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Sarcopenia Is Not a Prognostic Factor of Outcome in Patients With Cervical Cancer Undergoing Concurrent Chemoradiotherapy or Radiotherapy

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Abstract. *Background/Aim: The objective of this study was to determine if sarcopenia was a predictor of poor prognosis in patients with cervical cancer (CC) undergoing concurrent chemoradiation therapy (CCRT) or radiation therapy (RT). Materials and Methods: A total of 236 patients with CC undergoing CCRT or RT were retrospectively examined. We determined if clinical characteristics and survival were correlated with pretreatment sarcopenia, measured as psoas muscle index (PI) or skeletal muscle index (SMI). Results: Pretreatment PI and SMI were related to parametrial involvement with CC undergoing CCRT or RT (p=0.002, and, p=0.034, respectively). The median progression-free survival (PFS) and overall survival (OS) times in patients undergoing CCRT or RT were 29.0 and 34.5 months, respectively. Neither PI nor SMI were prognostic predictors in patients with CC undergoing CCRT or RT. Conclusion: Sarcopenia is not a predictive factor of outcome in patients with CC undergoing CCRT or RT.*

Cervical cancer (CC) is the fourth most common cancer in women worldwide, with approximately 266,000 cancer-related deaths in 2012 (1). Treatment options for CC include surgery, radiotherapy (RT), and/or chemotherapy, depending on tumor stage and additional risk factors. Concurrent chemoradiation therapy (CCRT) and RT have been used as primary treatments in patients with locally FIGO stages of CC, and platinum-based CCRT has been established as standard therapy in these patients (2-6).

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The focus of prognostic risk assessment has shifted towards the concept of frailty, defined as decreased reserve resulting from cumulative declines across multiple physiologic systems, increasing vulnerability to adverse events (7). An important feature of the frailty syndrome is loss of muscle tissue, referred to as sarcopenia (8). Sarcopenia includes disorders of homeostasis such as progressive wasting, weakness, and anorexia, and is commonly seen in cancer patients (9, 10). Loss of muscle can easily be evaluated using abdominal computed tomography (CT), which is routinely performed as part of an oncological evaluation. These methods provide an objective subclinical measurement of patient frailty and nutritional status, and can be used to gauge an individual's physical condition. Sarcopenia has been reported to be predictive for outcomes in various cancers, including ovarian, lung, breast, esophagus, stomach, pancreas, kidney, and colorectal cancers (11-18); however, sarcopenia has not been identified as a predictive factor in patients with CC. The present study therefore aimed to evaluate the correlations between psoas muscle and skeletal muscle sarcopenia and survival in patients with CC undergoing CCRT or RT.

Materials and Methods

Patients. The study protocol was approved by the Institutional Review Board of Okayama University Hospital (1704-012). Informed consent was obtained from all patients. The study population consisted of 236 patients with primary CC who were treated at the Department of Obstetrics and Gynecology of Okayama University Hospital between April 2004 and July 2018. All patients underwent a review of their medical history, physical examination, and routine clinical staging. Magnetic resonance imaging and computed tomography (CT)/positron emission tomography-CT were performed prior to treatment as part of the patients' initial clinical evaluation. The cancers were staged according to the 2018 FIGO staging system, and the extent of the tumor was represented diagrammatically on a tumor-staging form (Table I).

CT imaging analysis. Pre-treatment CT images were retrieved for analysis. A single axial image corresponding to the L3 vertebral body was selected for each CT. Skeletal muscles were quantified within predefined validated boundaries of −29 to +150 Hounsfield units using the software (Synapse Vincent; Fujifilm Medical, Tokyo, Japan). The entire skeletal muscle area comprising the abdominal, psoas, and paraspinal muscles was demarcated (Figure 1A). The cross-sectional areas of the psoas and skeletal muscles were normalized for patient height to calculate the respective indexes (cm^2/m^2) (PI and SMI). The volumes of the psoas and skeletal muscles in the region were measured using image-recognition software (Synapse Vincent; Fujifilm Medical, Tokyo, Japan).

