patients with locally advanced lower and middle rectal adenocarcinoma (n=91) in Stage II and III disease were retrospectively analyzed between 2016 and 2020. All patients were treated with nCCRT with Capecitabine and after 6-8 weeks of surgery and adjvant chemotherapy. SMI was calculated at L3 position on computed tomography before to start with nCCRT. NAR score was developed as a composite short-term endpoint for clinical trials involving neoadjuvant therapy for rectal cancer and can predict a response of the treatment. NAR score was defined as [5pN - 3 (cT - pT) + 12]2/9.61.

Results: The cohort included 61 men (67%) and 30 women (33%), with a total mean age of 63.4 (±8.4) years. The Kruskal-Wallis one-way analysis of variance showed that there were significant differences in NAR score only between high and intermediate (18.8 ± 4.4 *vs.* 25.7 ± 4.8; p = 0.044) and high and low SMI (18.8 ± 4.4 *vs.* 28.5 ± 5.2; p = 0.007). Moreover using ordinal logistic regression analysis after adjustment for age and sex, having low or intermediate SMI were associated with an increased likelihood of having higher NAR score (estimate = 1.59, 95% CI = 0.48-2.71, p = 0.005; estimate = 1.18, 95% CI = 0.12-2.24, p = 0.03).

Conclusions: Low muscle mass is a potential novel negative predictive marker of poor response to nCCRT.

Keywords: Skeletal muscle index; Neoadjuvant rectal score; Concurrent neoadjuvant chemoradiotherapy

Introduction

Colorectal cancer is the third most common reason for cancer diagnostic and cancer-related mortality worldwide recently [1]. In contrast to all colon cancers, rectal cancer (RC) due to the anatomical confinements of the bony pelvis characterized with invasive growth, has a different surgical approach and treatment strategies and outcomes [2,3]. Neoadjuvant concurrent chemoradiotherapy (nCCRT) has been established as the standard treatment for locally advanced RC in most parts of Europe and the United States due to the excellent local control of the approach [4,5].

nCCRT ensures down staging in two-thirds of all patients and pathologic complete response (pCR) in one-fifth of them [6-8]. Patients with pCR and near CR after neoadjuvant treatment are less likely to have a local tumor recurrence and more likely to have a better survival outcome [9-12].

Sarcopenia (low muscle mass) is a syndrome that causes a progressive and generalized loss of skeletal muscle. This condition often develops with age, although it may also emerge due to factors not related to age as malnutrition, immobility, inflammatory disease, and cancer [13]. Recent studies have reported sarcopenia to be associated with negative outcome after surgical treatment of RC. However, the effect of sarcopenia on the efficiency of nCCRT is not fully understood [14,15].

Recent studies have proposed that the development of sarcopenia, measured by the change in the skeletal muscle mass area (SMMA) at the L3 position on computed tomography (CT), could be a negative indicator of nCCRT response [16,17].

The neoadjuvant rectal (NAR) score was developed as a composite, short-term endpoint for clinical trials involving neoadjuvant therapy for RC. Studies have supported its utility as a predictor of overall survival in these patients [18]. No studies have investigated the relation between the presence of sarcopenia and NAR score.

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The aim of this study is to investigate the relationship between pre-treatment skeletal muscle index (SMI) and with NAR score in RC patients with nCCRT, followed by surgery and adjuvant chemotherapy.

Materials and Methods

Patient selections

In this single centre retrospective cohort study, we reviewed the cases of 91 patients from MHAT Uni Hospital Panagyurishte, Bulgaria "XXXX XXX XXXXXXXX XXXXXXXXXXXX, XXXXXXXX" with non-metastatic locally advanced rectal adenocarcinoma who underwent rectal surgery 6-8 weeks following nCCRT between April 2016 and April 2020. The procedure was approved by the scientific research ethics committee at the hospital. The eligibility criteria were as follows: (1) Pathologically confirmed diagnosis of rectal adenocarcinoma through a biopsy; (2) cT3-T4 or TxN+ tumors localized in the middle or distal rectum on computer tomography (CT) and magnetic resonance imaging (MRI); (3) Mesorectal excision 6-8 weeks after receiving long-term nCCRT; (4) Age above 18; elective surgery; (5) An Eastern Cooperative Oncology Group (ECOG) score of <2. The exclusion criteria for this study were distant metastasis and a history of other malignancies.

