Muscle wasting and survival following pre-operative chemoradiotherapy for locally advanced rectal carcinoma.

Running title: Muscle wasting during NACRT for LARC

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Abstract

Background & Aims Neoadjuvant chemoradiotherapy (NACRT) has increased local control in locally advanced rectal cancer. Reduced skeletal muscle mass (sarcopenia), or ongoing muscle wasting, is associated with decreased survival in cancer. This study aims to assess the change in body composition during NACRT and its impact on outcome using computed tomography (CT) imaging in locally advanced rectal cancer (LARC) patients.

Methods LARC patients treated with NACRT were selected from a prospectively maintained database and retrospectively analyzed. One-hundred twenty-two patients who received treatment between 2004 and 2012 with available diagnostic CT imaging obtained before and after NACRT were identified. Cross-sectional areas for skeletal muscle was determined, and subsequently normalized for patient height. Differences between skeletal muscle areas before and after NACRT were computed, and their influence on overall and disease-free survival was assessed.

Results A wide distribution in change of body composition was observed. Loss of skeletal muscle mass during chemoradiotherapy was independently associated with disease-free survival (HR0.971; 95% CI:0.946 – 0.996; p =0.025) and distant metastasis-free survival (HR0.942; 95% CI:0.898 – 0.988; p =0.013). No relation was observed with overall survival in the current cohort.

Conclusions Loss of skeletal muscle mass during NACRT in rectal cancer patients is an independent prognostic factor for disease-free survival and distant metastasis-free survival following curative intent resection.

Introduction

Colorectal cancer is the third most common malignancy among male and second most common malignancy among female patients worldwide. [1] It is a leading cause of cancer death in more developed countries. Rectal cancer accounts for up to 30% of all colorectal malignancies. For patients with locally advanced rectal cancer, neoadjuvant chemoradiotherapy (NACRT) combined with total mesorectal excision (TME) is considered best available treatment. [2, 3]

Recently, sarcopenia (muscle wasting) has been described as a potent prognostic marker in gastrointestinal and hepatopancreatobiliary malignancies. [4-15] Sarcopenic patients, i.e. patients with a lesser quantity of muscle mass, have an increased risk for early death. Age, cancer cachexia and oncological treatment may contribute to this state of low muscle mass. [16-18] Interestingly, NARCT itself has been reported to reduce skeletal muscle mass in esophagogastric cancer patients. [16] Another study confirmed these findings, and furthermore showed that greater loss of muscle mass during neoadjuvant treatment is associated with an increased risk of postoperative mortality. [19] Likewise, in non-resectable colorectal cancer patients, skeletal muscle loss after systemic chemotherapy is an independent, negative prognostic factor. [20] Interventions to stop or even reverse progressive muscle wasting in patients undergoing potentially curative anti-cancer therapy are currently being investigated and would, if found, provide new strategies in the management of cancer patients.

To this moment, the impact of NACRT on body composition in patients with locally advanced rectal cancer (LARC) has not yet been described. Therefore, in the current study we aim to (1) investigate whether NACRT induces a change in body composition in LARC patients, (2) assess the impact of change in body composition during NACRT on outcome (i.e. short-term outcome, overall survival, disease-free survival, and development of distant metastases).

Methods

Patients

All histologically confirmed, LARC patients who underwent NACRT and TME in the Erasmus MC Cancer Institute, a tertiary referral center in the Netherlands for locally advanced and stage IV colorectal cancer, between August 2004 and December 2012 289 patients were enrolled in a prospectively maintained database and retrospectively analyzed. The study protocol was approved by medical ethical committee of the Erasmus MC, University Medical Center, Rotterdam, The Netherlands (MEC-2017-239). LARC was defined as T3 or T4 rectal tumors (i.e. tumors located ≤ 15 cm of the anal verge as determined by MRI and colonoscopy) with clinical suspicion of narrow or involved circumferential resection margins (CRM) with or without potentially malignant lymph nodes, or rectal tumors with potentially malignant lymph nodes outside the TME plane, as previously described. [21] Collected data included details on patient age, gender, body-mass index (BMI), comorbidities, cancer stage, carcinoembryonic antigen (CEA), surgical and chemoradiotherapeutic treatment, clinical response rate, recurrence and survival. From the initial 289 patients, 122 patients received abdominal computed tomography (CT) imaging before standardized preoperative chemoradiotherapy (preCRT), and a restaging CT scan (postCRT) to identify any possible previously non-detectable distant metastases, according to local protocol. [22] Only patients with adequate preCRT and postCRT scans were considered eligible for inclusion in the current study.