Treatment. Patients were treated with a combination of external irradiation and intracavitary brachytherapy (ICBT) with curative intent. RT was delivered at 2.0 Gy per fraction once daily, 5 days per week, over 5 weeks. Dose to the whole pelvis was 50.0 Gy and ICBT as the high dose rate was 24 Gy/4 times. For CCRT, patients were treated with either cisplatin (40 mg/m^2 infusion weekly for six cycles), nedaplatin (30 mg/m^2 infusion weekly for eight cycles), or ifosfamide plus nedaplatin (ifosfamide [1 g/m^2] infusion on days 1–5 and nedaplatin [80 mg/m^2] infusion on day 1 of a 3-week cycle, for three cycles), as described previously (19, 20). CCRT was interrupted for up to 1 week in patients who exhibited a white blood cell (WBC) count <2,000/μl, neutrophil count <1,000/μl, platelet count <75,000/μl, or 24-h creatinine clearance <50 ml/min. If these side effects persisted for more than 1 week, no additional chemotherapy was given. RT was suspended indefinitely in patients who exhibited a WBC count <1,000/μl, neutrophil count <500/μl, platelet count <25,000/μl, or diarrhea (grade 4 or over). Eighty-one patients did not receive concurrent chemotherapy because of the presence of comorbidities or advanced age (≥75 years). The prognosis of patients with CC is associated with hemoglobin (Hb) levels during CCRT or RT (19-22), and our treatment policy therefore included administering red blood cell transfusions during CCRT or RT in patients with a Hb level <10.0 g/dl, until it increased to >10 g/dl.

Statistical analysis. Statistical analysis was performed using SPSS version 20.0 (SPSS Inc., Chicago, IL, USA). Statistical analyses were performed using the Mann–Whitney *U*-test for comparisons with controls. A receiver operating characteristic (ROC) analysis was carried out to define the optimal cut-off of PI and SMI in predicting progression-free survival (PFS) and overall survival (OS). For univariate and multivariate analyses, Cox regression was performed to select significant prognostic variables for PFS and OS, of which PI, SMI, stage, histology, lymph node metastasis, tumor maximum size, parametrium invasion, vagina invasion, and hypoalbuminemia, were analyzed as factors. Differences were considered statistically significant at $p<0.05$.

Table I. *Patient and tumor characteristics*.

Baseline characteristics	All patients
Age at diagnosis, y	Mean, 61; range=25-88 years
	Numbers (%)
FIGO 2018 Stage	
IB1	3 (1.3)
IB2	16 (6.8)
IB3	10 (4.2)
IIA1	12 (5)
IIA2	4 (1.7)
IIB	70 (29.7)
IIIA	3 (1.3)
IIIB	37 (15.7)
IIIC1	74 (31.3)
IVA	7 (3)
Histology	
SCC	201 (85.2)
AD	26 (11)
ADSQ	3 (1.3)
Other	6 (2.5)
Lymph node metastasis	
Negative	157 (66.5)
Positive	79 (33.5)
Parametrial involvement	
Negative	56 (23.7)
Positive	180 (76.3)
Vaginal invasion	
Negative	98 (41.5)
Positive	138 (58.5)
Tumor maximum size	
≤4.0 cm	84 (35.6)
>4.0 cm	152 (64.4)
Treatment	
CCRT	155 (65.7)
RT	81 (34.3)
Chemotherapy regimen (N=155)	
Weekly CDDP	112 (72.2)
Weekly nedaplatin	36 (23.2)
IN	7 (4.6)

SCC: Squamous cell carcinoma; AD: adenocarcinoma; ADSQ: adenosquamous carcinoma; CCRT: concurrent chemoradiation therapy; RT: radiation therapy; CDDP: cisplatin; IN: ifosfamide plus nedaplatin.

Results

All patients were aged between 25 and 88 years (median, 61.0 years). FIGO stage, histology, lymph node metastasis, parametrial involvement, vaginal invasion, maximum tumor size, treatment, and chemotherapy regimen are listed in Table I.

The median pre-treatment PI and SMI in patients undergoing CCRT or RT were 3.94 cm^2/mm^2 (range=0.92–8.07 cm^2/mm^2), and 36.56 cm^2/mm^2 (range=20.55–63.19 cm^2/mm^2), respectively. Inter-measurement correlations of PI and SMI in patients undergoing CCRT or RT were analyzed with data from CT scans. The correlations between PI and SMI in CCRT or RT patients were r=0.575, respectively (Figure 1B).

