Prognostic role of the skeletal musculature in oncology: significance, coherences and clinical implications

Prognostische Rolle der Skelettmuskulatur in der Onkologie: Bedeutung, Zusammenhänge und klinische Implikationen

Authors

Alexey Surov[1], Andreas Wienke[2], Ralf Gutzmer[3], Jan Borggrefe[1]

Affiliations

1 Department of Radiology, Neuroradiology and Nuclear Medicine, Johannes Wesling Medical Center, Ruhr University Bochum, Germany
2 Institute of Medical Epidemiology, Biostatistics, and Informatics, Martin Luther University Halle Wittenberg, Halle, Germany
3 Department of Dermatology, Johannes Wesling Medical Center, Ruhr University Bochum, Germany

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Correspondence

Herr Prof. Alexey Surov
Department of Radiology, Neuroradiology and Nuclear Medicine, Johannes Wesling Hospital Minden, Hans-Nolte Str 1, 44801 Minden, Germany
Tel.: +49/5 71/79 00
Alexey.Surov@muehlenkreiskliniken.de

ABSTRACT

Background Sarcopenia is defined as a loss of muscle mass and strength as well as decreased physical performance.
Method The present study provides a systematic overview of the current literature in regard to the prognostic role of sarcopenia in oncology.
Conclusion In oncologic patients, sarcopenia occurs in 39.6 % of cases in a curative setting and in 49.2 % in a palliative setting. Sarcopenia is associated with dose-limiting toxicity. Furthermore, sarcopenia is associated with the occurrence of postoperative complications. Also, reduced muscle mass limits its overall survival in most tumors both in a curative and a palliative setting. Therefore, analysis of the skeletal musculature on staging CT should be implemented in the clinical routine in oncology.

Key Points

- In oncologic patients, the prevalence of sarcopenia is 39.6 % in a curative setting and 49.2 % in a palliative setting.
- Sarcopenia is associated with dose-limiting toxicity and treatment response.
- Sarcopenia predicts overall survival in oncologic patients.

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ZUSAMMENFASSUNG

Hintergrund Sarkopenie ist durch einen Verlust von Muskelkraft, Muskelmasse und –funktion charakterisiert. Sie ist ein sehr häufiges Syndrom bei onkologischen Patienten, quantitativ messbar und prognostisch bei vielen Tumorentitäten klinisch relevant.
Methode Mit einer systematischen Analyse der publizierten Meta-Analysen gibt die vorliegende Arbeit eine Übersicht zum aktuellen Kenntnisstand und der prognostischen Rolle der Sarkopenie in der Onkologie.
Schlussfolgerung Die Prävalenz der Sarkopenie beträgt bei onkologischen Patienten 39,6 % im kurativen Setting und 49,2 % im palliativen Setting. Sarkopenie ist stark assoziiert mit der dosislimitierenden Toxizität von Tumortherapien. Sarkopenie beeinflusst das Ansprechen auf antitumorale Therapien deutlich. Das Vorliegen der Sarkopenie korreliert mit dem Auftreten schwerer postoperativer Komplikationen in der Onkochirurgie. Sie ist ein limitierender Faktor für das Gesamtüberleben bei den meisten onkologischen Erkrankungen sowohl im kurativen als auch im palliativen Setting. Der Zustand der Skelettmuskulatur sollte daher in den radiologischen Staging-Berichten bei onkologischen Patienten erwähnt werden.

Kernaussagen

- Die Prävalenz der Sarkopenie bei onkologischen Patienten beträgt 39,6 % im kurativen Setting und 49,2 % im palliativen Setting.
- Sarkopenie ist stark assoziiert mit der dosislimitierenden Toxizität und dem Therapieansprechen.
- Sarkopenie beeinflusst das Gesamtüberleben im kurativen wie auch palliativen Setting.

Background

Sarcopenia is characterized by a loss of muscle strength, mass, and function [1]. Sarcopenia is common in patients with advanced malignant diseases [2, 3]. Due to the high prevalence of sarcopenia, it is currently the subject of intensive research. In oncological visceral surgery, sarcopenia can be a better predictor of 1-year mortality, morbidity, and postoperative complications in various diseases compared to other physiological reserve metrics like the "frailty index" and the Eastern Cooperative Oncology Group (ECOG) score. Therefore, sarcopenia is more important as a predictive factor than disease-specific scores [4, 5]. Moreover, a connection between pretherapeutic sarcopenia and toxicity of various chemotherapies was observed [6].