Preoperative chemoradiotherapy and surgical resection

All patients received preoperative chemoradiation therapy as a long course (50 Gy) delivered in 25 fractions in accordance to the Dutch guidelines, i.e. chemoradiotherapy for rectal cancer classified as

LARC. Capecitabine (825 mg/m^2) was administered orally twice a day during radiotherapy days, and radiotherapy was administered via a three-field technique, using one posterior and two lateral portals, a four-field box or with five fields using intensity modulated radiotherapy. [23]

TME was performed after completing chemoradiation, if considered eligible for resection. A midline laparotomy was carried out in all patients. A primary anastomosis was performed whenever possible. A diverting ileostomy was created at the discretion of the treating physician. In T4 tumors involving the sphincter apparatus after NACRT, an abdominoperineal resection was performed. In T4 tumors involving adjacent structures after NACRT (e.g. prostate, uterus, bladder) these were resected simultaneously. Intraoperative radiotherapy was applied if the circumferential resection margin (CRM, ≤ 2 mm) was considered to be at risk. [24]

Postoperative follow-up

Patients follow up was done on an outpatient basis by periodic six months CT imaging or abdominal ultrasonography during the first two postoperative years, followed by yearly imaging for the remainder of the follow-up. Serum CEA determination was done at intervals of three to six months during the first three years of follow-up, and subsequently every six months during the final years of follow-up. Patients were followed up for at least 5 years in case of no recurrence. None of the patients were treated with adjuvant chemotherapy according to the Dutch guidelines. The national civil registry was consulted for definitive survival data.

Assessment of body composition

Body composition was measured on standard diagnostic CT scans with FatSeg version 4.0 (Erasmus MC – BIGR, Rotterdam, Netherlands). Cross-sectional areas (cm^2) of skeletal muscle mass was measured at the level of the third lumbar vertebrae as previously described. [15]

Statistical analysis

Continuous data are presented as mean ± SD or median (IQR) as appropriate. Categorical data are presented as number counts and percentages. The Student's *t*-test was used for assessment of differences between groups for continuous variables. The χ^2 or Fisher's exact test was used for assessment of differences between groups for categorical variables where appropriate. Skeletal muscle mass was normalized for patient height (skeletal muscle index [SMI]). Paired *t*-test was used for the between group comparisons of continuous variables for SMI on preCRT and postCRT scans. Relative change in cross-sectional areas (Δ CSA = postCRT / preCRT) were computed for SMI. Gender specific tertiles were determined for Δ SMI. Overall and disease-free survival rates were calculated using the non-parametric Kaplan–Meier method and subsequently compared with the log rank test. Univariate and multi-variable Cox regression analyses were performed to investigate the association between Δ SMI and survival. Hazard Ratios (HR) with 95% confidence intervals (95% CI) were computed. Furthermore, age, gender, diabetes, BMI, tumor location, CEA, surgical procedure, intraoperative radiotherapy, pathologic T-, N- and M- stage, circumferential resection margin, and pathologic complete response were included in the univariate Cox regression analysis. These variables were checked for interaction and confounding. They were subsequently included in the multivariable model if a p-value < 0.05 was found in univariate analysis.

All statistical analyses were performed using SPSS version 21.0 (SPSS, Chicago, Illinois, USA). A p-value < 0.05 was considered statistically significant.