The distributions of pre-treatment PI and SMI in patients undergoing CCRT or RT were examined according to the clinical characteristics of the overall population (Table II). Pre-treatment PI and SMI in patients undergoing CCRT or RT were significantly correlated with parametrial involvement ($p=0.002$ and $p=0.034$). However, pre-treatment PI and SMI in patients undergoing CCRT or RT did not recognize any other risk factors such as stage,

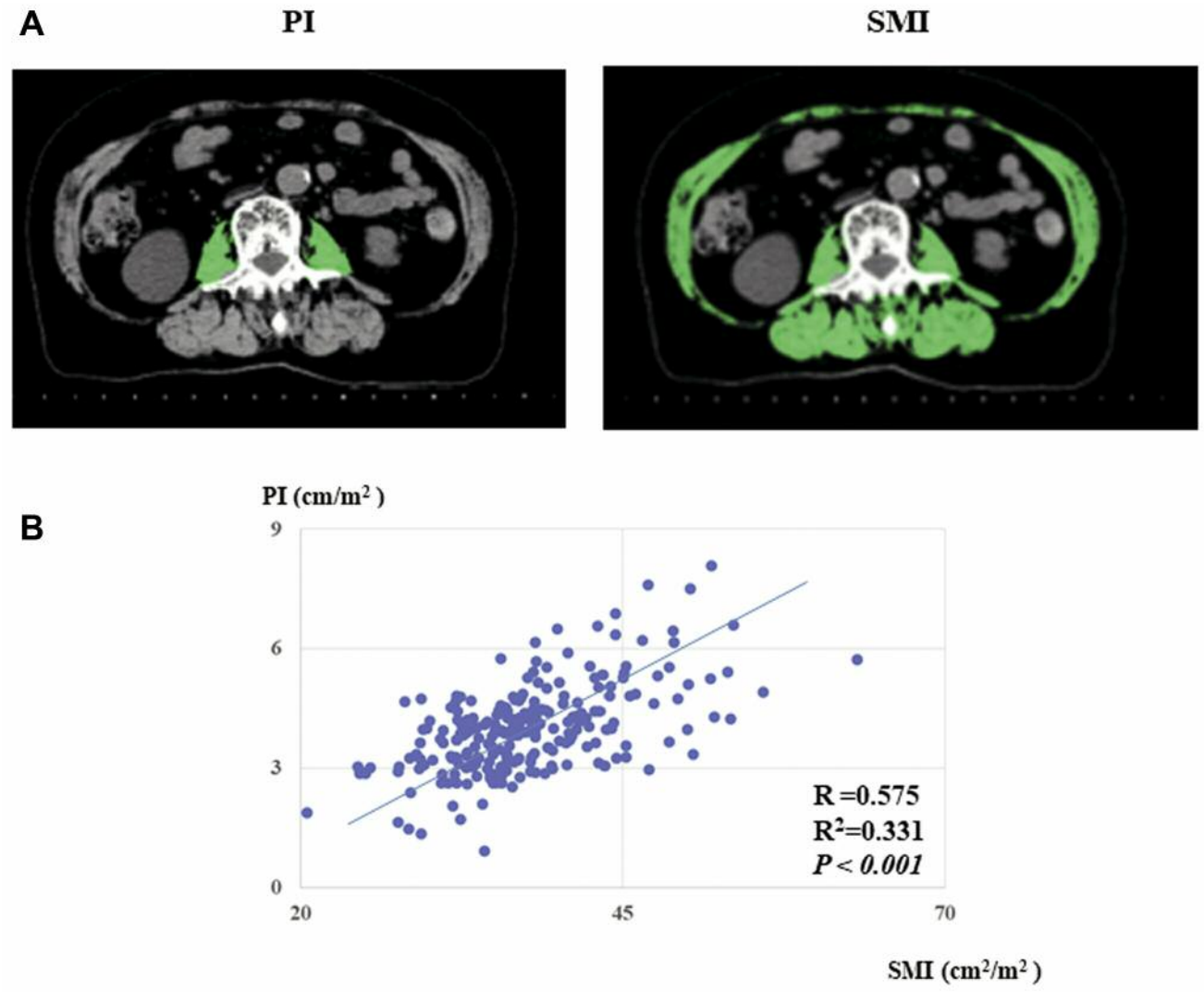

Figure 1. *(A) Patient with sarcopenia. Pretreatment psoas muscle index (PI) 4.46 cm^2/m^2 and skeletal muscle index (SMI) 35.38 cm^2/m^2 measured according to attenuation thresholds of −29 to +150 Hounsfield units. (B) Regression analyses for PI and SMI in 263 patients with cervical cancer (CC) undergoing concurrent chemoradiation therapy (CCRT) or radiation therapy.*

histology, lymph node metastasis, tumor maximum size, vagina invasion, and hypoalbuminemia.