When staging oncological patients, imaging methods can provide quick and objective evaluation of skeletal muscle quality and quantity. In the case of computed tomography as a frequently used imaging method, calculations of skeletal muscle mass are usually based on the total area of all skeletal muscles on the axial plane at the level of L3 [7–9] (▶ **Fig. 1**). With AI, these measurements can already be performed fully automatically by prototypes in that skeleton segmentation, automatic slice selection, and slice-specific segmentation of the musculature at the level of L3 are performed. The muscle area determined based on the CT slice at the level of L3 correlates very well with the total body muscle mass [7, 9–12]. Segmentation of skeletal muscle on computed tomography is performed based on the HU values. Thus, a muscle-specific cut-off value of -29 to + 150 HU is used for measuring muscle tissue [7, 9, 10]. On magnetic resonance imaging, muscle segmentation is performed based on the contrast between muscle tissue and fat. Primarily T1-weighted sequences and sequences with which the fat and water content can be quantified (Dixon sequences) are used to visualize the muscle morphology (▶ **Fig. 2**).

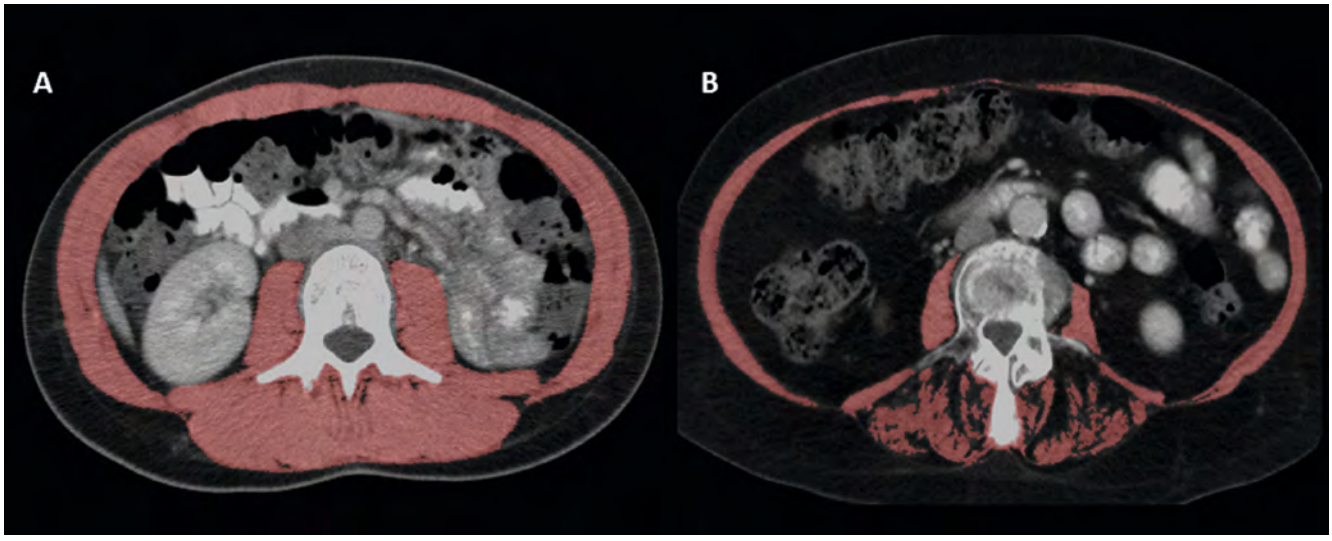
The skeletal muscle index (SMI) can be calculated from the muscle area and the body size (SMI = muscle area [cm^2]/body size [m] squared) [7, 9–12]. The muscle area can be determined on staging CT or MRI images with the help of both commercial and free computer programs and is now performed in the clinical routine.

Various cut-off values for the determination of reduced muscle mass are published in the literature (▶ **Table 1**).

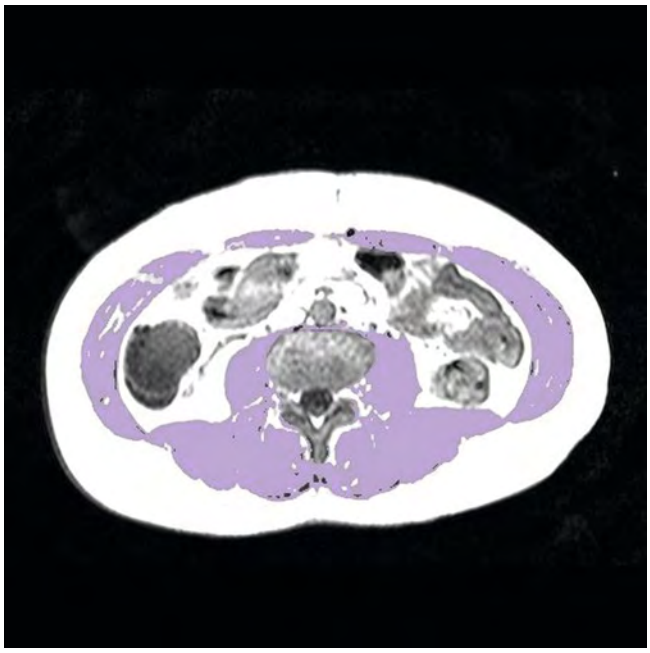
The present study describes the role of sarcopenia in oncology and provides an overview of the current scientific results.