All patients who underwent R0 surgery for locally advanced RC with nCCRT were enrolled in the present study. Radiotherapy was performed once (2.0 Gy) daily to reach a total dose of 50 Gy. Capecitabine (1600mg/m^2) was the only chemotherapy agent administered concurrently with RT. Capecitabine was simultaneously given with RT, per os (p.o.), on weekdays, followed by a two-day rest interval on weekends. This cycle was repeated during irradiation. After surgery and restaging CT or PET/CT, all patients were treated with adjuvant chemotherapy.

The pathologic stage of the patients was established based on the American Joint Committee on Cancer (AJCC) Colon and Rectum Staging Manual, 8th Edition [19].

Data collection

The data collected included demographics, body mass index (BMI) within the previous week, histologically confirmed diagnosis, tumor-node-metastasis stage (TNM stage), clinical and pathological stage, radiology reports prior starting with nCCRT and after surgery, date of progression as determined by the radiology reports and date of death or last follow-up. Peripheral blood samples were collected from patients that were included in the study, on the day of the first - daily fraction nCCRT and on the day of the control CT, after surgery. Of interest were the following pre-treatment hematological and biochemistry parameters: absolute neutrophil count (ANC), absolute lymphocyte count (ALC) and absolute platelet count (APC), which enable calculation of the NLR (ANC/ALC) and PLR (APC/ALC).

Measurement of SMI

We performed a computed tomography prior nCCRT and after surgery in order to evaluate the effects of neoadjuvant therapy. We calculated the SMI (cm^2/m^2) before neoadjuvant treatment. The skeletal muscle area (cm^2) was calculated at the level L3, from computed tomography images by, a single investigator, who was blinded to the patient outcomes [4]. To normalize the SMI for body size, the skeletal muscle area was divided by the square of the body height (m^2). These values were then divided by the pre-SMI and multiplied by 100 to determine the rate of the SMI (Figure 1). Patients were divided into three groups according to the SMI - low (up to the 33th percentile), intermediate (between the 33th and 66th percentile) and high (over the 66th percentile), where the median SMI was 48.30 the value to the 33th percentile was 45.38 and the value of 66th percentile - 64.80.

Determination of the NAR score

The NAR score incorporates cT to account for tumor downstaging, and pT and pN that are influenced directly by preoperative treatment [18]. The NAR score was defined as [5pN - 3(cT - pT) + 12]2/9.61. For pT category and pN category, a relative weight of 3 and 5 was suggested to reflect the impact of these variables, based on the nomogram of Valentini [20]. The constant 12 is included to maintain all scores inside the brackets as positive. The scaling factor 9.61 was introduced to ensure that the final scores range from 0 to 100. NAR score was categorized as low (<33th percentile), intermediate (33-66th percentile), and high (>66th percentile), where the median NAR score was 20.3 the value in 33th percentile was 14.98 and the value in 66th percentile - 30.07.

Statistical design and analysis

Data was managed and analyzed using SPSS software ver. 23. The demographic characteristics were expressed as frequencies and percentages for categorical variables and as medians and means with standard deviations for quantitative variables. The Kruskal-Wallis test, χ^2 test and Spearman correlation were used to compare and evaluate the correlations between the biomarkers and the clinicopathological characteristics of the patients such as age, gender etc. Correspondence analysis was used to describe simultaneously the relationships between the values of NAR score and SMI in the categories for each variable. To assess the correlations between test results, who values were interpreted as follows: <0.39, weak correlation; 0.40-0.59, moderate correlation; 0.60-0.79, strong correlation; and ≥0.80, very strong correlation. Ordinal regression was used to search for associations between divided into 3 categories of NAR score and independent variables. Disease - free survival (DFS) is defined as the time from surgery to recurrence of tumor or death. Survival curves according to the NAR scores were estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. Two-tailed p-values (≤0.05) were considered significant.