The median progression-free (PFS) and overall survival (OS) times for patients undergoing CCRT or RT in this study were 29.0 and 34.5 months, respectively. The follow-up periods ranged from 1-165 months (CCRT or RT) for both PFS and OS. A total of 155 CCRT or RT patients (65.7%) remained alive with no evidence of disease at the last follow-up, 68 patients (28.8%) had died of disease, and 11 patients (5.5%) were alive with disease.

ROC curve analyses were used to determine the pre-treatment PI and SMI of cut-off values to predict recurrence and survival. The analyses identified PI <3.90 cm^2/m^2 as the most accurate cut-off value for predicting recurrence (area under the curve [AUC]=0.542) and survival (AUC=0.520). The most accurate cut-off value for SMI was 36.55 cm^2/m^2 for predicting recurrence (AUC=0.511) and survival (AUC=0.504) (Figure 2).

The correlations between clinical factors and PFS or OS were assessed using univariate and multivariate analysis (Table III). In univariate analysis on PFS, stage, lymph node metastasis, tumor maximum size, parametrium invasion, and hypoalbuminemia were significantly associated with PFS ($p<0.001$, $p<0.001$, $p=0.001$, $p=0.003$, and $p=0.027$, respectively). The univariate analysis on OS results suggested that stage, lymph node metastasis, tumor maximum size, parametrium invasion, and hypoalbuminemia were significantly associated with OS ($p=0.031$, $p<0.001$, $p=0.004$, $p=0.014$ and $p=0.039$, respectively). In multivariate analysis on PFS, lymph