Prevalence of sarcopenia in oncology

Sarcopenia is very common in cancer patients. The prevalence of sarcopenia is 39.6 % in the curative setting and 49.2 % in the palliative setting [13] and varies between the individual tumor entities (▶ **Table 2**). Patients with esophageal cancer, cholangiocarcinoma, sarcomas, prostate cancer, and urothelial carcinoma frequently have concomitant sarcopenia (> 50 % in each case).



▶ **Fig. 1** Measurement of skeletal muscle based on computed tomography. Skeletal muscle is marked in red. **A** Patient with normal muscle area, SMI = 70 cm^2/m^2. **B** Patient with reduced muscle area (sarcopenia), SMI = 39 cm^2/m^2. Both patients have the same BMI = 25.



▶ **Fig. 2** Measurement of skeletal muscle based on MRI.

Prognostic role of sarcopenia in oncology

Sarcopenia is considered a causal factor and not just an epiphenomenon of cancer diseases. In addition to its broad prevalence in the population, sarcopenia can be caused by different factors like impaired food intake due to an obstructive tumor, insufficient food intake, alcohol and tobacco consumption, and tumor-associated inflammation [3, 4, 10]. Moreover, chemotherapeutic agents can damage skeletal muscle. Finally, skeletal muscle interacts intensively with the immune system and produces specific cytokines and peptides that have positive immunological effects and thus affect the course of the disease and treatment [3, 4, 9, 10].

Sarcopenia and dose-limiting toxicity

In accordance with the current literature, sarcopenia is highly associated with dose-limiting toxicity (DLT) of medication-based tumor therapies. In the curative setting, patients with reduced muscle mass have a higher risk of developing DLT compared to patients with normal muscle mass (OR = 2.48, 95 %CI (1.77–3.48), p < 0.00 001) [6].

Sarcopenia has a significant effect on DLT also in the palliative setting. In patients undergoing conventional chemotherapy, the effect of sarcopenia is moderate: OR = 2.14, 95 %CI (1.38–3.31), p = 0.0006 [6]. The effect of sarcopenia is measurably greater in patients receiving different kinase inhibitors: OR = 3.08, 95 %CI (1.87–5.09), p = 0.00 001 [6]. In contrast, sarcopenia has no relative effect on DLT in the case of immunotherapies: OR = 1.30, 95 % CI (0.79–2.11), p = 0.3 [6].

▶ **Table 1** Established cut-off values for skeletal muscle on computed tomography (European and North American populations).

Authors	Men (cm^2/m^2)	Women (cm^2/m^2)
Prado et al. [7]	< 52.4	< 38.6
Martin et al. [9]	BMI < 25 kg/m^2: < = 43 BMI > = 25 kg/m^2: < = 53.0	< 41
Baracos et al. [10]	< 55.4	< 38.9
van Vledder et al. [11]	< 43.8	< 41.1
Camus et al. [12]	< 55.8	< 38.9

Sarcopenia and treatment response

Sarcopenia is a highly significant predictive factor for the objective response rate of chemotherapies in the curative setting: OR = 0.24, 95 %CI (0.12–0.50), p = 0.0001 [14]. In conventional palliative chemotherapy, sarcopenia does not play a predictive role for the objective response rate according to the current results of meta-analyses: OR = 0.94, 95 % CI (0.57–1.55), p = 0.81 [14]. The reduced muscle mass also has no prognostic significance for the prediction of treatment response in patients receiving palliative treatment with kinase inhibitors: OR = 0.74, 95 %CI (0.44–1.26), p = 0.27 [14]. In relation to palliative immunotherapies, the objective response rate did not have any predictive power: OR = 0.74, 95 %CI (0.54–1.01), p = 0.06 [14].

Sarcopenia and postoperative complications

Sarcopenia is highly associated with severe postoperative complications in diverse gastrointestinal tumors, RR = 1.40, 95 % CI (1.20–1.64), p < 0.001 [5]. The greatest effect was observed in patients with gastric cancer, RR = 1.97, 95 % CI (1.11–3.51), p = 0.02 [5]. In contrast, sarcopenia had no relevant effect on postoperative complications in patients with colon cancer and esophageal cancer [5].

Sarcopenia and survival

In the curative setting, reduced muscle mass has a significant effect on overall survival [15]. The maximum negative effect of sarcopenia was reported in bronchial carcinoma followed by urothelial carcinoma and squamous cell carcinoma in the head/neck region (▶ **Table 3**). In the case of hepatocellular carcinoma, pancreatic cancer, cholangiocarcinoma, squamous cell carcinoma of the head/neck region, and gastric cancer, sarcopenia is an independent predictive factor for overall survival. Sarcopenia also has a significant effect on disease-free survival in most cancers (▶ **Table 3**). This effect is particularly pronounced in squamous cell carcinoma of the head/neck region, cholangiocarcinoma, gastric cancer, and hepatocellular carcinoma.