Results

Baseline characteristics and their relations with NAR score

In this single center retrospective study we included 91 patients (males were 61 (67%) and females were 30 (33%)) who were treated with nCCRT with Capecitabine. The mean patients age was 63.4 ± 8.4 years at the time of diagnosis. There were 20 well-differentiated G1 tumors (22%), 68 moderately differentiated G2 tumors (74.7%) and 3 poorly differentiated G3 tumors (3.3%). The clinical TNM stages before nCCRT were II and III in 37 (40.6%) and 54 (59.4%) patients, respectively. The pathological stages after nCCRT were as follows: pathological stage I, n=34 (37.4%) pathological stage II, n=10 (11%) and pathological stage III, n=47 (51.6%). The pathological stage I

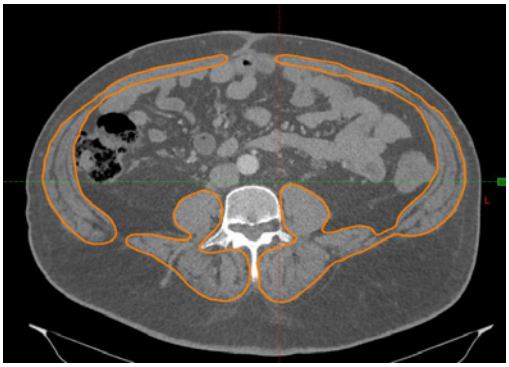

Figure 1: Measurement of skeletal muscle index (SMI). Orange is the skeletal muscle mass; SMI = L3 skeletal muscle cross-sectional area (cm^2)/ height^2 (m^2).

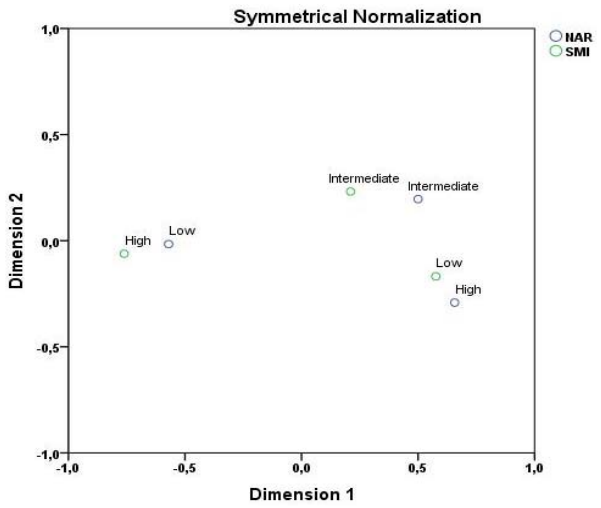

Figure 2: Correspondence analysis was used to describe relationship between the levels of neoadjuvant rectal (NAR) score and skeletal muscle index (SMI). For each variable, the distances between category points in the plot reflect the relationships between the categories with similar categories plotted close to each other.

included 12 (13.2%) patients with near CR (very few tumor cells in fibrotic tissue).

Low SMI had 30 (33%), intermediate SMI had 30 (33%) and high SMI had 31 (34%) of then patients. Clinical characteristics of the patients and relations with NAR score were summarized in (Table 1). Chi-squared analysis between the levels of the NAR score and clinicopathological characteristics in the patients was performed. Levels of the NAR score were not related to patients age at the time of the diagnosis (p = 0.24), gender (p = 0.70) (Table 1). There were no significant differences between values of BMI, NLR and PLR and NAR score (Table 1). The levels of the NAR score were significantly related with clinical (p=0.012), pathological (p<0.001) stage, SMI (p=0.046) and recurrence (p<0.001) (Table 1). Further to describe relationship between the levels of NAR and SMI we used correspondence analysis (Figure 2).

Associations of the levels of SMI and NAR score

The Kruskal-Wallis one-way analysis of variance showed that

Table 1: Relationship between baseline clinicopathological characteristics of patients and neoadjuvant rectal (NAR) score.

Characteristic	NAR score			p-value
	Low	Intermediate	High	
Age				0.24
≥65	29(64.4%)	13(44.8%)	10(58.8%)	
<65	16(35.6%)	16(55.2%)	7(41.2%)	
Gender				0.7
Male	32(71.1%)	18(62.1%)	11(64.7%)	
Female	13(28.9%)	11(37.9%)	6(35.3%)	
Grade				0.85
1	9(20.0%)	8(27.6%)	3(17.6%)	
2	35(77.8%)	20(69%)	13(76.5%)	
3	1(2.2%)	1(3.4%)	1(5.9%)	
SMI				0.046
Low	10(22.2%)	12(41.4%)	8(47.1%)	
Intermediate	13(28.9%)	11(37.9%)	6(35.3%)	
High	22(48.9%)	6(20.7%)	3(17.6%)	
Clinical stage				0.012
II	17(37.8%)	10(34.5%)	0(0%)	
III	28(62.2%)	19(65.5%)	17(100%)	
Pathological stage				<0.001
I	34(75.6%)	0(0%)	0(0%)	
II	10(22.2%)	0(0%)	0(0%)	
III	1(2.2%)	29(100%)	17(100%)	
BMI	24.7±3.4	24.9±3.6	28.6±2.9	0.36
NLR	3.7±1.1	4.0±0.95	3.4±0.91	0.53
PLR	131.2±59.6	158.1±83.1	111.4±52.3	0.51
Recurrence				<0.001
No	36(80%)	12(41.4%)	2(11.8%)	
Yes	9(20%)	17(58.6%)	15(88.2%)	