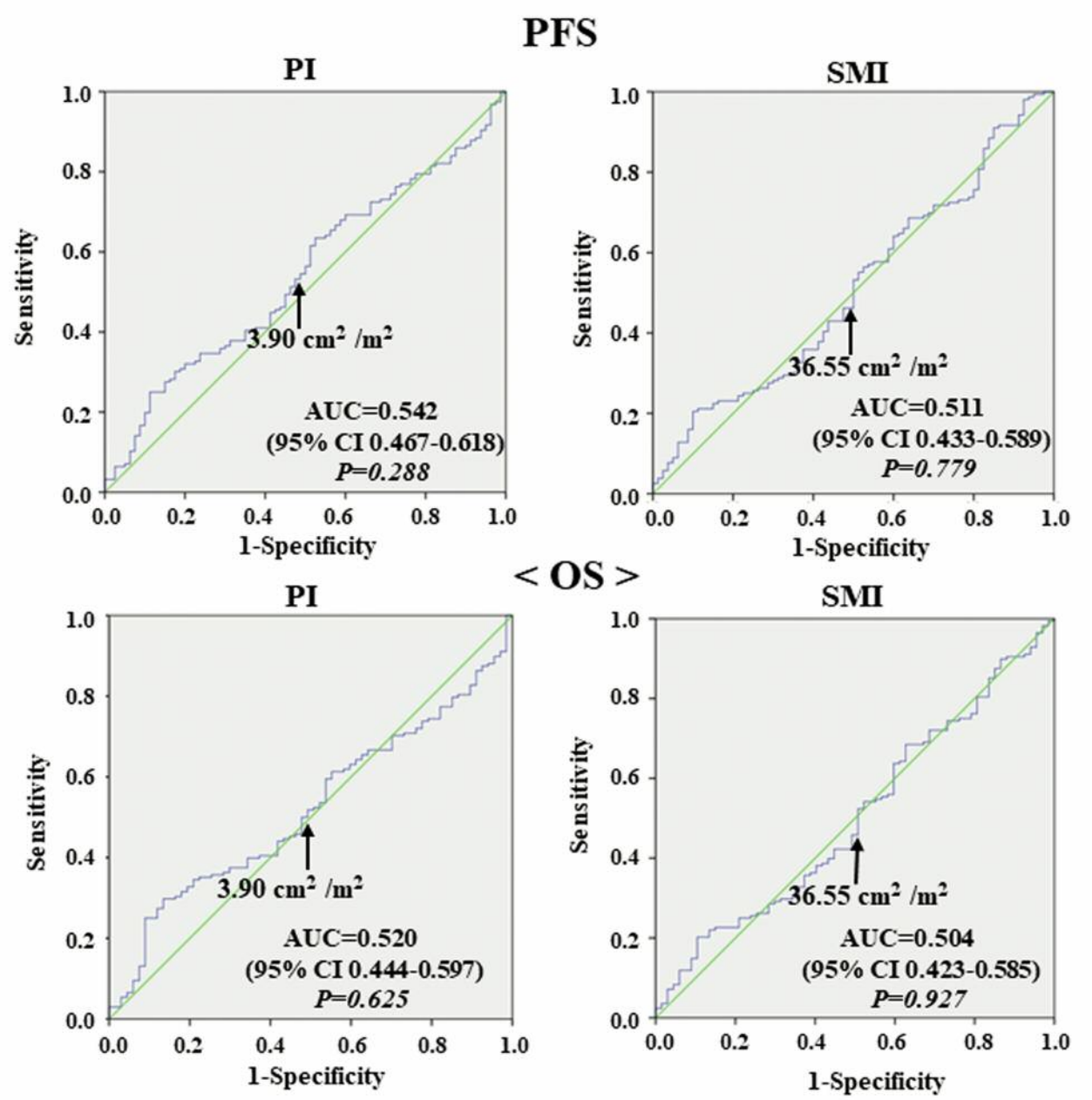

Figure 2. *Receiver operating characteristic curves for pretreatment psoas muscle index (PI) and skeletal muscle index (SMI) in patients with cervical cancer undergoing concurrent chemoradiation therapy (CCRT) or radiation therapy (RT). Optimal PI cut-off value to predict recurrence was 3.90 cm²/m² (area under the curve [AUC]=0.542; 95%CI=0.467–0.618; p=0.288), optimal SMI cut-off value to predict recurrence was 36.55 cm²/m² (AUC=0.511; 95%CI=0.433–0.589; p=0.799). Optimal PI cut-off value to predict survival was 3.90 cm²/m² (AUC=0.520, 95%CI=0.444-0.597; p=0.625). Optimal SMI cut-off value to predict survival was 36.55 cm²/m² (AUC=0.504; 95%CI=0.423-0.585; p=0.927).*

node metastasis and tumor maximum size were significantly associated with PFS (p=0.036, and p=0.026, respectively). The multivariate analysis on OS results suggested that lymph node metastasis and tumor maximum size were significantly associated with OS (p=0.016, and p=0.026, respectively). Interestingly, neither PI nor SMI were prognostic factors in patients with CC undergoing CCRT or RT.

Discussion

Prognostic factors in patients with CC generally reflect tumor aggressiveness, including stage, size, histological type, and metastasis to regional lymph nodes at the time of diagnosis (23, 24). Several factors related to the general condition of the patient also influence prognosis. The apparent prognostic

Table II. *Associations of PI and SMI with clinical factors on cervical cancer.*

Variable	Numbers	PI	*p*-Value	SMI	*p*-Value
Stage			0.829		0.473
I-II	115	3.95±1.11		36.97±6.73	
III-IV	121	3.92±1.03		36.38±5.85	
Histology			0.834		0.886
SCC	198	3.95±1.10		36.57±6.25	
Non-SCC	38	3.91±0.96		36.41±6.82	
Lymph node metastasis			0.594		0.272
Negative	157	3.91±1.10		36.2±6.73	
Positive	79	3.99±1.06		37.10±5.49	
Tumor maximum size			0.446		0.99
≤4.0 cm	87	3.98±1.07		36.56±6.79	
>4.0 cm	149	3.87±1.07		36.57±6.01	
Parametrium invasion			0.002*		0.034*
Negative	56	4.30±1.13		38.42±7.47	
Positive	180	3.80±1.02		36.10±5.51	
Vagina invasion			0.594		0.926
Negative	98	3.88±1.25		36.55±7.13	
Positive	138	3.96±0.95		36.63±5.68	
hypoalbuminemia			0.979		1
<3.0 mg/dl	8	3.94±1.08		36.56±6.30	
≥3.0 mg/dl	228	3.95±1.09		36.56±6.50	

PI: Psoas index; SMI: skeletal muscle index; CCRT: concurrent chemoradiation therapy; RT: radiation therapy; SCC: squamous cell carcinoma.