Results

Clinical characteristics and body composition

One hundred and twenty-two patients, with a median follow-up of 41 months (IQR 26 – 62) were eligible for inclusion (Table 1). During the follow-up period, 50 (41.0%) patients developed recurrent or metastatic disease, and 35 patients (28.7%) died. Forty (32.8%) patients had metastatic disease at onset of NACRT. Twenty-nine (23.8%) patients were treated by liver first approach. [25, 26] Eleven patients underwent synchronous resection. In the studied population, median length of hospital stay was 8 (IQR: 7 – 11) days.

Abdominal CT-imaging was obtained at median 48 (IQR: 35 – 65) days prior to onset of NACRT. Restaging scans were obtained at a 28 (IQR: 21.5 – 39.5) days after completion of NACRT. Following NACRT, mean skeletal muscle index (SMI) remained unchanged. Despite minimal changes in the mean SMI, a wide distribution in change of body composition was observed.

Loss of muscle mass and disease stage

After NACRT, lower SMI was found in patients with cT4 tumours when compared to patients with cT3 tumours (48.1 ± 8.3 versus 44.7 ± 8.2, p = 0.024). No association between clinical disease stage and Δ SMI was observed.

For analytical purposes, gender-specific tertiles for Δ SMI were created (< -1.95%; -1.95% – 1.84%; > 1.84% for male patients and < -4.53%; -4.53% – 1.90%; > 1.90% for female patients). Comparing patients in the obtained tertiles for Δ SMI, no differences in patient demographic and clinical characteristics (i.e. age, gender, BMI, clinical TNM staging, CEA, tumor height, surgical procedure, and

IORT), pathologic TNM staging, pathologic CRM, and pathologic complete response were observed. There was a weak negative relationship between pre-NACRT SMI and Δ SMI (Pearson's r: -0.254; p = 0.005), i.e. patients with a higher quantity of muscle mass prior to NACRT experienced greater loss of muscle mass. Vaso-invasion was present in 10 (31.2%) patients in the lower tertile, 3 (8.8%) in the middle tertile, and in 3 (9.4%) patients in the upper tertile for Δ SMI respectively (p = 0.021).

Overall survival

The one-, three-, and five-year overall survival (OS) rates in the current cohort were 93%, 77%, and 69% respectively. A median survival time was not reached. Patients in the lower tertile for Δ SMI had one-, three-, and five-year OS rates of 95%, 68%, and 68% respectively; patients in the middle tertile for Δ SMI had one-, three-, and five-year OS rates of 95%, 82%, and 65%; and patients in the higher tertile for Δ SMI had one-, three-, and five-year OS rates of 90%, 80%, and 74% (Figure 1, log-rank p = 0.520).

Additionally, gender-specific cut-off values for sarcopenia as previously reported in literature were investigated for their impact on overall survival. [17] No association could be found between sarcopenia pre-operatively (i.e. using the post-NACRT CT scan) and OS (HR: 1.313; 95% CI: 0.675 – 2.551; p = 0.422) or sarcopenia pre-NACRT and OS (HR 1.183; 95% CI: 0.607 – 2.305; p = 0.621).

Disease-free survival

The one-, two-, and three- -year disease-free survival (DFS) rates were 72%, 62%, and 57% respectively. Eight (6.6%) patients developed local recurrence, and 46 (37.7%) patients developed distant metastases. A median DFS time was not reached. An association was observed between Δ SMI and DFS in log-rank analysis (Figure 2) and in multivariable analysis (HR 0.971; 95% CI: 0.946 – 0.996; p = 0.025). Moreover,

analysis of patients without evidence of metastatic disease at presentation revealed that Δ SMI was an independent predictor for the development of distant metastases following curative intent treatment in multivariable Cox-regression analysis (HR 0.942; 95% CI: 0.898 – 0.988; p = 0.013) (Table 3). The one-, three-, and five-year DMFS rates were 74%, 51%, and 51% respectively for patients in the lowest tertile for Δ SMI, compared with 77%, 73%, and 73% respectively for patients in the middle tertile for Δ SMI, and 100%, 92%, and 85% respectively for patients in the upper tertile for Δ SMI (Figure 3).