Table 2: Ordinal logistic regression analysis for predicting neoadjuvant rectal (NAR) score.

Marker	Estimate[a] Adjusted	95% CI	P-value
SMI - low	1.59	0.48-2.71	0.005
SMI - Intermediate	1.18	0.12-2.24	0.03

[a]Adjusted for gender and age.

there were significant differences in NAR score only between high and intermediate (18.8 ± 4.4 *vs.* 25.7 ± 4.8; p = 0.044) and high and low SMI (18.8 ± 4.4 *vs.* 28.5 ± 5.2; p = 0.007) (Figure 3). A significantly negative correlation was detected between NAR score and SMI (rho = - 0.365; p < 0.001). Moreover, using ordinal logistic regression analysis, after adjustment for age and sex, having low or intermediate SMI were associated with an increased likelihood of having higher NAR score (estimate = 1.59, 95% CI = 0.48-2.71, p = 0.005; estimate = 1.18, 95% CI = 0.12-2.24, p = 0.03) (Table 2).

Clinical outcomes and the prognostic role of the NAR score

Median duration of the follow-up was 32 months. Local or distant

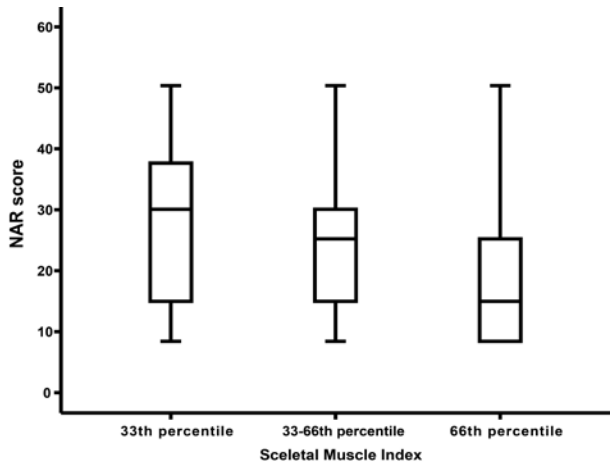

Figure 3: Comparison of the neoadjuvant rectal (NAR) score according to skeletal muscle index (SMI) of patients. The Kruskal-Wallis one-way analysis of variance showed that there were significant differences in NAR score only between high and intermediate (18.8 ± 4.4 *vs.* 25.7 ± 4.8; p=0.044) and high and low SMI (18.8 ± 4.4 *vs.* 28.5 ± 5.2; p=0.007).

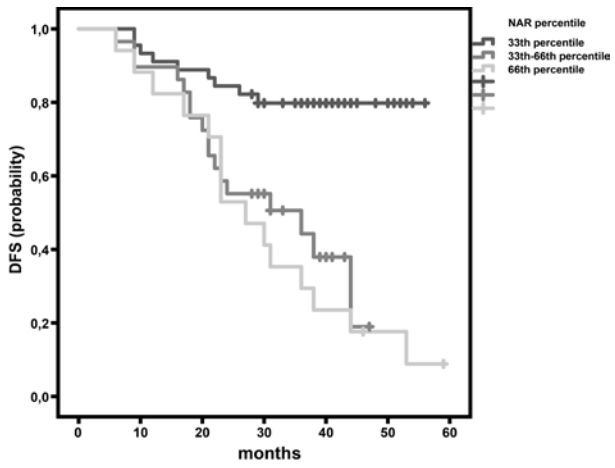

Figure 4: Kaplan-Maier estimates of disease free survival (DFS). DFS of patients with high, intermediate and low levels of neoadjuvant rectal score (NAR) score were compared. Patients with low NAR score had a significantly longer mean DFS (48.2 months; 95% CI 43.50-52.83) than patients with intermediate and high NAR score (31.01 months; 95% CI 25.99-36.18; 29.88 months; 95% CI 22.48-37.27 respectively; log-rank test p<0.001).

recurrence occurred in 41 (45%) patients. Patients with low NAR score had a significantly longer mean DFS (48.2 months; 95% CI= 43.50 - 52.83) than patients with intermediate and high NAR score (31.01 months; 95% CI= 25.99 - 36.18; 29.88 months; 95% CI= 22.48 - 37.27 respectively; log-rank test p<0.001) (Figure 4).

