Society of Medical Education & Research

2026, Volume 6, Issue 1, Page No: 112-129
ISSN: 3108-4834

Archive of International Journal of Cancer and Allied Science

Impact of Cachexia and Sarcopenia on Outcomes of Synchronous Oligometastatic Non-Small Cell Lung Cancer: A Multicenter Intention-to-Treat Analysis

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Abstract

In advanced NSCLC, a specific subgroup of patients exhibits synchronous oligometastatic disease (sOMD), characterized by a low metastatic burden identified at initial diagnosis. Given the established association of cachexia and sarcopenia with reduced survival, these features could help guide decisions on the appropriateness of radical intervention. This retrospective multicenter investigation included all patients with thoroughly staged (via FDG-PET and brain imaging) sOMD fulfilling the EORTC criteria. The study evaluated associations between cachexia and/or sarcopenia and clinical outcomes. Among 439 patients identified from 2015 to 2021, 234 were eligible and formed the study population. Median age was 67 years, 52.6% were male, and the median number of metastases was 1. Cachexia was present in 46 (19.7%) patients, sarcopenia in 34 (14.5%), and both conditions co-occurred in 21 (9.0%). With a median follow-up of 49.7 months, median progression-free survival (PFS) and overall survival (OS) reached 8.6 and 17.3 months, respectively. Patients without cachexia or sarcopenia exhibited a trend toward improved PFS compared with those affected by either or both. Multivariate analysis revealed no independent association between cachexia or sarcopenia and inferior survival, irrespective of radical treatment delivery. Elevated CRP levels correlated with poorer survival and may represent a useful prognostic marker to support selection of patients likely to benefit from LRT. Despite standardized oligometastatic classification and comprehensive staging, the analyzed subgroups were small. Consequently, larger prospective studies are warranted to confirm these observations and further elucidate the underlying hypothesis.

Keywords: NSCLC, Synchronous oligometastatic disease, Intention to treat, Progression-free survival, Overall survival, Sarcopenia

Introduction

Non-small cell lung carcinoma (NSCLC) accounts for the majority of cancer-related deaths worldwide, primarily because most patients are diagnosed with advanced disease following a prolonged asymptomatic period [1]. Within the spectrum ranging from localized to disseminated NSCLC, synchronous oligometastatic disease affects roughly 20–50% of cases and is defined by a small number of metastases (generally three to five, confined to no more than three organs) detected at the time of primary tumor diagnosis [2, 3]. This entity represents a distinct subset within stage IV disease, in which certain patients may achieve durable disease control or a potential cure by combining local radical therapy (LRT, including minimally invasive surgery or stereotactic radiation therapy (SRT)) with systemic agents [4-7]. Current guidelines recommend considering LRT in addition to systemic therapy for responding oligometastatic NSCLC, although supporting evidence remains limited [8-10]. Modern first-line regimens

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Received: 22 December 2025; **Accepted:** 03 April 2026

How to cite this article: Petrova E, Georgiev I, Stoyanov N, Kolev P. Impact of Cachexia and Sarcopenia on Outcomes of Synchronous Oligometastatic Non-Small Cell Lung Cancer: A Multicenter Intention-to-Treat Analysis. Arch Int J Cancer Allied Sci. 2026;6(1):112-29. https://doi.org/10.51847/fb8srJY6k0

centered on immune checkpoint inhibitors (ICI) and tyrosine kinase inhibitors (TKI) are particularly relevant for patients managed with curative intent. Preclinical models suggest that ICI and SRT interact synergistically through immunomodulatory mechanisms [11, 12]. Clinically, a single-arm phase II trial (n = 51) of pembrolizumab administered after LRT reported superior PFS compared with historical benchmarks [11, 13]. Likewise, a phase III randomized trial (n = 133, NCT02893332) evaluating first-generation EGFR TKI alone or combined with radiotherapy in synchronous oligometastatic EGFR-mutated NSCLC indicated a survival benefit from the addition of radiotherapy [14]. However, both studies and similar trials are limited by selection bias, incomplete staging in many participants, and enrollment restricted to those with favorable characteristics (e.g., good response to systemic therapy or solitary metastasis without mediastinal nodal disease) [15].

Independent of disease stage, cachexia and sarcopenia are each linked to poorer prognosis [16-18]. Cachexia is a multifactorial syndrome driven by systemic inflammation, featuring progressive skeletal muscle wasting that is refractory to nutritional support and associated with declining functional status, impaired performance status (PS), and reduced tolerance to chemotherapy [18]. It may also compromise ICI efficacy through inflammatory pathways [19]. Sarcopenia has similarly been associated with shorter survival in patients receiving first-line ICI or EGFR-TKI [20]. High prevalence of cachexia and its adverse impact on survival have been documented across localized and advanced NSCLC cohorts **(Table 1)** [16-18, 21]. Nevertheless, these reports vary considerably in their definitions and measurement techniques for cachexia and sarcopenia. Data addressing synchronous oligometastatic NSCLC, particularly in unselected intention-to-treat populations, are notably absent.