There was no association between pre-operative sarcopenia and DFS using pre-defined cut-off values (HR: 1.153; 95% CI: 0.662 – 2.009; p = 0.615). Likewise, there was no association between pre-NACRT sarcopenia and DFS (HR 0.910; 95% CI: 0.521 – 1.592; p = 0.742).

Discussion

This study describes the change in body composition which may be observed in patients undergoing NACRT for locally advanced rectal cancer. This is the first study to show that loss of muscle mass during NACRT, assessed by use of routinely obtained diagnostic CT images, has a strong association with disease-free survival and distant metastasis-free survival. This technique is inexpensive, readily available, and may thus help identify patients at risk for detrimental outcome. The results of this study may be used to determine inclusion criteria for future clinical studies investigating treatment regiments aimed at stopping or reversing muscle loss in cancer patients, as well as for future clinical studies investigating follow-up regiments following curative intent rectal cancer surgery.

A wide variation was observed in the amount of muscle loss during NACRT. As such, tumor biology rather than NACRT per se is more likely to be the causative factor inducing this catabolic state. Opposed to what we expected, we did not observe any association between disease-stage and the amount of muscle loss during NACRT. However, we did observe an association between vascular invasion and muscle loss during NACRT. Colorectal cancer is known to be associated with different molecular subtypes, with no association to TNM staging. [27] Select molecular subtypes may be associated with a more aggressive tumor biology and stronger systemic catabolic response. A study investigating the association between colorectal cancer genotyping and muscle wasting is currently being undertaken by our research group.

Skeletal muscle loss during NACRT was associated with poor disease-free survival, and a higher risk of developing distant metastasis during follow-up in the current population. These findings are in line with prior literature on esophageal cancer and non-resectable colorectal cancer patients. [19, 20] Another study showed that loss of muscle mass during NACRT is associated with increased postoperative mortality following surgical resection for esophageal cancer. [19] Yet another study reported non-

resectable colorectal cancer patients receiving systemic therapy to have a reduction in both progression-free survival and overall survival if skeletal muscle loss was observed during treatment. [20] While loss of muscle mass during NACRT was strongly associated with DFS and DMFS, single time point measurements for sarcopenia that are widely used were not predictive of survival in the current population.

Despite mounting evidence for sarcopenia and muscle wasting to be associated with poor survival and decreased quality of life [28, 29], it is still unknown whether targeted treatment of muscle wasting may improve outcome. Over the past decade our understanding of muscle wasting in cancer has greatly increased [30, 31], and has led to the initiation of clinical trials investigating interventional strategies aimed at halting or reversing cancer related muscle wasting. [32-35] Whether these treatment regimens are efficacious remains to be answered, but if so the interval between chemoradiotherapy and surgery might offer a perfect window of opportunity to improve the overall condition of LARC patients.

There are several limitations to this present study, some of which have already been described. Information regarding change of bodyweight was not gathered routinely in this cohort. Furthermore, information regarding possible lack of appetite, anorexia, was not available on a consistent basis. Likewise, no information regarding physical status and performance was available for these patients. Lastly, although suggestively differences in tumor biology may explain the findings reported within this study, validating this hypothesis was not within the scope of the current study. Data regarding vaso-invasion, perineural growth, and lymphoinvasion was missing for a considerable number of patients. Due to consequential loss of power we did not include these prognostic factors in our multivariable analyses.

Conclusions

This study found loss of skeletal muscle mass during, but not necessarily attributable to, neoadjuvant chemoradiotherapy in resectable rectal cancer patients to be a novel independent prognostic factor for disease-free survival and distant metastasis-free survival following total mesorectal excision. This knowledge may benefit in patient expectation management following curative intent treatment, as well as provide grounds for future clinical studies investigating whether there may be a role for adjuvant therapy in patients showing greatest loss of muscle mass, i.e. who were found to have the highest rate of metastasis development.