Discussion

In the present study, we confirmed the potential prognostic role of the NAR score in patients with locally advanced RC. Moreover, we found for the first time an association between the levels of SMI and NAR score. This may allows the clinician to identify patients at risk for poor response to nCCRT. Body mass index (calculated as weight in kilograms divided by the height in meters squared) is the most common measure of body size in cancer patients, and its associations with survival have shown controversial results [21]. This is thought to be due to the inability of this method to discriminate between muscle and adipose tissue, which have different impacts on survival [21]. Thus, the measurement of sarcopenia *via* computed tomography (CT) scan at the L3 position was introduced in the clinic [16,22-31].

Sarcopenia is a syndrome characterized by the loss of both muscle mass and muscle function, a reduction in quality of life, and resulting in physical disability and even death [13]. Although there are differences in the definitions used for cachexia and sarcopenia, they are often indistinguishable in clinical practice, and cachexia and its key feature inflammation can lead to sarcopenia [32]. Cancer-associated cachexia is a well-known negative prognostic marker, with an incidence of up to 40% in the cancer population [33]. An interval measurement of low skeletal muscle at the level of the L3 vertebra on CT was reported to have negative outcomes after colorectal cancer surgery [34]. It is not yet fully understood how sarcopenia results in such negative outcomes. A study by Takeda et al. established an adverse effect of sarcopenia on survival in rectal cancer patients who received nCCRT [15]. However, their extensive study did not specify the number of patients with pathological complete response, which may be associated with survival.

Cancer patients are particularly likely to develop sarcopenia because of the catabolic change in proteins caused by excessive inflammatory reactions and their poor nutrition status, due to hypermetabolism and appetite loss. Thus, the association between sarcopenia and cancer has recently received a great deal of attention. Previous studies have shown that sarcopenia is associated with postoperative complications and a poor prognosis in various carcinomas [35-40].

There are data connecting the clinical impact of the NAR score and the prognostic value with the pathological stage after nCCRT. Thus, the NAR score was proposed as a clinical trial surrogate endpoint using only the cT stage, pT stage, and pN stage according to the Valentini nomogram for OS [18,20]. In the NSABP R-04 trial patients with a low NAR score were reported to show a better 5-year OS [41]. George et al. demonstrated that the pT stage and pN stage are potentially influenced by nCCRT, and tumor downstaging is more important than the absolute pathological stage [18].

Sarcopenia is a negative marker for the achievement of pCR in post - nCCRT surgery among patients with non-metastatic locally advanced rectal cancer [14,15]. This finding suggests that the SMI of patients upon initial diagnosis is an important factor in oncologic outcomes. CT was also found to be a beneficial option for the establishment of a sarcopenia diagnosis [13].

Some earlier studies have indicated that sarcopenia has a negative effect on disease-free survival and overall survival, although the rate of response to neoadjuvant therapy has never been discussed [14,15]. Globally, nCCRT has become the standard treatment for locally advanced rectal cancer. The NAR score had predictive value than pathological response, and it could help in predicting DFS in local advance rectal cancer patients after nCCRT [42]. Nevertheless, the NAR score alone may not be the most suitable prognostic factor for local advance rectal cancer [43-45]. Song et al. demonstrated that the prognostic value of the tumor regression grade remained significant, even after adjusting for other well-established prognostic factors,

such as the pN stage, in multivariate analysis [46].

Several limitations were identified in our study. First, our study was single center, retrospective and had a relatively small sample size; therefore, there is a potential for biases. It was underpower for robust survival analysis; therefore our results are only hypothesis generating and need to be confirmed. Moreover, not all authors accept NAR score as a valid surrogate endpoint [41,47-49].

Despite these limitations, our study proposes for the first time that SMI may be used to select the "fragile" patients, who are at the higher risk to respond poorly to radiotherapy. This may help clinicians to select appropriately patients for surgery or radiotherapy.

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