ORIGINAL ARTICLE

European Journal of BREAST HEALTH

DOI: 10.4274/ejbh.galenos.2026.2026-6-5
Eur J Breast Health 2026;22(4):485-493

Predictive Value of CT-Derived Skeletal Muscle Metrics for Pathologic Complete Response in Breast Cancer Patients Receiving Neoadjuvant Chemotherapy

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ABSTRACT

Objective: To investigate the predictive value of computed tomography (CT)-derived body composition parameters for pathological complete response (pCR) in breast cancer patients receiving neoadjuvant chemotherapy (NAC).

Materials and Methods: Female patients who received NAC between January 2010 and December 2022 were retrospectively evaluated. Skeletal muscle index (SMI) and muscle density [mean Hounsfield unit (HU)] were measured at the L3 vertebral level on pretreatment CT. Clinicopathological variables, including molecular subtype, histological grade, and clinical stage, were recorded. Treatment response was categorized as pCR or non-pCR. Univariate and multivariate logistic regression analyses were performed to identify independent predictors of pCR. Receiver operating characteristic (ROC) analysis was used to assess the predictive performance of SMI and HU.

Results: A total of 365 patients (mean age, 50.2±11.79 years) were included, and pCR was achieved in 27.9% of cases. Molecular subtype was the strongest independent predictor of treatment response, with the highest pCR rates observed in HER2-positive tumors and the lowest in luminal tumors. Histological grade was associated with pCR in univariate analysis but lost significance in multivariate analysis. Neither SMI nor HU independently predicted pCR. Additional analyses according to molecular subtype demonstrated no significant associations between SMI, HU, and treatment response in luminal, HER2-positive, or triple-negative breast cancer subgroups. ROC analyses showed poor discriminatory performance of both parameters in the overall cohort and subtype-specific analyses (area under the curve range, 0.477–0.565).

Conclusion: Molecular subtype remains the primary predictor of treatment response following NAC. In contrast, CT-derived SMI and muscle density showed no predictive value for pCR in either the overall cohort or molecular subtype-specific analyses, suggesting that tumor biology plays a more dominant role than body composition in determining treatment response.

Keywords: Breast carcinoma; neoadjuvant chemotherapy; computed tomography; skeletal muscle index; body composition

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Received: 14.06.2026 **Accepted:** 29.08.2026 **Available Online Date:** 23.09.2026
Cite this article as: Rona G, Özdal Sayer A, Yıldırım S, Odabaş H, Doğan B, Kökten Ş. Predictive value of CT-derived skeletal muscle metrics for pathologic complete response in breast cancer patients receiving neoadjuvant chemotherapy. Eur J Breast Health. 2026;22(4):485-493

KEY POINTS

- Computed tomography (CT)-derived skeletal muscle index and muscle density did not predict pathological complete response, either in the overall cohort or within individual molecular subtypes.
- CT-derived body composition parameters, including skeletal muscle index and muscle density, are not associated with treatment response.
- Body mass index and skeletal muscle index may reflect similar biological characteristics, while muscle density reflects muscle quality as a distinct parameter.

Introduction

Breast cancer is the most common malignancy among women worldwide and remains one of the leading causes of cancer-related morbidity and mortality (1, 2). Neoadjuvant chemotherapy (NAC) is widely used, particularly in locally advanced and selected early-stage breast cancers, to reduce tumor size, facilitate breast-conserving surgery, and evaluate treatment response (3, 4). Pathological complete response (pCR) achieved after NAC is an important prognostic marker and has been strongly associated with long-term survival in selected patient groups (5-7).

Identifying factors that can predict treatment response is of great importance for patient selection and the development of personalized treatment strategies. Among the predictive factors, molecular subtypes reflecting tumor biology are known to play a fundamental role in determining response to NAC. Higher pCR rates have been reported particularly in HER2-positive and triple-negative subtypes, whereas response rates are lower in luminal subtypes (7-10). In addition, not only tumor-related characteristics but also factors such as age, tumor grade, clinical stage, and Ki-67 are thought to influence treatment response (11-14).