Table 1. Impact of cachexia and sarcopenia on survival in patients with NSCLC at different disease stages, as reported in recent publications.

Authors	Clinical setting	Study design	No. of patients	Cachexia/Sarcopenia evaluated	Definition of cachexia/Sarcopenia	Treatment	Outcomes (Cachexia/Sarcopenia vs. Non-Cachexia/Sarcopenia)
Madeddu *et al*. [19]	Advanced NSCLC	Prospective, monocenter study	74	Cachexia and sarcopenia	Cachexia: (1) weight loss ≥5% within the previous 6 months, or (2) weight loss >2% with BMI <20. Sarcopenia: skeletal muscle index (SMI) at L3: women <39 cm^2/m^2; men <55 cm^2/m^2	Immune checkpoint inhibitor (ICI) therapy	Cachexia was an independent predictor of poorer survival among patients receiving ICI treatment. Sarcopenia was not significantly associated with progression-free survival (PFS) or overall survival (OS).
Matsuo *et al*. [22]	Advanced or recurrent NSCLC	Retrospective, monocenter study	183	Cachexia	Weight loss ≥5% within the previous 6 months, or weight loss >2% with BMI <20	PD-1/PD-L1 inhibitor therapy	Cachexia was associated with significantly shorter median PFS (2.1 vs. 5.1 months, $p < 0.001$) and OS (5.6 vs. 15.0 months, $p < 0.001$). Multivariate analysis showed that cachexia combined with poor performance status (PS) was associated with inferior survival.
Morimoto *et al*. [23]	All stages of NSCLC (81% stage III–IV) and recurrent disease	Retrospective, multicenter study	196	Cachexia	Weight loss ≥5% within the previous 6 months, or weight loss >2% with BMI <20	Chemoimmunotherapy	In the overall population, cachexia was associated with significantly shorter median PFS (6.7 vs. 9.3 months, $p = 0.04$), while no significant difference in OS was observed. Among patients with PD-L1 expression ≥50%, no significant differences in PFS or OS were observed.

Burtin *et al*. [24]	Stage I–III NSCLC	Prospective, monocenter study	936	Sarcopenia	Low fat-free mass index (FFMI): women <15 kg/m²; men <17 kg/m² [25], combined with handgrip weakness [26]	Primary radiotherapy (RT), sequential chemoradiotherapy (CRT), or concurrent CRT	In patients with PS 0–1, handgrip weakness and low FFMI were significant prognostic factors for OS. In patients with PS ≥2, neither handgrip weakness nor low FFMI was associated with OS.
Bolte *et al*. [27]	Advanced NSCLC	Retrospective, monocenter study	92	Sarcopenia	Sex-specific 25th percentile of psoas muscle index (PMI) at L3 within the study cohort	Chemoimmunotherapy	Sarcopenia was associated with significantly shorter median OS (9.1 vs. 22.3 months, p = 0.003).
Hasenauer *et al*. [28]	Stage I–III NSCLC	Retrospective, monocenter study	401	Sarcopenia	SMI at L3: women <38.5 cm²/m²; men <52.4 cm²/m²	Video-assisted thoracoscopic surgery (VATS) pulmonary resection	Sarcopenia was associated with increased postoperative complications and prolonged hospital stay.
Karaman *et al*. [29]	Stage III NSCLC	Retrospective, monocenter study	56	Sarcopenia	SMI at L3: women <38.5 cm²/m²; men <52.4 cm²/m²	Concurrent CRT or RT alone	Sarcopenia was associated with significantly shorter median OS (19.0 vs. 38.0 months, p < 0.04).
Katsui *et al*. [30]	Stage III NSCLC	Retrospective, monocenter study	60	Sarcopenia	SMI and PMI at L3; cut-off values determined using time-dependent ROC curve analysis	Concurrent CRT	Patients with low SMI had lower 1-, 3-, and 5-year OS rates compared with those with high SMI (63.6%, 53.8%, and 17.9% vs. 92.1%, 59.6%, and 51.0%, respectively).
Lyu *et al*. [20]	Advanced NSCLC	Retrospective, monocenter study	131	Sarcopenia	SMI at L3: women <31.6 cm²/m²; men <40.2 cm²/m²	EGFR tyrosine kinase inhibitor (EGFR-TKI) or ICI therapy	Sarcopenia was associated with significantly shorter median PFS (6.4 vs. 15.1 months, p < 0.001) and OS (13.0 vs. 26.0 months, p < 0.001). Sarcopenia was an independent predictor of both poorer OS and PFS.
Yuan *et al*. [31]	Stage III–IV NSCLC	Retrospective, monocenter study	202	Sarcopenia	SMI at L3: women <32.5 cm²/m²; men <44.7 cm²/m²	Treatment according to NCCN guidelines	Sarcopenia was associated with significantly shorter median PFS (8.0 vs. 13.1 months, p = 0.02) and OS (13.3 vs. 25.8 months, p = 0.003).