Table III. *Prognostic factors for progression-free survival and overall survival with cervical cancer selected by Cox's univariate and multivariate analysis.*

	Univariate analysis			Multivariate analysis		
	Hazard ratio	95%CI	*p*-Value	Hazard ratio	95%CI	*p*-Value
Progression-free survival						
PI (<3.90 cm^2/m^2)	1.176	0.758-1.823	0.469		-	
SMI (<36.55 cm^2/m^2)	1.143	0.738-1.773	0.549		-	
FIGO (Stage III-IV)	3.355	2.039-5.523	<0.001*	1.651	0.827-3.294	0.155
Histology (non-SCC)	1.088	0.601-1.971	0.781		-	
Lymph node metastasis	2.966	1.908-4.610	<0.001*	1.883	1.043-3.398	0.036*
Tumor maximum size (>4.0 cm)	2.644	1.508-4.636	0.001*	1.95	1.082-3.514	0.026*
Parametrium invasion	2.856	1.427-5.715	0.003*	1.706	0.812-3.584	0.158
Vagina invasion	1.538	0.963-2.456	0.071		-	
Hypoalbuminemia (<3.0 mg/dl)	2.781	1.123-6.888	0.027*	0.524	0.072-3.841	0.525
Overall survival						
PI (<3.90 cm^2/m^2)	1.118	0.692-1.805	0.648		-	
SMI (<36.55 cm^2/m^2)	1.126	0.697-1.818	0.628		-	
FIGO (Stage III-IV)	2.143	1.287-3.568	0.031*	0.847	0.380-1.889	0.685
Histology (non-SCC)	1.343	0.732-2.461	0.341		-	
Lymph node metastasis	2.497	1.544-4.037	<0.001*	2.471	1.186-5.146	0.016*
Tumor maximum size (>4.0 cm)	2.44	1.331-4.471	0.004*	2.042	1.090-3.825	0.026*
Parametrium invasion	2.513	1.201-5.261	0.014*	1.8	0.821-3.948	0.142
Vagina invasion	1.41	0.852-2.336	0.181		-	
Hypoalbuminemia (<3.0 mg/dl)	2.914	1.053-8.065	0.039*	0.667	0.090-4.946	0.692

PI: Psoas muscle index; SMI: skeletal muscle index. *$p<0.05$.

performance of sarcopenia could be explained by its uniqueness in reflecting both tumor aggressiveness and patient-related factors. Sarcopenia develops as a consequence of tumor progression, tumor-induced systemic inflammation, or metabolic aberration, and its presence indicates tumor aggressiveness. Previous studies reported that a significant loss of skeletal muscle could serve as a predictor of poor survival in patients with CC undergoing CCRT (25, 26). However,

pretreatment sarcopenia (PI or SMI) has not been shown to be a predictive factor in patients with CC. This study was the first to evaluate if pretreatment sarcopenia predicted a poor prognosis in CC patients undergoing CCRT or RT.

The combination of tumor aggressiveness and host factors in sarcopenia may reflect the presence of both a systemic response and progressive nutritional decline in cancer patients. We investigated the correlations between clinical characteristics and pretreatment sarcopenia in CC patients undergoing CCRT or RT, and showed that both pretreatment SMI and PI were related to parametrial involvement, but conversely, most tumor aggressiveness and host factors, such as stage, histology, lymph node metastasis, tumor maximum size, vagina invasion, and hypoalbuminemia, did not correlate with sarcopenia.

Sarcopenia has been shown to predict outcomes in various cancers, including ovarian, lung, breast, esophagus, stomach, pancreas, kidney, and colorectal cancers (11-18). In contrast, however, sarcopenia was not a predictive factor in esophageal and ovarian cancers (27-29). ROC curve analyses were used to determine optimal PI and SMI cut-off values to predict recurrence and survival. The cut-off values of PI and SMI were 3.90 cm^2/m^2, and 36.55 cm^2/m^2 for recurrence and survival, respectively. Accordingly, the current study found that neither PI nor SMI was a prognostic factor in patients with CC treated with either CCRT or RT.

The multivariate analyses showed that lymph node metastasis and tumor maximum size were independent prognostic factors for recurrence and survival in our study population. Therefore, lymph node metastasis and tumor maximum size may be useful in reflecting both tumor aggressiveness and host factors in cervical cancer patients. Pretreatment PI and SMI in CCRT or RT patients wasn't associated with lymph node metastasis and tumor maximum size. These results suggest that evaluation of pretreatment sarcopenia (PI or SMI) will not provide additional prognostic value to routine assessments in CC patients undergoing CCRT or RT, because it does not reflect tumor aggressiveness or host factors in these patients.

Further prospective studies with more patients and longer follow-up periods are needed to provide more definitive data to help clarify the significance of the current findings.

In conclusion, the presence of sarcopenia did not predict the outcome of CC patients undergoing CCRT or RT.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Concept, draft preparation, writing, review and editing of manuscript: H.M., K.N., C.O. Data analysis: H.M., Y.M., N.I., T.N., K.K. Supervision: H.M. S.K., K.N.

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