Computed tomography (CT)-based measurements, including skeletal muscle index (SMI) and mean muscle density [Hounsfield unit, (HU)], provide objective information regarding muscle quantity and quality (15). Sarcopenia and low muscle density have been associated with poor prognosis, increased toxicity, and decreased survival in various cancer types (16). However, studies investigating the effect of these parameters on response to NAC in breast cancer have reported inconsistent results (17-24).

Particularly regarding pCR, the contribution of body composition remains unclear. Therefore, the role of CT-based muscle parameters in predicting treatment response compared with molecular and clinical factors should be evaluated in greater detail.

The aim of this study was to investigate the factors affecting pCR in breast cancer patients receiving NAC and, in particular, to evaluate the predictive value of CT-based body composition parameters, including SMI and muscle density, in this process.

Materials and Methods

Ethics

This retrospective study was approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (approval no. 2024/010.99/9/12, date: 25.10.2024), and the requirement for informed consent was waived.

Study Population

Female patients diagnosed with invasive breast cancer and treated with NAC between January 2010 and December 2022 were retrospectively evaluated. A total of 519 consecutive patients were initially identified. Patients were excluded if they were male (n = 3), had no pretreatment positron emission tomography (PET)/CT examination (n = 57), had CT images with artifacts precluding accurate body composition measurements (n = 10), had metastatic disease at diagnosis (n = 32), or had incomplete clinicopathological or pathological response data (n = 52). The final study population consisted of 365 female patients.

Clinical Data

Patient data including age, weight, height, body mass index (BMI), menopausal status, histological subtype, molecular subtype, treatment protocol, and pathological treatment response were retrieved from hospital records. Estrogen (ER) and progesterone (PR) positivity were defined as nuclear staining in ≥1% of tumor cells according to American Society of Clinical Oncology/College of American Pathologists recommendations. HER2 status was determined by immunohistochemistry (IHC), and cases with an equivocal (2+) IHC result were further evaluated by fluorescence *in situ* hybridization (FISH). HER2 positivity was defined as IHC 3+ or IHC 2+ with *HER2* gene amplification on FISH. Molecular subtype was classified into three groups according to institutional clinical practice: triple-negative breast cancer (ER–/PR–/HER2–), HER2-positive breast cancer (HER2-positive irrespective of hormone receptor status), and luminal breast cancer (hormone receptor-positive/HER2-negative). Ki-67 expression was classified as low (<20%) or high (≥20%). ER Standard anthracycline- and taxane-based NAC regimens were administered. HER2-positive patients additionally received anti-HER2 targeted therapy according to institutional protocols, while selected triple-negative patients received carboplatin.

Adjuvant endocrine therapy was administered to hormone receptor-positive patients when indicated. Patients with clinical stage I disease received NAC when they had biologically aggressive tumors, including HER2-positive or triple-negative breast cancer, according to multidisciplinary team recommendations.

pCR was defined as the absence of residual invasive carcinoma in both the breast and axillary lymph nodes (ypT0/is ypN0), according to the College of American Pathologists classification. Residual cancer burden was not evaluated (25). Clinical nodal stage was categorized as N0 and N1–3 for statistical analysis. Missing data were not imputed. Analyses were performed using available data, and the valid number of observations is reported for each variable in the tables.

For statistical analyses, patients were categorized into pCR and non-pCR groups.

CT Analysis

Non-contrast CT images obtained from PET/CT examinations performed for pretreatment staging were used for analysis (General Electric Healthcare, Discovery IQ-5Ring). Imaging parameters were as follows: tube voltage 120 kVp, mAs 23, slice thickness 2.5 mm, and slice gap 2 mm.

