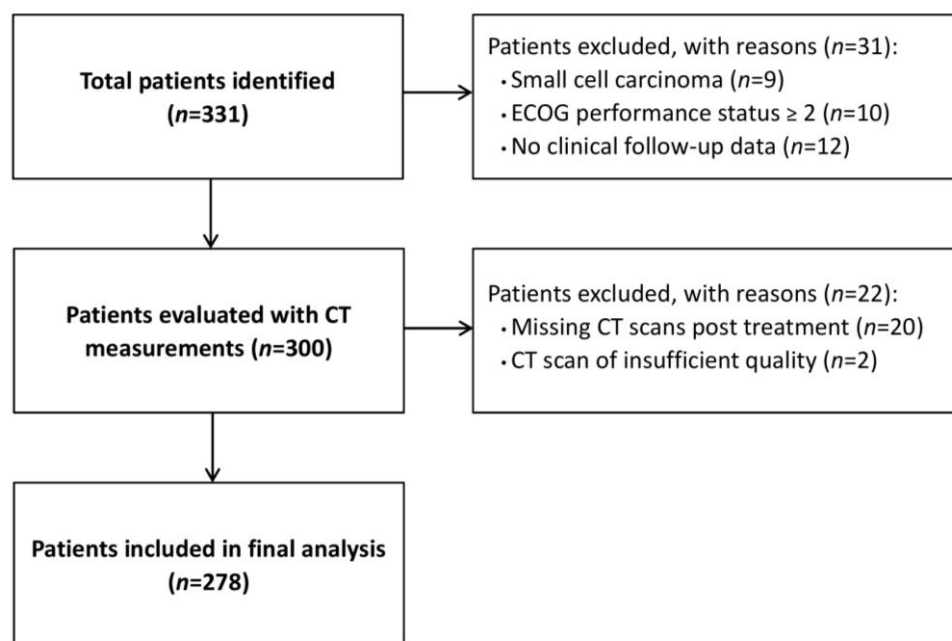


Muscle Loss after Chemoradiotherapy as a Biomarker of Distant Failures in Locally Advanced Cervical Cancer

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Supplementary Materials



Supplementary Figure S1. Flow chart for patient inclusion.

Supplementary Table S1. Body composition parameters according to SMI change groups, values expressed as mean \pm standard deviation, unless stated otherwise.

Characteristics	Overall (n = 278)	SMI loss (n = 90)	SMI maintained (n = 188)	p-value
Pre-treatment BMI (kg/m²)	23.4 \pm 4.3	23.4 \pm 4.8	23.4 \pm 4.1	0.90
Weight loss \geq 5%, n (%)	58 (20.9)	24 (26.7)	34 (18.1)	0.10
Pre-treatment SMI (cm²/m²)	39.8 \pm 7.3	40.6 \pm 7.0	39.4 \pm 7.4	0.20
Pre-treatment sarcopenia ^a , n (%)	92 (33.1)	26 (28.9)	66 (35.1)	0.30
Post-treatment SMI (cm²/m²)	39.3 \pm 7.6	36.0 \pm 6.5	40.9 \pm 7.6	<0.001
Post-treatment sarcopenia ^a , n (%)	97 (34.9)	44 (48.9)	53 (28.2)	0.001
Pre-treatment SMD (HU)	35.6 \pm 9.5	35.6 \pm 9.2	35.6 \pm 9.6	0.84
Pre-treatment myosteotosis ^a , n (%)	92 (33.1)	31 (34.4)	61 (32.4)	0.74
SMD change (%/150 days)	-2.9 \pm 12.4	-11.2 \pm 10.0	1.0 \pm 11.5	<0.001
SMD maintained	154 (55.4)	23 (25.6)	131 (69.7)	<0.001
SMD loss \geq 5%	124 (44.6)	67 (74.4)	57 (30.3)	
Pre-treatment TATI (cm²/m²)	97.7 \pm 44.5	96.9 \pm 47.8	98.0 \pm 42.9	0.62
Pre-treatment low TATI ^a , n (%)	186 (66.9)	57 (63.3)	129 (68.6)	0.38
TATI change (%/150 days)	-3.0 \pm 15.7	-5.8 \pm 16.5	-1.7 \pm 15.2	0.04
TATI maintained	153 (55.0)	41 (45.6)	112 (59.6)	0.03
TATI loss \geq 5%	125 (45.0)	49 (54.4)	76 (40.4)	

Abbreviations: BMI, body mass index; HU, Hounsfield unit; IQR, interquartile range; SMD, skeletal muscle density; SMI, skeletal muscle index; TATI, total adipose tissue index. ^a SMI < 36.3 cm²/m²,

SMD < 30.7 HU, and TATI < 112.2 cm²/m² were defined as sarcopenia, myosteatorsis, and low TATI, respectively.