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Conflict of interest All authors declare they have no conflict of interest.

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Table 1. Baseline Demographic and Clinical characteristics of the 122 Patients Included in the Study

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		Number of patients	Median (IQR)
Age (years)			61 (53.0 – 66.3)
Gender (M : F)		71 : 51 (58.2% : 41.8%)	
Cardiac comorbidity (excluding hypertension)		10 (8.2%)	
Respiratory comorbidity		19 (15.6%)	
Diabetes		14 (11.5%)	
BMI (kg/m^2)*			24.3 (22.0 – 26.8)
Tumor location (cm)*	< 6	60 (49.6%)	
	≥ 6	61 (50.4%)	
CEA (ng/mL)*	< 5	32 (43.2%)	
	≥ 5	42 (56.8%)	
Clinical T-stage*	T3	65 (53.7%)	
	T4	56 (46.3%)	
Clinical N-stage*	N-	25 (20.7%)	
	N+	96 (79.3%)	
Clinical M-stage*	M0	82 (67.2%)	
	M1	40 (32.8%)	
Time interval between NACRT and resection (days)			70 (62.5 – 84.5)
Pathologic T-stage*	ypT0	25 (20.7%)	
	ypT1	4 (3.3%)	
	ypT2	16 (13.2%)	
	ypT3	52 (43.0%)	
	ypT4	24 (19.8%)	
Pathologic N-stage*	ypN0	84 (69.4%)	
	ypN1	25 (20.7%)	
	ypN2	12 (9.9%)	
Pathologic M-stage	ypM0	83 (68.0%)	
	ypM1	39 (32.0%)	
CRM	R0	100 (82.0%)	
	R1	20 (16.4%)	
	R2	2 (1.6%)	
Vaso-invasion*	No	82 (83.7%)	
	Yes	16 (16.3%)	
Perineural growth*	No	82 (83.7%)	
	Yes	16 (16.3%)	
Lymphoinvasion*	No	60 (95.2%)	
	Yes	3 (4.8%)	
Surgical procedure (all open procedures)	LAR	45 (36.9%)	
	APR	45 (36.9%)	
	Pelvic exenteration	32 (26.2)	
Intraoperative radiotherapy		16 (13.1%)	
SMI pre-NACRT (cm^2/m^2)			46.6 (41.2 – 53.4)
SMI post-NACRT (cm^2/m^2)			46.9 (40.2 – 53.1)

*Data missing for some patients. M : F: Male : Female. BMI: Body-mass index. CEA: Carcinoembryonic antigen. SMI: Skeletal muscle index assessed at the third lumbar vertebrae, and standardized for patient height. NACRT: Neo-adjuvant chemoradiotherapy. CRM Circumferential resection margin, an R1 resection was defined as a circumferential resection margin < 2mm.

Table 2. Univariate and Multivariate Cox Regression Analysis for Disease-Free Survival

		Univariate analysis		Multivariable analysis	
		Hazard Ratio	*P*	Hazard Ratio	*P*
Gender	Male	1.00 (reference)			
	Female	1.04 [0.59 – 1.81]	0.899		
Age	Per year	0.98 [0.96 – 1.00]	0.089		
Diabetes	No	1.00 (reference)			
	Yes	0.52 [0.16 – 1.68]	0.278		
Δ SMI	Per 1% change	0.96 [0.94 – 0.99]	**0.004**	0.97 [0.95 – 1.00]	**0.025**
BMI	Per kg/m^2	1.04 [0.97 – 1.12]	0.238		
Tumor location (cm)	< 6	1.00 (reference)			
	≥ 6	0.85 [0.48 – 1.48]	0.557		
CEA (ng/mL)	< 5	1.00 (reference)			
	≥ 5	1.56 [0.76 – 3.20]	0.223		
Surgical procedure	LAR	1.00 (reference)			
	APR	1.38 [0.71 – 2.70]	0.342		
	Pelvic exenteration	1.79 [0.87 – 3.67]	0.111		
Intraoperative radiotherapy	No	1.00 (reference)			
	Yes	2.11 [1.05 – 4.22]	**0.035**	1.44 [0.47 – 4.39]	0.523
Pathologic T-stage	ypT0 – ypT3	1.00 (reference)			
	ypT4	2.10 [1.13 – 3.89]	**0.019**	1.23 [0.56 – 2.71]	0.608
Pathologic N-stage	ypN0	1.00 (reference)			
	ypN1 or ypN2	2.44 [1.38 – 4.30]	**0.002**	1.85 [1.01 – 3.40]	**0.047**
CRM	R0	1.00 (reference)			
	R1 or R2	2.19 [1.17 – 4.13]	**0.015**	1.04 [0.37 – 2.94]	0.944
PCR	Yes	1.00 (reference)			
	No	3.72 [1.34 – 10.35]	**0.012**	2.75 [0.92 – 8.20]	0.069