Measurements were performed using Infinitt PACS software (Healthcare IT, Seoul, South Korea) on axial CT images at the L3 vertebral level, which is the most widely validated anatomical landmark for CT-based body composition assessment and correlates strongly with whole-body skeletal muscle mass. Skeletal muscle was identified using a HU threshold of −29 to +150 HU. The psoas, erector spinae, quadratus lumborum, and abdominal wall muscles were manually segmented by two radiologists with 9 and 6 years of experience, respectively. Before the measurements, the two radiologists jointly reviewed the measurement protocol and agreed on a standardized methodology. Each patient was subsequently evaluated independently by one of the two radiologists. Interobserver agreement was assessed using the intraclass correlation coefficient (ICC). Skeletal muscle area (SMA) and HU were recorded. SMI was calculated as SMA divided by height squared (cm^2/m^2) and analyzed as a continuous variable without applying a predefined sarcopenia cut-off.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 27 (IBM Corp., Armonk, NY, USA). Continuous variables were presented as mean ± standard deviation or median (minimum-maximum), while categorical variables were expressed as frequencies and percentages. Normality was assessed using the Shapiro-Wilk test.

Comparisons between two groups were performed using the independent samples t-test or Mann-Whitney U test, as appropriate. Categorical variables were compared using Pearson's chi-square test or Fisher's exact test. Correlations between continuous variables were evaluated using Spearman correlation analysis.

Binary logistic regression analysis was performed to identify factors associated with treatment response. A multivariable model including variables significant in the univariable analyses was used to identify independent clinicopathological predictors. A second hypothesis-driven model including age, clinical stage, molecular subtype, Ki-67, SMI, and HU evaluated the independent predictive value of CT-derived skeletal muscle parameters. SMI and HU were retained regardless of univariable significance because they were the primary variables of interest. Receiver operating characteristic (ROC) curve analysis assessed the discriminative performance of SMI and HU for predicting pCR. A p-value <0.05 was considered statistically significant.

Results

A total of 365 patients with a mean age of 50.2±11.79 years were included in the study. pCR was achieved in 27.95% of the patients, whereas 72.05% did not achieve pCR. The majority of the patients were overweight or obese (78.9%), and the most common tumor type was invasive ductal carcinoma (92.3%). Most tumors were grade 2–3 (94.3%). Regarding molecular subtype distribution, luminal subtype (48.8%) was the most common, followed by HER2-positive (39.7%) and triple-negative (11.5%) subtypes (Table 1). Among the 145 HER2-positive tumors, 93 (64.1%) were hormone receptor-positive and 52 (35.9%) were hormone receptor-negative. Interobserver agreement was good for SMI [ICC = 0.883, 95% confidence interval (CI): 0.753–0.944] and excellent for HU (ICC = 0.998, 95% CI: 0.996–0.999).

Comparisons according to treatment response demonstrated statistically significant associations between pCR and histological diagnosis, histological grade, and molecular subtype (Table 2). pCR rates were higher in HER2-positive tumors and lower in luminal subtypes. No significant associations were observed between pCR and age, clinical stage, Ki-67, SMI, or HU values.

In multivariate analysis including histological factors, only molecular subtype remained statistically significant, whereas histological grade lost its independent significance (Table 3).

In the final multivariate model, molecular subtype was identified as the only independent predictor of treatment response (Table 4). Using the triple-negative subtype as the reference category, the risk of non-pCR was higher in the luminal subtype [odds

ratio (OR): 4.241; 95% CI: 1.780–10.106; $p = 0.001$] and lower in the HER2-positive subtype (OR: 0.393; 95% CI: 0.180–0.859; $p = 0.019$). SMI ($p = 0.217$) and HU ($p = 0.331$) were not found to have independent effects on treatment response. Age, clinical stage, and Ki-67 were also not significant in multivariate analysis.