Supplementary Table S2. Change of body composition parameters during treatment.

Variable	First CT scan	Second CT scan	Relative Change per 150 days (%)		
	Mean ± SD	Mean ± SD	Mean	95% CI	<i>p</i> -value
BMI (kg/m²)					
SCC	23.3 ± 4.4	22.9 ± 4.3	-1.9	-2.5 to -1.4	<0.001
Adenocarcinoma	24.1 ± 3.9	23.6 ± 3.7	-2.0	-3.6 to -0.3	0.03
SMI (cm²/m²)					
SCC	39.9 ± 7.3	39.6 ± 7.5	-0.5	-1.6 to 0.7	0.45
Adenocarcinoma	39.0 ± 7.2	37.3 ± 8.1	-5.0	-9.1 to -0.9	0.02
SMD (HU)					
SCC	35.6 ± 9.5	34.6 ± 9.6	-2.4	-4.0 to -0.9	0.002
Adenocarcinoma	35.8 ± 9.2	33.5 ± 9.4	-6.7	-11.3 to -2.2	0.005
TATI (cm²/m²)					
SCC	97.7 ± 45.3	93.7 ± 42.8	-3.2	-5.2 to -1.1	0.002
Adenocarcinoma	97.1 ± 38.3	93.7 ± 33.8	-2.1	-7.0 to 2.7	0.38

SCC, squamous cell carcinoma.

Supplementary Table S3. Patterns of failure according to body composition groups.

	Distant failure (total)	<i>p</i> -value	Distant failure alone	<i>p</i> -value	Distant plus Pelvic failure	<i>p</i> -value	Pelvic failure alone	<i>p</i> -value
Weight change		0.63		0.81		0.70		0.35
Weight maintained (<i>n</i> = 220)	43 (19.5)		35 (15.9)		8 (3.6)		7 (3.2)	
Weight loss ≥ 5% (<i>n</i> = 58)	13 (22.4)		10 (17.2)		3 (5.2)		0 (0.0)	
SMI change		<0.001		<0.001		<0.001		0.22
SMI maintained (<i>n</i> = 188)	18 (9.6)		17 (9.0)		1 (0.5)		3 (1.6)	
SMI loss ≥ 5% (<i>n</i> = 90)	38 (42.2)		28 (31.1)		10 (11.1)		4 (4.4)	
SMD change		<0.001		0.02		0.003		0.25
SMD maintained (<i>n</i> = 154)	19 (12.3)		18 (11.7)		1 (0.6)		2 (1.3)	
SMD loss ≥ 5% (<i>n</i> = 124)	37 (29.8)		27 (21.8)		10 (8.1)		5 (4.0)	
TATI change		0.08		0.12		0.55		0.13
TATI maintained (<i>n</i> = 153)	25 (16.3)		20 (13.1)		5 (3.3)		6 (3.9)	
TATI loss ≥ 5% (<i>n</i> = 125)	31 (24.8)		25 (20.0)		6 (4.8)		1 (0.8)	

Abbreviations: SMD, skeletal muscle density; SMI, skeletal muscle index; TATI, total adipose tissue index. Data are expressed as the absolute number of events (%).

Supplementary Table S4. Univariable Cox proportional hazards model for 3-year distant recurrence-free survival ($n = 278$).