BMI: Body-mass index. CEA: Carcinoembryonic antigen. SMI: Skeletal muscle index assessed at the third lumbar vertebrae, and standardized for patient height. NACRT: Neo-adjuvant chemoradiotherapy. CRM Circumferential resection margin. PCR Pathological complete response.

Table 3. Univariate and Multivariate Cox Regression Analysis for Distant Metastasis-Free Survival in Patients without Evidence of Metastatic Disease at Presentation

		Univariate analysis		Multivariable analysis	
		Hazard Ratio	*P*	Hazard Ratio	*P*
Gender	Male	1.00 (reference)			
	Female	1.38 [0.58 – 3.27]	0.469		
Age	Per year	0.98 [0.95 – 1.02]	0.274		
Diabetes	No	1.00 (reference)			
	Yes	0.04 [0.00 – 21.38]	0.319		
Δ SMI	Per 1% change	0.93 [0.88 – 0.98]	**0.007**	0.94 [0.90 – 0.99]	**0.013**
BMI	Per kg/m^2	1.10 [0.99 – 1.22]	0.084		
Tumor location (cm)	< 6	1.00 (reference)			
	≥ 6	0.42 [0.16 – 1.09]	0.073		
CEA (ng/mL)	< 5	1.00 (reference)			
	≥ 5	1.31 [0.42 – 4.10]	0.638		
Surgical procedure	LAR	1.00 (reference)			

	APR	1.80 [0.60 – 5. 37]	0.294		
	Pelvic exenteration	2.09 [0.66 – 6.60]	0.209		
Intraoperative radiotherapy	No	1.00 (reference)			
	Yes	2.61 [0.96 – 7.14]	0.061		
Pathologic T-stage	ypT0 – ypT3	1.00 (reference)			
	ypT4	1.90 [0. 73 – 4.89]	0.186		
Pathologic N-stage	ypN0	1.00 (reference)			
	ypN1 or ypN2	3.68 [1.56 – 8.69]	**0.003**	3.49 [1.46 – 8.35]	**0.005**
CRM	R0	1.00 (reference)			
	R1 or R2	2.32 [0.90 – 5.98]	0.082		
PCR	Yes	1.00 (reference)			
	No	29.94 [0.37 – 2424.34]	0.129		

BMI: Body-mass index. CEA: Carcinoembryonic antigen. SMI: Skeletal muscle index assessed at the third lumbar vertebrae, and standardized for patient height. NACRT: Neo-adjuvant chemoradiotherapy. CRM Circumferential resection margin. PCR Pathological complete response.

Figure 1. Loss of skeletal muscle mass during neoadjuvant chemoradiotherapy does not affect overall survival in rectal patients following surgical resection (log rank test p = 0.520).