Table 1. Descriptive characteristics of the patients

	Statistics
Treatment response	
pCR	102 (27.95%)
Non-pCR	263 (72.05%)
Age	50.2±11.79
Menopausal	
Premenopausal	191 (52.33%)
Postmenopausal	174 (47.67%)
Family history	
No	315 (86.30%)
Yes	46 (12.60%)
Unknown	4 (1.10%)
ECOG performance	
0-1	313 (85.75 %)
≥2	50 (13.70 %)
Unknown	2 (0.55 %)
BMI	
Normal/underweight	77 (21.10%)
Overweight	118 (32.32%)
Obese	170 (46.58%)
Histological type	
Invasive ductal carcinoma	337 (92.33 %)
Invasive lobular carcinoma	17 (4.66 %)
Other	11 (3.01%)
Inflammatory breast cancer	
Yes	11 (3.02%)
No	364 (96.98%)
Histological grade	
Grade 1	20 (5.47%)
Grade 2	218 (59.73%)
Grade 3	113 (30.96%)
Unknown	14 (3.84%)
ER	
Negative	96 (26.30%)
Positive	269 (73.70%)
PR	
Negative	137 (37.53%)
Positive	228 (62.47%)
Cerb-B2	
Negative	220 (60.27%)
Positive	145 (39.73%)
Molecular subtype	
TN	42 (11.50%)
Her2	145 (39.73%)
Luminal	178 (48.77%)
Ki-67	
Low	54 (14.79%)
High	276 (75.62%)
Unknown	35 (9.59%)
Clinical T stage	
T1	99 (27.12%)
T2	222 (60.82%)
T3/4	37 (10.14%)
Unknown	7 (1.92%)
Clinical N stage	
N0	24 (6.58%)
N1-3	337 (92.32%)
Unknown	4 (1.10%)
Clinical stage	
Stage 1	43 (11.78%)
Stage 2	213 (58.36%)
Stage 3	105 (28.77%)
Unknown	4 (1.09%)
NAC regimen	
Anthracycline and taxane	343 (93.97%)
Other	22 (6.03%)
Surgical treatment	
BCS	155 (42.47%)
Mastectomy	210 (57.53%)
SMI	55.59 (29.22–97.24)
HU	26.3 (1.17–46.87)

n: Number of patients; pCR: Pathological complete response; BMI: Body mass index; ECOG: Eastern Cooperative Oncology Group, ER: Estrogen; PR: Progesterone; TN: Triple-negative; NAC: Neoadjuvant chemotherapy; BCS: Breast conserving surgery; SMI: Skeletal muscle index; HU: Hounsfield unit; %: Column percentage; continuous variables are presented as mean ± standard deviation or median (min-max)

Table 2. Comparison of variables according to treatment response

	Treatment response		Test statistics	*p*-value
	pCR (*n* = 102)	Non-pCR (*n* = 263)		
Age	49.52±10.6	50.47±12.23	0.465	0.642
Histological type			**9.222**	**0.010**
Invasive ductal carcinoma	101 (99.0%)	236 (89.7%)		
Invasive lobular carcinoma	0 (0.0%)	17 (6.5%)		
Other	1 (1.0%)	10 (3.8%)		
Histological grade			**14.488**	**0.001**
Grade 1	2 (2%)	18 (6.8%)		
Grade 2	51 (50.0%)	167 (63.5%)		
Grade 3	46 (45.1%)	67 (25.5%)		
Unknown	3 (2.9%)	11 (4.2%)		
Molecular subtype			**64.040**	**0.001**
TN	13 (12.7%)	29 (11.0%)		
Her2	72 (70.6%)	73 (27.8%)		
Luminal	17 (16.7%)	161 (61.2%)		
Ki-67			4.347	0.114
Low	9 (8.8%)	45 (17.1%)		
High	84 (82.4%)	192 (73.0%)		
Unknown	9 (8.8%)	26 (9.9%)		
Clinical stage			0.374	0.829
Stage 1	10 (9.8%)	33 (12.5%)		
Stage 2	59 (57.8%)	154 (58.6%)		
Stage 3	29 (28.4%)	76 (28.9%)		
Unknown	4 (4%)	0 (0.0%)		
SMI	55.62 (38.14–97.24)	55.59 (29.22–93.34)	0.053	0.958
HU	26.77 (6.73–46.87)	26.26 (1.17–41.92)	0.534	0.593

n: Number of patients; pCR: Pathological complete response; TN: Triple negative; SMI: Skeletal muscle index; HU: Hounsfield unit; %: Column percentage; continuous variables are presented as mean ± standard deviation or median (min-max)