Sarcopenia is also prognostically significant in the palliative setting. However, its influence on overall survival is less pro-

▶ **Table 2** Prevalence of sarcopenia in various tumors [13].

Tumors	Prevalence of sarcopenia, %	
	Curative setting	Palliative setting
Esophageal cancer	50.2	74.2
Breast cancer	31.6	41.3
Colorectal cancer	39.4	53.0
Cholangiocarcinoma	55.6	No data
Gastric cancer	31.8	40.3
Head-neck squamous cell carcinoma	39.9	No data
Hepatocellular carcinoma	35.4	38.2
Bronchial carcinoma	36.0	51.5
Melanoma	No data	29.6
Ovarian cancer	47.7	33.8
Pancreatic cancer	41.0	41.7
Prostate cancer	51.9	76.1
Renal cell carcinoma	41.2	55.0
Sarcoma	62.0	31.5
Thyroid cancer	No data	51.0
Urothelial carcinoma	50.0	66.7
Cervical cancer	48.8	No data
Total	**39.6**	**49.2**

nounced than in the curative setting (▶ **Table 4**). In colorectal cancer, urothelial carcinoma, hepatocellular carcinoma, prostate cancer, and pancreatic cancer, reduced muscle mass is an independent parameter influencing overall survival.

Sarcopenia also has a relevant effect on progression-free survival in renal cell carcinoma, urothelial carcinoma, bronchial carcinoma, and ovarian cancer (▶ **Table 4**).

Discussion

The current studies presented in this review article show that sarcopenia is a prognostically relevant factor in oncology. It can be measured in a cost-effective manner during staging and is a reproducible and quantifiable parameter. The diagnosis of sarcopenia on CT or MRI can therefore improve care by allowing more precise risk stratification and personalized oncological therapy.

The relationship between skeletal muscle and clinical outcome in oncology is multifactorial. There are multiple mechanisms that provoke and/or regulate sarcopenia in oncological patients [3, 16, 17]. On the one hand, tumors can mechanically impair food intake. This applies to malignancies of the upper gastrointestinal tract as well as various head-neck tumors, esophageal cancer, and/or stomach cancer. On the other hand, oncology patients often have insufficient food intake [18]. Alcohol and/or tobacco consumption also plays an important role. Tumor-associated inflammation is also an important factor in the pathophysiology of sarcopenia [3, 16–20]. It induces a metabolic change and cell apoptosis of skeletal muscle mediated by proinflammatory cytokines like tumor necrosis factor alpha, interleukin-1, and interleukin-6 [17, 19, 20]. In addition, other cytokines like myostatin, activin, and the transforming growth factor-beta are significantly elevated in cancer patients and trigger the decomposition of myofibrillar muscle proteins [19]. Chemotherapeutic agents like cisplatin can also damage skeletal muscle [21]. Finally, most tumor patients are old and tumor-related sarcopenia develops in these patients at the same time as preexisting age-related sarcopenia.

The phenomenon of sarcopenia predicting the toxicity of oncological treatment in patients is multicausal [17, 22, 23]. Sarcopenia could result in changes in the distribution, metabolism, and clearance of cancer medications [17, 22–24]. Studies have shown that the plasma concentration of diverse chemotherapeutic agents in patients with sarcopenia is indeed elevated [25–27]. This phenomenon was observed in breast cancer [25, 28], hepatocellular carcinoma [29], medullary thyroid cancer [30], and colorectal cancer [31]. For example, patients with sarcopenia and medullary thyroid cancer had an increased average serum concentration of vandetanib (1037 ng/ml vs. 745 ng/ml, $p = 0.04$) [30]. Moreover, dose-limiting toxic reactions occurred more frequently in patients with sarcopenia than in patients with normal muscle mass (73 % vs. 14 %, $p = 0.004$) [30]. The observed relationships between sarcopenia and drug concentration in plasma can be explained by the fact that skeletal muscle is a significant component of lean body mass (LBM) [17, 23, 24]. LBM includes metabolically active tissue like the liver and kidneys, intracellular and extracellular water, skeletal muscle, and bone [17, 23, 24, 26]. Moreover, the entire LBM can be determined based on the muscle cross-sectional area [26]: LBM (kg) = 0.30 × [skeletal muscle area at L3 on CT (cm^2)] + 6.06.