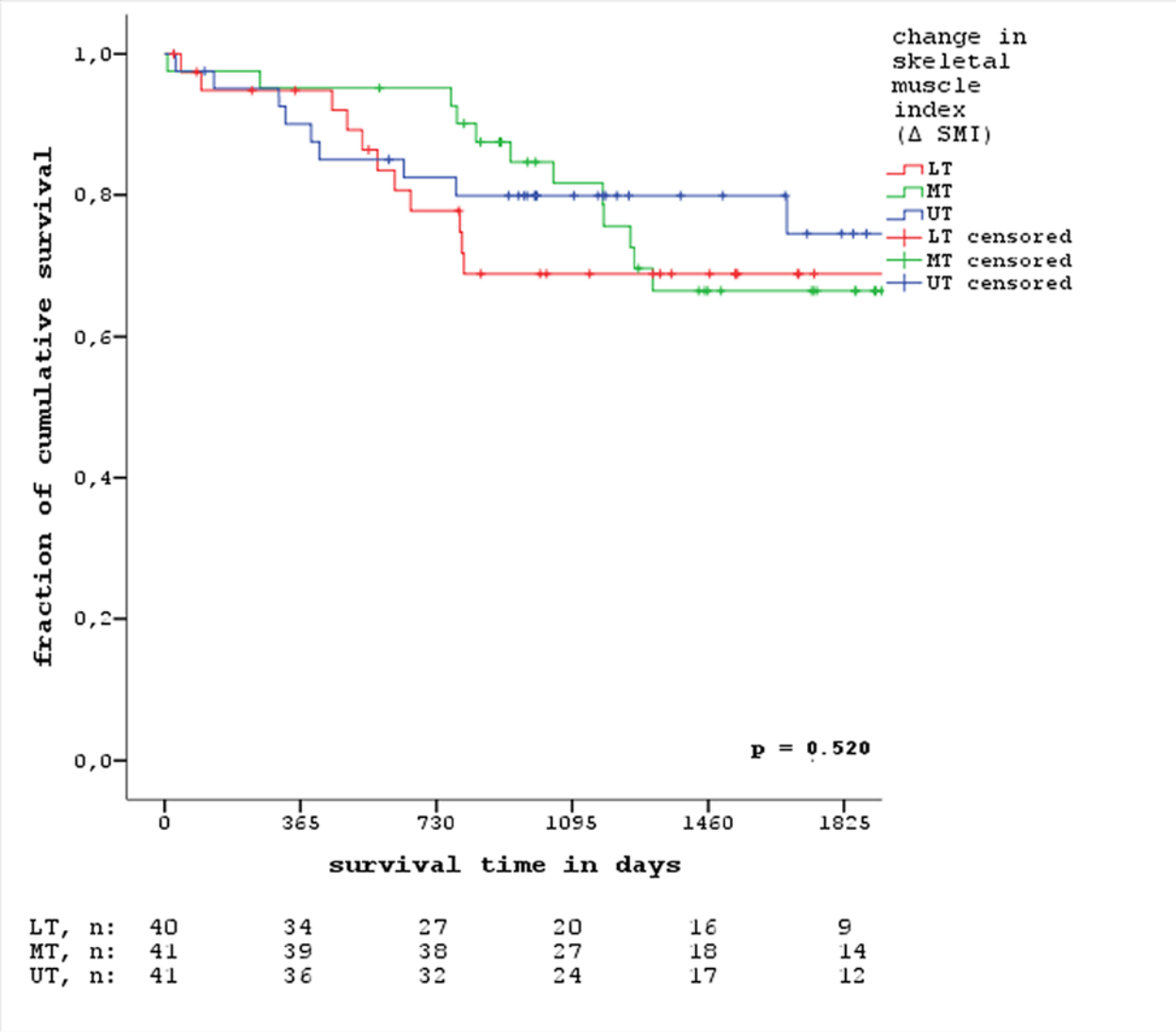

Figure 2. Loss of skeletal muscle mass during neoadjuvant chemoradiotherapy is associated with impaired disease-free survival in rectal cancer patients following surgical resection (log-rank p = 0.027).