Abbreviations: NSCLC—non-small cell lung cancer; BMI—body mass index; CASCO—cachexia score; SMI—skeletal mass index; ICI—immune checkpoint inhibitor; PFS—progression-free survival; OS—overall survival; PD-L1—programmed death ligand 1; PS—performance status; FFMI—fat-free mass index; RT—radiation therapy; CRT: chemoradiation; PMI—Psoas muscle index; VATS—video-assisted thoracic surgery; ROC—receiver operating characteristic; EGFR—epidermal growth factor receptor; TKI—tyrosine kinase inhibitor; NCCN—National Comprehensive Cancer Network.

If cachexia and sarcopenia are also predictive of adverse outcomes regarding survival and toxicity in synchronous OMD (sOMD), this information could refine clinical decision-making concerning the use of radical treatment. The current study therefore examined the relationship between these conditions and key clinical endpoints (survival and toxicity) within a fully staged, intention-to-treat cohort of patients diagnosed with sOMD.

Materials and Methods

Patient inclusion and study design

This investigation adopted a retrospective design and involved two tertiary centers in the Netherlands (Maastricht UMC+ and Zuyderland MC). It included every patient identified with newly diagnosed

synchronous oligometastatic NSCLC during the study period. Records from all thoracic oncology multidisciplinary team (MDT) meetings conducted between January 2015 and December 2021 were systematically reviewed. Given that institutional protocols mandate discussion of all new NSCLC diagnoses at the MDT, the risk of overlooking eligible cases was minimal. The definition of synchronous oligometastatic disease (sOMD) followed the European Organization for Research and Treatment of Cancer (EORTC) consensus, requiring no more than five metastatic lesions involving a maximum of three distinct organs, as confirmed through baseline fluorodeoxyglucose positron emission tomography-computed tomography (FDG-PET-CT) and brain imaging (magnetic resonance imaging (MRI) being the preferred modality). Participants were required to be at least 18 years old at the time of diagnosis. Additional inclusion criteria stipulated that the MDT had endorsed an oligometastatic management strategy (independent of whether the plan was ultimately executed), no history of another cancer within the previous five years (except carcinoma in situ), absence of a second primary lung cancer, and no enrollment in any clinical trial for first-line therapy.

Data on baseline variables were retrieved from electronic health records and comprised age, sex, World Health Organization performance status (WHO-PS), body weight at diagnosis, percentage weight change in the six months before diagnosis, height, smoking history (including pack-years), tumor histology, laboratory parameters obtained within 30 days preceding treatment commencement or at the time of histopathological confirmation, results of molecular testing and programmed death-ligand 1 (PD-L1) expression, TNM classification according to the eighth edition of the American Joint Committee on Cancer (AJCC) with specification of metastatic sites and count, MDT designation as oligometastatic NSCLC, recommendation for local radical therapy (LRT), and details regarding initial systemic treatment. Therapeutic response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [32]. Additional information collected included actual administration of LRT, adverse events documented in clinical notes and graded per the Common Terminology Criteria for Adverse Events (CTCAE version 5.0), date of disease progression, subsequent therapeutic interventions, and date of last known follow-up or death. Cachexia was identified using standard criteria: unintentional weight reduction of more than 5% over the preceding six months, or weight loss exceeding 2% in individuals with a body mass index (BMI) of 20 kg/m² or lower [33].

Sarcopenia involves diminished muscle strength, quantity, and performance, potentially attributable to cachexia, advanced age, or additional contributors [34]. As sarcopenia can be modified and arises from various etiologies, the study analyzed cachexia and sarcopenia as separate categories to delineate their respective effects on clinical outcomes. The European Working Group on Sarcopenia in Older People (EWGSOP) endorses cross-sectional muscle assessment at the L3 vertebral level as a reliable proxy for sarcopenia evaluation [35]. Sarcopenia can be further characterized as muscle mass values falling 2 standard deviations below those observed in healthy young reference populations [36]. In the present work, the Psoas Muscle Index (PMI) was computed by dividing the psoas muscle cross-sectional area (cm²) by height squared (m²) [37] and utilized as a surrogate indicator of sarcopenia. Measurements were performed on diagnostic CT scans when available, or otherwise on low-dose CT images, specifically at the inferior margin of the third lumbar vertebra (L3). Since validated PMI thresholds at L3 are lacking, sex-stratified cut-offs were established using the lowest quartile within the study population: 6.05 mm²/m² for males and 4.20 mm²/m² for females.