According to the literature, the chemotherapy dose per LBM is a strong predictor of DLT [23, 24]. To date, Sjøblom et al. have shown that the gemcitabine dose per kg LBM is associated with grade 3–4 hematological toxicity in patients with lung cancer [27]. Moreover, Williams et al. examined the pharmacokinetics and toxicity of 5-fluorouracil (5FU) in patients with colorectal cancer and determined that patients with grade 3/4 toxicity received a higher dose of 5FU per kg LBM [31]. Similar results were observed by Prado et al. for breast cancer [22, 25, 28]. The higher plasma concentration of the drug in patients with sarcopenia could be related to the fact that the chemotherapy dose is calculated on the basis of the body surface area (BSA). However, the BSA does not reflect body composition [22–24]. Moreover, patients with the same BSA have major differences in LBM [23, 24, 32].

In addition, an excessive dose of chemotherapeutic agents in patients with sarcopenia can be the result of decreased activity of the liver cytochromes involved in the metabolism of chemotherapeutic agents [17, 23, 24]. In an experimental study, a significant decrease in the activity of liver cytochromes was observed in rats with sarcopenia [33].

Interestingly, the relationship between DLT and sarcopenia can differ depending on the treatment setting. Curative chemotherapy is more aggressive than palliative chemotherapy and the risk

▶ **Table 3** Effect of sarcopenia on survival in different tumors in a curative setting [15].

Overall survival						
Diagnosis	**Univariable analysis**			**Multivariable analysis**		
	HR	**95 %CI**	**p-value**	**HR**	**95 %CI**	**p-value**
HNSCC	2.2	1.72–2.84	0.00 001	2.05	1.55–2.72	0.00 001
Pancreatic cancer	1.8	1.41–2.28	0.00 001	1.62	1.27–2.07	0.0001
Bronchial carcinoma	2.9	2.31–3.62	0.00 001			
Cholangiocarcinoma	2.0	1.47–2.73	0.01	2.26	1.75–2.26	0.00 001
Gastric cancer	1.9	1.68–2.12	0.00 001	2.02	1.71–2.38	0.00 001
Colorectal cancer	1.8	1.57–2.14	0.00 001			
Esophageal cancer	1.6	1.25–1.95	0.0001			
HCC	2.0	1.56–2.44	0.00 001	2.17	1.48–3.19	0.0001
Urothelial carcinoma (kidney)	2.5	1.09–5.85	0.003			
Bladder cancer	1.6	1.37–1.94	0.45			
Renal cell carcinoma	1.6	1.19–2.24	0.2			
Breast cancer	1.7	1.25–2.33	0.032			
Disease-free survival						
Diagnosis	**Univariable analysis**			**Multivariable analysis**		
	HR	**95 %CI**	**p-value**	**HR**	**95 %CI**	**p-value**
HNSCC	2.0	1.63–2.45	0.00 001	1.64	1.33–2.03	0.00 001
Pancreatic cancer	1.7	1.29–2.24	0.0002	1.86	1.34–2.6	0.0002
Bronchial carcinoma	1.66	1.0–2.74	0.05			
Cholangiocarcinoma	1.89	1.12–3.17	0.02	2.2	1.75–2.75	0.00 001
Colorectal cancer	1.55	1.29–1.88	0.00 001			
Esophageal cancer	1.73	1.04–2.87	0.03			
HCC	1.85	1.44–2.37	0.00 001	1.79	1.28–2.5	0.0006
Gastric cancer				1.97	1.71–2.26	0.00 001

HNSCC: head/neck squamous cell carcinoma; HCC: hepatocellular carcinoma.

of DLT in patients with sarcopenia is higher in the curative setting. More importantly, the relationship between sarcopenia and DLT depends on the treatment substances. The relationship between sarcopenia and DLT is greatest in patients undergoing kinase inhibitor therapy. Moreover, the effect of sarcopenia on treatment-based toxicity is lowest in patients treated with checkpoint inhibitors.

The exact reason for this is not yet clear. Various chemotherapeutic agents probably have a different distribution in the compartments of the body [22–24].

Further important aspects regarding the role of skeletal muscle in homeostasis are known. According to the literature, skeletal muscle functions like an endocrine organ in that it synthesizes and releases a specific group of cytokines and peptides, known as myokines. There are multiple interactions between skeletal muscle and the immune system [34]. For example, patients with sarcopenia have a lower average number of CD8 + T-cells than patients without sarcopenia [34]. Skeletal muscle cells interact with immune cells, express the main histocompatibility complexes I and II and affect T-cell function [35]. Moreover, skeletal muscles produce myokines with immunological effects [36]. For example, interleukin (IL)-15 is a myokine that stimulates the proliferation and activation of natural killer cells and CD8 + T-lymphocytes [37]. Thus, intravenous administration of IL-15 resulted in a significant increase in circulating CD8 + T-cells and NK-cells in patients with various tumors [37, 38]. Theoretically, reduced musculature can result in the production of a smaller amount of myokines. Moreover, it was able to be shown that immunotherapy in combination with the administration of IL-15 extended the survival of mice with tumors [39]. A lower IL-15 level can presumably affect the efficacy of immunotherapy.