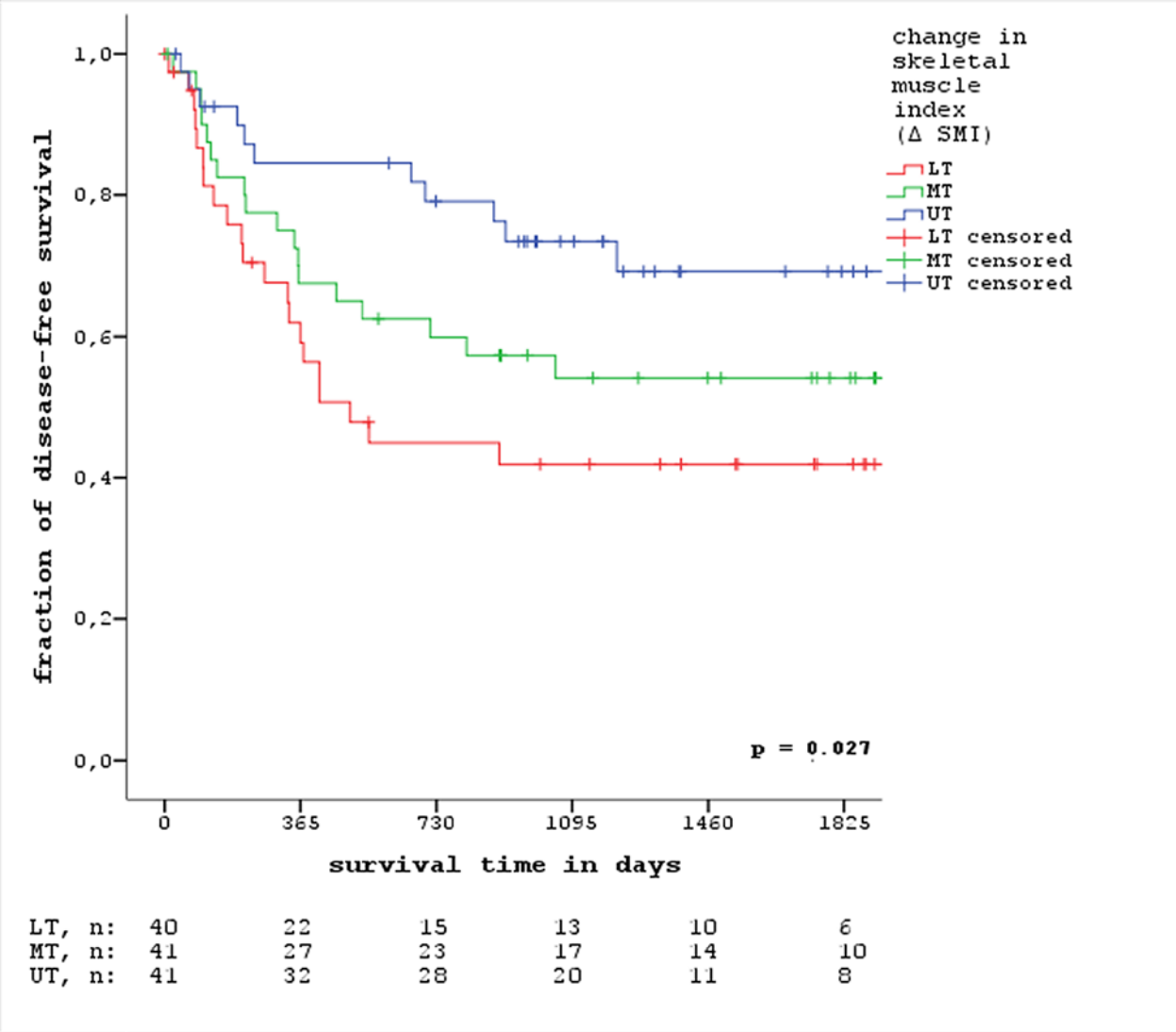

Figure 3. Loss of skeletal muscle mass during neoadjuvant chemoradiotherapy is associated with the development of distant metastases following curative intent treatment in patients without evidence of metastatic disease at presentation (log-rank p = 0.009).