Table 3. Multivariable logistic regression model including variables significant in univariable analysis

	β	Standard error	Wald	*p*	OR	95% CI for OR	
						Lower limit	Upper limit
Constant	1.572	0.851	3.411	0.065	4.817		
Grade 1			5.765	0.056			
Grade 2	-0.367	0.807	0.206	0.650	0.693	0.142	3.374
Grade 3	-1.018	0.816	1.555	0.212	0.361	0.073	1.789
TN			46.099	**0.001**			
Her2	-0.949	0.401	5.595	**0.018**	0.387	0.176	0.850
Luminal	1.182	0.453	6.803	**0.009**	3.260	1.341	7.922

Variables entered in step 1: histological grade, and molecular subtype. Outcome variable: non-pCR (reference category: pCR). Reference categories: Grade 1 and triple-negative subtype. β: Regression coefficient; CI: Confidence interval; TN: Triple negative; OR: Odds ratio; pCR: Pathological complete response

Table 4. Final multivariable logistic regression model evaluating the independent predictive value of CT-derived skeletal muscle parameters for treatment response

	β	Standard error	Wald	*p*	OR	95% CI for OR	
						Lower limit	Upper limit
Constant	3.224	1.400	5.304	0.021	25.132		
Age	0.001	0.013	0.000	0.995	1.000	0.975	1.026
Stage 1			3.578	0.167			
Stage 2	-0.801	0.432	3.432	0.064	0.449	0.193	1.048
Stage 3	-0.792	0.473	2.804	0.094	0.453	0.179	1.144
TN			5.980	**0.001**			
Her2	-0.933	0.399	5.483	**0.019**	0.393	0.180	0.859
Luminal	1.445	0.443	10.637	**0.001**	4.241	1.780	10.106
Ki-67-low			1.923	0.382			
Ki-67-high	-0.421	0.457	0.847	0.357	0.656	0.268	1.609
Ki-67-unknown	0.124	0.619	0.040	0.841	1.132	0.336	3.813
SMI	-0.014	0.012	1.526	0.217	0.986	0.964	1.008
HU	-0.017	0.018	0.943	0.331	0.983	0.949	1.018

Variables entered in step 1: age, clinical stage, molecular subtype, Ki-67, SMI, and HU mean. Outcome variable: non-pCR (reference category: pCR). Reference categories: Stage 1, triple-negative subtype, and low Ki-67. β: Regression coefficient; CI: Confidence interval; TN: Triple negative; SMI: Skeletal muscle index; HU: Hounsfield unit; OR: Odds ratio; pCR: Pathological complete response; CT: Computed tomography

Correlation analyses between SMI, BMI, and HU demonstrated a moderate positive correlation between BMI and SMI (r = 0.446; p<0.001), a weak-to-moderate negative correlation between BMI and HU (r = -0.337; p<0.001), and a weak negative correlation between SMI and HU (r = -0.210; p<0.001).

The discriminative performance of SMI and HU for predicting pCR was evaluated using ROC analysis. The area under the curve value was 0.498 for SMI (p = 0.958) and 0.518 for HU (p = 0.574) (Figure 1).

Exploratory subgroup analyses were performed according to molecular subtype (luminal, HER2-positive, and triple-negative breast cancer). No statistically significant associations were observed between SMI, HU, and pCR within any molecular subtype. Similarly, subtype-specific logistic regression and ROC analyses did not demonstrate meaningful predictive performance of either parameter (Table 5).