It is clear that the relationships between the clinical treatment result and skeletal muscle in oncology is complex and multifactorial. Further experimental studies are therefore needed to clarify the exact mechanisms of these interactions. Regardless of the physiological mechanisms, this information is very important for daily clinical practice and could be helpful for treatment selection. Therefore, the determination of sarcopenia based on a measure-

▶ **Table 4** Effect of sarcopenia on survival in different tumors in a palliative setting [15].

Overall survival						
Diagnosis	**Univariable analysis**			**Multivariable analysis**		
	HR	**95 %CI**	**p-value**	**HR**	**95 %CI**	**p-value**
Pancreatic cancer	1.56	1.21–2.02	0.0006	1.77	1.39–2.26	0.00 001
HCC	2.11	1.44–3.11	0.0001	2.24	1.6–3.14	0.0001
Breast cancer	1.36	0.62–2.97	0.105			
Colorectal cancer	1.34	0.94–1.91	0.1	2.05	1.18–3.56	0.01
Prostate cancer	1.24	0.56–2.74	0.6	1.87	1.14–3.06	0.01
Gastric cancer	1.31	0.96–1.77	0.06	1.21	0.94–1.56	0.13
Renal cell carcinoma	1.64	0.9–2.99	0.1	1.55	0.91–2.63	0.1
Urothelial carcinoma	2.75	1.77–4.28	0.00 001	2.77	1.91–4.02	0.00 001
Bronchial carcinoma	2.38	1.84–3.82	0.0004			
Cervical cancer	1.1	0.93–1.31	0.28			
Endometrial cancer	1.42	0.92–2.1	0.07			
Ovarian cancer	1.4	1.2–1.64	0.0001			
Melanoma	1.67	1.11–2.52	0.01			
Lung cancer	1.61	1.24–2.1	0.001			
Esophageal cancer	1.51	1.21–1.89	0.0003			
Progression-free survival						
Diagnosis	**Univariable analysis**					
	HR	**95 %CI**	**p-value**			
Colorectal cancer	1.49	0.94–2.35	0.09			
Gastric cancer	1.76	0.66–4.66	0.26			
Renal cell carcinoma	2.02	1.24–3.27	0.004			
Urothelial carcinoma	2.43	1.59–3.74	0.0001			
Ovarian cancer	1.3	1.03–1.64	0.03			
Melanoma	1.49	0.98–2.26	0.06			
Bronchial carcinoma	1.98	1.32–2.97	0.001			

HCC: Hepatocellular carcinoma.

ment during staging CT can be a next step on the path to personalized oncology.

To improve clinical treatment results, muscle mass and function can be positively influenced by various measures. For example, it was shown that fitness programs and protein-rich nutrition reduced sarcopenia in patients with gastric cancer and greatly improved the postoperative course [40].

Several studies indicate that reduced muscle density or myosteatosis plays a predictive role in various tumors [41, 42]. However, scientific data with sufficient evidence is only currently available for bronchial carcinoma, colorectal cancer, gastric cancer, and pancreatic cancer [42–45]. Moreover, the effect of myosteatosis on survival rates is lower than that of sarcopenia [42–45].

In addition, individual publications were able to show that modern medical imaging post-processing methods, e. g., radiomics, also allow sensitive analysis of muscle quality [46, 47]. The literature in this regard is based solely on individual studies. Therefore, definitive population-based statements currently cannot be made [46, 47].

Our analysis identified some deficiencies in the current literature regarding the clinical relevance of sarcopenia in oncology. Most publications are retrospective and thus have a corresponding bias. Moreover, the published studies only reported the results of regression analyses. Other important statistical values like negative predictive value were not analyzed.

Conclusion

Sarcopenia is a major clinical problem in oncology. It affects all relevant outcome parameters in oncology patients and should therefore be included in risk stratification. The condition of skeletal muscle should therefore be taken into consideration in radiology staging reports for oncology patients.

Conflict of Interest

The authors declare that they have no conflict of interest.