Distant recurrence-free survival		
Variable	Hazard ratio (95% CI)	<i>p</i>-value
Age, continuous	1.00 (0.98–1.02)	0.92
ECOG performance status		
0	Reference	
1	0.85 (0.30–2.35)	0.75
Pre-treatment BMI, continuous	0.99 (0.93–1.06)	0.79
BMI change, per 1%/150 days decrease	1.03 (0.97–1.11)	0.31
Weight loss ($\geq -5.0\%$)	1.17 (0.60–2.28)	0.65
Pre-treatment SMI, categorical		
Non-sarcopenia	Reference	
Sarcopenia ^a	1.05 (0.58–1.89)	0.87
SMI change, per 1%/150 days decrease	1.11 (1.08–1.14)	<0.001
SMI change, categorical		
SMI maintain	Reference	
SMI loss ($\geq -5.0\%$)	7.76 (4.11–14.67)	<0.001
Pre-treatment SMD, categorical		
Non-myosteotosis	Reference	
Myosteotosis ^a	0.94 (0.52–1.71)	0.85
SMD change, per 1%/150 days decrease	1.04 (1.01–1.06)	0.002
SMD maintain	Reference	
SMD loss ($\geq -5.0\%$)	2.39 (1.34–4.28)	0.003
Pre-treatment TATI^a, categorical		
High TATI	Reference	
Low TATI ^a	0.70 (0.39–1.23)	0.21
TATI change, per 1%/150 days decrease	1.02 (1.01–1.03)	0.04
TATI maintain	Reference	
TATI loss ($\geq -5.0\%$)	1.64 (0.93–2.88)	0.09
FIGO stage		
IB-II	Reference	
III-IVA	3.89 (2.21–6.83)	<0.001
PLNs involvement		
Negative	Reference	
Positive	2.92 (1.57–5.42)	0.001
Radiation field		
Pelvic radiotherapy	Reference	
Extended-field radiotherapy	0.76 (0.43–1.34)	0.35
Pathology		
Squamous cell carcinoma	Reference	
Adenocarcinoma	3.83 (2.06–7.13)	<0.001
SCC-Ag level, continuous	1.02 (1.01–1.02)	<0.001
Chemotherapy		
No	Reference	
Yes	1.02 (0.43–2.40)	0.96

Abbreviations: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HU, Hounsfield unit; PLN, pelvic lymph node; SCC-Ag, squamous cell carcinoma antigen; SMD, skeletal muscle density; SMI, skeletal muscle index; TATI, visceral adipose tissue index. ^a SMI < 36.3 cm²/m², SMD < 30.7 HU, and TATI < 112.2 cm²/m² were defined as sarcopenia, myosteotosis, and low TATI, respectively.

Supplementary Table S5. Univariable and multivariable Cox proportional hazards model for 3-year distant recurrence-free survival for patients with squamous cell carcinoma ($n = 246$).

Variable	Univariable		Multivariable	
	Hazard ratio (95% CI)	<i>p</i> -value	Hazard ratio (95% CI)	<i>p</i> -value
Age, continuous	1.01 (0.98–1.03)	0.55		
ECOG performance status				
0	Reference			
1	1.15 (0.41–3.26)	0.79		
Pre-treatment BMI, continuous	0.97 (0.90–1.06)	0.50		
Weight loss ($\geq -5.0\%$)	1.38 (0.65–2.94)	0.41		
Pre-treatment SMI, categorical				
Non-sarcopenia	Reference			
Sarcopenia	1.06 (0.53–2.14)	0.86		
SMI change				
SMI maintain	Reference		Reference	
SMI loss ($\geq -5.0\%$)	6.71 (3.28–13.74)	<0.001	5.86 (2.85–12.08)	<0.001
Pre-treatment SMD, categorical				
Non-myosteotosis	Reference			
Myosteotosis	0.76 (0.37–1.59)	0.47		
SMD change				
SMD maintain	Reference			
SMD loss ($\geq -5.0\%$)	1.69 (0.87–3.28)	0.12		
Pre-treatment TATI^a, categorical				
High TATI	Reference			
Low TATI	0.63 (0.33–1.24)	0.18		
TATI change				
TATI maintain	Reference		Reference	
TATI loss ($\geq -5.0\%$)	2.26 (1.14–4.48)	0.02	2.26 (1.11–4.62)	0.03
FIGO stage				
IB-II	Reference		Reference	
III-IVA	5.00 (2.54–9.84)	<0.001	2.76 (1.35–5.67)	0.01
PLNs involvement				
Negative	Reference		Reference	
Positive	3.35 (1.57–7.15)	0.002	2.44 (1.09–5.46)	0.03
Radiation field				
Pelvic radiotherapy	Reference			
Extended-field radiotherapy	0.91 (0.47–1.76)	0.77		
SCC-Ag level, continuous	1.02 (1.01–1.03)	<0.001	1.02 (1.01–1.03)	<0.001
Chemotherapy				
No	Reference			
Yes	0.91 (0.35–2.34)	0.84		

Abbreviations: BMI, body mass index; CI, confidence interval; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynaecology and Obstetrics; HU, Hounsfield unit; PLN, pelvic lymph node; SCC-Ag, squamous cell carcinoma antigen; SMD, skeletal muscle density; SMI, skeletal muscle index; TATI, total adipose tissue index. ^a SMI < 36.3 cm²/m², SMD < 30.7 HU, and TATI < 112.2 cm²/m² were defined as sarcopenia, myosteotosis, and low TATI, respectively.



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