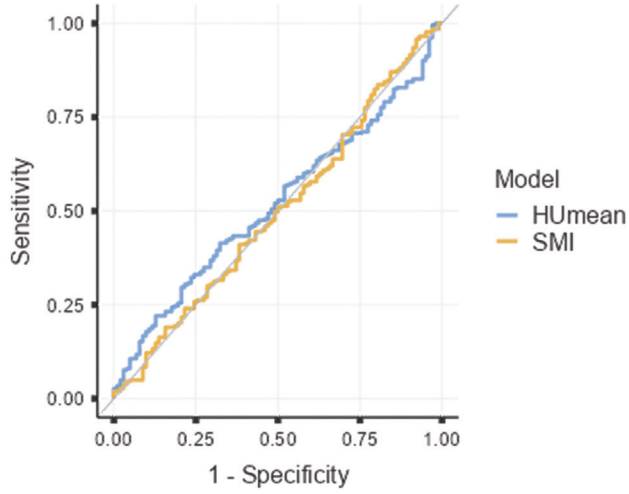

Figure 1. ROC analysis of SMI and HU for predicting pathological complete response

ROC: Receiver operating characteristic; SMI: Skeletal muscle index; HU: Hounsfield unit

Discussion and Conclusion

In this study, factors predicting pCR to NAC in breast cancer patients were evaluated. Our results demonstrated that molecular subtype was the strongest and independent predictor of treatment response, whereas CT-based body composition parameters, including SMI and HU, did not have independent predictive value for pCR.

The determining role of molecular subtype on treatment response is consistent with the literature. Several studies have shown higher pCR rates in HER2-positive tumors and lower response rates in luminal subtypes (26-29). This finding supports the dominant effect of tumor biology on treatment sensitivity. Similarly, in our study, the probability of achieving pCR was significantly higher in HER2-positive patients, whereas it was lower in the luminal subtype.

Table 5. Receiver operating characteristic analysis of SMI and mean muscle attenuation for predicting pathological complete response

Variables	Cut-off	AUC	Std. error	*p*	Asymptotic 95% CI		Sensitivity	Specificity
					Lower bound	Upper bound		
SMI	≤79.91	0.498	0.0339	0.958	0.432	0.565	95.82	7.84
HU	≤18.20	0.518	0.0320	0.574	0.455	0.581	22.05	87.25

AUC: Area under the curve, SMI: Skeletal muscle index; HU: Hounsfield unit; CI: Confidence interval; Std.: Standard

Although histological grade was significant in univariate analysis, it lost its independent significance in multivariate analysis. This finding may be related to the biological association between histological grade and molecular subtype. Since HER2-positive and triple-negative tumors are generally high-grade tumors, the independent contribution of grade may have disappeared under the dominant effect of molecular subtype in the multivariate model. Consistent with our findings, previous studies have shown that although high grade is associated with pCR, it is not an independent predictive factor by itself (28, 30, 31).

In the present study, SMI and HU were not identified as independent factors for predicting treatment response. Previous studies investigating the relationship between body composition and treatment response have reported inconsistent results. Some studies demonstrated that low SMI values were associated with lower pCR rates, although SMI was not identified as an independent predictive factor (16, 22, 23). In contrast, other studies found no significant association between SMI and pCR (18, 21, 24). Similarly, Isıklar et al. (17) did not find a significant association between BMI and pCR, consistent with our results. In a meta-analysis by Zhang et al. (19), a weak negative association between BMI and pCR was reported. The heterogeneous findings among studies evaluating body composition and NAC response may be related to differences in measurement techniques, patient selection criteria, and analytical approaches. In particular, evaluating body composition as categorical variables versus continuous variables may lead to different results. In the study by Butler et al. (21), although SMI was not an independent factor for treatment response, it was associated with long-term survival outcomes. This finding suggests that SMI may be more closely related to the patient's general condition and prognosis rather than direct tumor response. In addition, SMI and HU are dynamic parameters that may change during NAC due to treatment-related toxicity, nutritional status, systemic inflammation, and changes in physical activity (32-34). Therefore, a single pre-treatment measurement may not reflect the dynamic changes associated with treatment response. Another possible explanation for the lack of association between skeletal muscle parameters and pCR is the relatively homogeneous body composition of our cohort, as approximately 79% of the patients were overweight or obese. This may have reduced the variability of SMI and limited our ability to detect modest associations. In addition, sarcopenic obesity may partly explain why muscle quantity alone was not associated with treatment response. Future studies including more heterogeneous populations are warranted.