References

[1] Cruz-Jentoft AJ, Bahat G, Bauer J et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing 2019; 48: 16–31

[2] Ali S, Garcia JM. Sarcopenia, Cachexia and Aging: Diagnosis, Mechanisms and Therapeutic Options – A Mini-Review. Gerontology 2014; 60: 294–230

[3] Rier HN, Jager A, Sleijfer S et al. The Prevalence and Prognostic Value of Low Muscle Mass in Cancer Patients: A Review of the Literature. Oncologist 2016; 21 (11): 1396–1409

[4] Buettner S, Wagner D, Kim Y et al. Inclusion of Sarcopenia Outperforms the Modified Frailty Index in Predicting 1-Year Mortality among 1326 Patients Undergoing Gastrointestinal Surgery for a Malignant Indication. J Am Coll Surg 2016; 222: 397–407

[5] Simonsen C, de Heer P, Bjerre ED et al. Sarcopenia and Postoperative Complication Risk in Gastrointestinal Surgical Oncology: A Meta-analysis. Ann Surg 2018; 268 (1): 58–69

[6] Surov A, Pech M, Gessner D et al. Low skeletal muscle mass is a predictor of treatment related toxicity in oncologic patients. A meta-analysis. Clin Nutr 2021; 40 (10): 5298–5310

[7] Prado CM, Lieffers JR, McCargar LJ et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. Lancet Oncol 2008; 9 (7): 629–635

[8] Shachar SS, Williams GR, Muss HB et al. Prognostic value of sarcopenia in adults with solid tumours: A meta-analysis and systematic review. Eur J Cancer 2016; 57: 58–67

[9] Martin L, Birdsell L, Macdonald N et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. J Clin Oncol 2013; 31 (12): 1539–1547

[10] Baracos VE, Reiman T, Mourtzakis M et al. Body composition in patients with non-small cell lung cancer: A contemporary view of cancer cachexia with the use of computed tomography image analysis. Am J Clin Nutr 2010; 91: 1133S–1137S

[11] van Vledder MG, Levolger S, Ayez N et al. Body composition and outcome in patients undergoing resection of colorectal liver metastases. Br J Surg 2012; 99: 550–557

[12] Camus V, Lanic H, Kraut J et al. Prognostic impact of fat tissue loss and cachexia assessed by computed tomography scan in elderly patients with diffuse large B-cell lymphoma treated with immunochemotherapy. Eur J Haematol 2014; 93: 9–18

[13] Surov A, Wienke A. Prevalence of sarcopenia in patients with solid tumors: A meta-analysis based on 81,814 patients. JPEN J Parenter Enteral Nutr 2022; 46 (8): 1761–1768

[14] Surov A, Strobel A, Borggrefe J et al. Low skeletal muscle mass predicts treatment response in oncology: a meta-analysis. Eur Radiol 2023; 33 (9): 6426–6437

[15] Surov A, Wienke A, Gutzmer R et al. Time to include sarcopenia into the oncological routine. Eur J Cancer 2023; 190: 112939

[16] Williams GR, Dunne RF, Giri S et al. Sarcopenia in the Older Adult With Cancer. J Clin Oncol 2021; 39 (19): 2068–2078

[17] Hilmi M, Jouinot A, Burns R et al. Body composition and sarcopenia: The next-generation of personalized oncology and pharmacology? Pharmacol Ther 2019; 196: 135–159

[18] van der Meij BS, Teleni L, McCarthy AL et al. Cancer cachexia: an overview of diagnostic criteria and therapeutic approaches for the accredited practicing dietitian. J Hum Nutr Diet 2021; 34 (1): 243–254

[19] Cohen S, Nathan JA, Goldberg AL. Muscle wasting in disease: molecular mechanisms and promising therapies. Nat Rev Drug Discov 2015; 14 (1): 58–74

[20] Armstrong VS, Fitzgerald LW, Bathe OF. Armstrong Cancer-Associated Muscle Wasting-Candidate Mechanisms and Molecular Pathways. Int J Mol Sci 2020; 21 (23): 9268

[21] Sakai H, Asami M, Naito H et al. Exogenous insulin-like growth factor 1 attenuates cisplatin-induced muscle atrophy in mice. J Cachexia Sarcopenia Muscle 2021; 16. doi:10.1002/jcsm.12760

[22] Prado CM, Maia YL, Ormsbee M et al. Assessment of nutritional status in cancer-the relationship between body composition and pharmacokinetics. Anticancer Agents Med Chem 2013; 13 (8): 1197–1203

[23] Hopkins JJ, Sawyer MB. A review of body composition and pharmacokinetics in oncology. Expert Rev Clin Pharmacol 2017; 10 (9): 947–956

[24] Hopkins JJ, Sawyer MB. Interactions of lean soft-tissue and chemotherapy toxicities in patients receiving anti-cancer treatments. Cancer Chemother Pharmacol 2018; 82 (1): 1–29

[25] Prado CMM, Baracos VE, McCargar LJ et al. Body composition as an independent determinant of 5-fluorouracil-based chemotherapy toxicity. Clinical Cancer Research 2007; 13 (11): 3264–3268

[26] Mourtzakis M, Prado CM, Lieffers JR et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. Appl Physiol Nutr Metab 2008; 33: 997–1006

[27] Sjøblom B, Grønberg BH, Benth JŠ et al. Low muscle mass is associated with chemotherapy-induced haematological toxicity in advanced non-small cell lung cancer. Lung Cancer 2015; 90 (1): 85–91

[28] Prado CM, Baracos VE, McCargar LJ et al. Sarcopenia as a determinant of chemotherapy toxicity and time to tumor progression in metastatic breast cancer patients receiving capecitabine treatment. Clin Cancer Res 2009; 15 (8): 2920–2926

[29] Mir O, Coriat R, Blanchet B et al. Sarcopenia predicts early dose-limiting toxicities and pharmacokinetics of sorafenib in patients with hepatocellular carcinoma. PLoS One 2012; 7 (5): e37563

[30] Massicotte MH, Borget I, Broutin S et al. Body composition variation and impact of low skeletal muscle mass in patients with advanced medullary thyroid carcinoma treated with vandetanib: results from a placebo-controlled study. J Clin Endocrinol Metab 2013; 98 (6): 2401–2408

[31] Williams GR, Deal AM, Shachar SS et al. The impact of skeletal muscle on the pharmacokinetics and toxicity of 5-fluorouracil in colorectal cancer. Cancer Chemother Pharmacol 2018; 81 (2): 413–417

[32] Cespedes Feliciano EM, Chen WY, Lee V et al. Body Composition, Adherence to Anthracycline and Taxane-Based Chemotherapy, and Survival After Nonmetastatic Breast Cancer. JAMA Oncol 2020; 6 (2): 264–270

[33] Cvan Trobec K, Kerec Kos M, Trontelj J et al. Influence of cancer cachexia on drug liver metabolism and renal elimination in rats. J Cachexia Sarcopenia Muscle 2015; 6 (1): 45–52

[34] Kitano Y, Yamashita YI, Saito Y et al. Sarcopenia Affects Systemic and Local Immune System and Impacts Postoperative Outcome in Patients with Extrahepatic Cholangiocarcinoma. World J Surg 2019; 43 (9): 2271–2280

[35] Afzali AM, Müntefering T, Wiendl H et al. Skeletal muscle cells actively shape (auto)immune responses. Autoimmun Rev 2018; 17 (5): 518–529

[36] Nelke C, Dziewas R, Minnerup J et al. Skeletal muscle as potential central link between sarcopenia and immune senescence. EBioMedicine 2019; 49: 381–388

[37] Conlon KC, Lugli E, Welles HC et al. Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer. J Clin Oncol 2015; 33: 74–82

[38] Dubois SP, Miljkovic MD, Fleisher TA et al. Short-course IL-15 given as a continuous infusion led to a massive expansion of effective NK cells: implications for combination therapy with antitumor antibodies. J Immunother Cancer 2021; 9 (4): e002193

[39] Yu P, Steel JC, Zhang M et al. Simultaneous blockade of multiple immune system inhibitory checkpoints enhances antitumor activity mediated by interleukin-15 in a murine metastatic colon carcinoma model. Clin Cancer Res 2010; 16: 6019–6028

[40] Yamamoto K, Nagatsuma Y, Fukuda Y et al. Effectiveness of a preoperative exercise and nutritional support program for elderly sarcopenic patients with gastric cancer. Gastric Cancer 2017; 20: 913–918

[41] Nowak S, Kloth C, Theis M et al. Deep learning-based assessment of CT markers of sarcopenia and myosteatosis for outcome assessment in patients with advanced pancreatic cancer after high-intensity focused ultrasound treatment. Eur Radiol 2023. doi:10.1007/s00330-023-09974-6

[42] Aleixo GFP, Shachar SS, Nyrop KA et al. Myosteatosis and prognosis in cancer: Systematic review and meta-analysis. Crit Rev Oncol Hematol 2020; 145: 102839

[43] Fang T, Gong Y, Wang Y. Prognostic values of myosteatosis for overall survival in patients with gastric cancers: A meta-analysis with trial sequential analysis. Nutrition 2023; 105: 111866. doi:10.1016/j.nut.2022.111866

[44] Feng S, Mu H, Hou R et al. Prognostic value of myosteatosis in patients with lung cancer: a systematic review and meta-analysis. Int J Clin Oncol 2022; 27 (7): 1127–1138

[45] Lee CM, Kang J. Prognostic impact of myosteatosis in patients with colorectal cancer: a systematic review and meta-analysis. J Cachexia Sarcopenia Muscle 2020; 11 (5): 1270–1282

[46] Iwashita K, Kubota H, Nishioka R et al. Prognostic Value of Radiomics Analysis of Skeletal Muscle After Radical Irradiation of Esophageal Cancer. Anticancer Res 2023; 43 (4): 1749–1760

[47] Saalfeld S, Kreher R, Hille G et al. Prognostic role of radiomics-based body composition analysis for the 1-year survival for hepatocellular carcinoma patients. J Cachexia Sarcopenia Muscle 2023. doi:10.1002/jcsm.13315