Exploratory subgroup analyses according to molecular subtype yielded findings consistent with the overall cohort. However, these analyses, particularly in the triple negative subgroup, should be interpreted cautiously because of the limited sample size and statistical power. Larger multicenter studies are needed to validate these findings.

In our study, no significant association was observed between HU and pCR. However, Mun et al. (20) demonstrated a possible association between HU and treatment response in a study including only triple-negative breast cancer patients receiving immunotherapy-containing treatment regimens. These findings indicate that treatment response may be strongly influenced not only by patient-related factors but also by tumor biology and treatment type. In our cohort, which included a heterogeneous patient population with different molecular subtypes receiving standard NAC, no independent association was observed between SMI, HU, and pCR.

In addition, the moderate correlation between BMI and SMI in our study suggests that these two parameters partly reflect similar biological characteristics. In contrast, the weak negative correlations involving HU suggest that muscle quality may reflect different biological properties compared with muscle quantity. These findings support the idea that functional and metabolic characteristics of body composition may be more important than quantitative measurements alone.

The poor discriminative performance of SMI and HU in ROC analysis further suggests that these parameters have limited clinical utility in predicting pCR. These findings also suggest that body composition parameters may be more closely associated with treatment tolerance, treatment-related complications, or long-term outcomes rather than direct treatment response.

This study has several limitations. First, its retrospective design may have introduced selection bias. In addition, the majority of the study population was overweight or obese, which may have limited the variability of body composition parameters. Furthermore, other body composition parameters, including adipose tissue measurements, as well as functional muscle assessments and metabolic biomarkers, were not included in the analysis. Muscle attenuation measurements were obtained from the low-dose CT component of PET/CT, which may have affected HU measurements. Finally, the relatively long study period may have introduced temporal heterogeneity despite the use of the same PET/CT system and generally consistent NAC regimens throughout the study period.

In conclusion, pretreatment CT-derived skeletal muscle parameters did not provide additional predictive value for pCR beyond molecular subtype in this relatively large single-center cohort. These findings add to the existing evidence suggesting that pretreatment body composition alone has limited utility for predicting treatment response. Larger prospective multicenter studies are warranted.

Ethics

Ethics Committee Approval: This retrospective study was approved by the University of Health Sciences Türkiye, Kartal Dr. Lütfi Kırdar City Hospital Scientific Research Ethics Committee (approval no. 2024/010.99/9/12, date: 25.10.2024).

Informed Consent: The requirement for informed consent was waived.

Acknowledgments

For transparency, the authors note that an artificial intelligence assisted language model (ChatGPT, OpenAI) was utilized to support language correction. This assistance was limited to linguistic refinement; all scientific content, critical analysis, and final editorial decisions were made exclusively by the authors.

Footnotes

Authorship Contributions

Surgical and Medical Practices: G.R., A.Ö.S., S.Y., H.O., Ş.K.; Concept: G.R., A.Ö.S., S.Y., H.O., B.D., Ş.K.; Design: G.R., A.Ö.S., S.Y., H.O., B.D., Ş.K.; Data Collection and/or Processing: G.R., A.Ö.S., S.Y., Ş.K.; Analysis and/or Interpretation: G.R., A.Ö.S., S.Y., H.O., B.D., Ş.K.; Literature Search: G.R., A.Ö.S.; Writing: G.R., A.Ö.S., S.Y., H.O., B.D., Ş.K.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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