Statistical analysis

Analyses were executed with IBM SPSS Statistics version 28 (Chicago, IL, USA). Baseline patient characteristics were summarized descriptively. Comparisons between groups employed the Chi-square test for discrete variables and one-way ANOVA for continuous data. Progression-free survival (PFS) and overall survival (OS) were determined from the date of histopathological confirmation and estimated via the Kaplan–Meier technique. Median follow-up time was calculated using the reverse Kaplan–Meier method, with censoring applied at the final contact date for patients remaining event-free. Logistic regression models were applied for both univariate and multivariate assessment of factors associated with one-year PFS and OS. Statistical significance was defined as a p-value below 0.05.

Results and Discussion

Baseline characteristics of patients

Overall, 439 cases of synchronous oligometastatic NSCLC were detected throughout the observation period. Exclusion criteria eliminated 205 patients for the following reasons: absence of planned radical intervention (n = 84), concurrent other primary tumor (n = 59), incomplete staging workup (n = 32), involvement in a therapeutic clinical trial (n = 25), and loss to follow-up after transfer to another institution (n = 5). Patient selection is summarized in **Figure 1**. The multidisciplinary team decided against radical treatment in these 84 individuals due to suboptimal performance status (n = 55), extensive disease volume incompatible with ablative approaches (n = 20), or explicit patient refusal of additional therapy post-diagnosis (n = 9). In three instances, patients presented with a WHO-PS score of 3 attributable to symptomatic brain metastasis-related edema; however, prompt clinical recovery following steroid therapy enabled the MDT to classify them as appropriate candidates for LRT. Among the 234 fully staged patients for whom radical-intent management was advised, 142 (60.7%) ultimately received LRT after demonstrating response to upfront systemic treatment. Non-completion of LRT was attributed to disease progression on induction therapy (n = 46), clinical decline during induction precluding response assessment (n = 43), or complete remission achieved with induction therapy alone (n = 3).

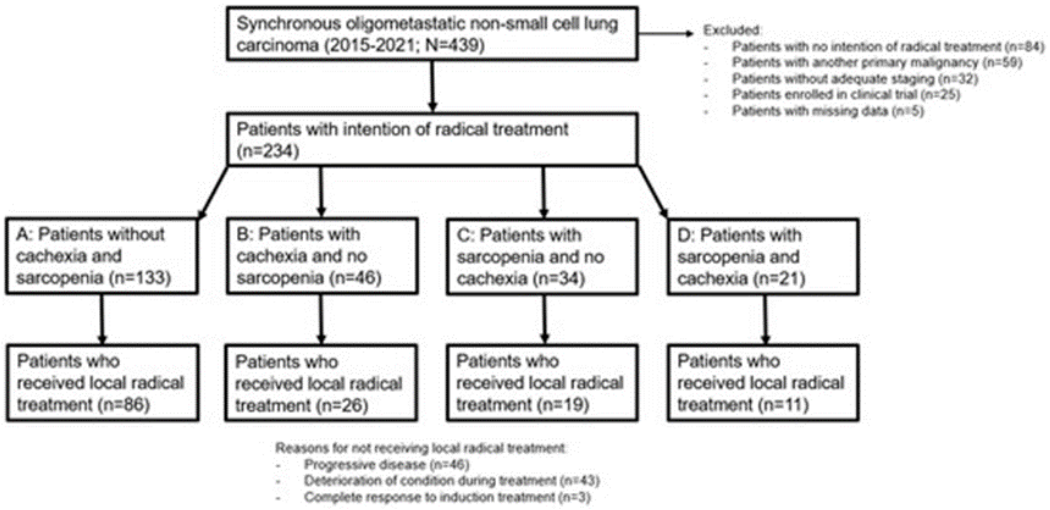


Figure 1. Flowchart of patient inclusion and selection.

To examine the effects of cachexia and sarcopenia, the cohort was stratified into four distinct subgroups according to the presence of these conditions **(Figure 1)**. Group A included patients free from both cachexia and sarcopenia, Group B comprised those with cachexia exclusively, Group C those with sarcopenia alone, and Group D those exhibiting both. **Table 2** displays the baseline demographic and clinical profiles of the 234 participants stratified by cachexia and sarcopenia status. In addition to the anticipated variations in BMI, PMI, and weight loss, notable intergroup differences emerged in WHO-PS, smoking history, serum albumin concentrations, and the systemic treatment regimens employed.

Table 2. Baseline clinical characteristics.

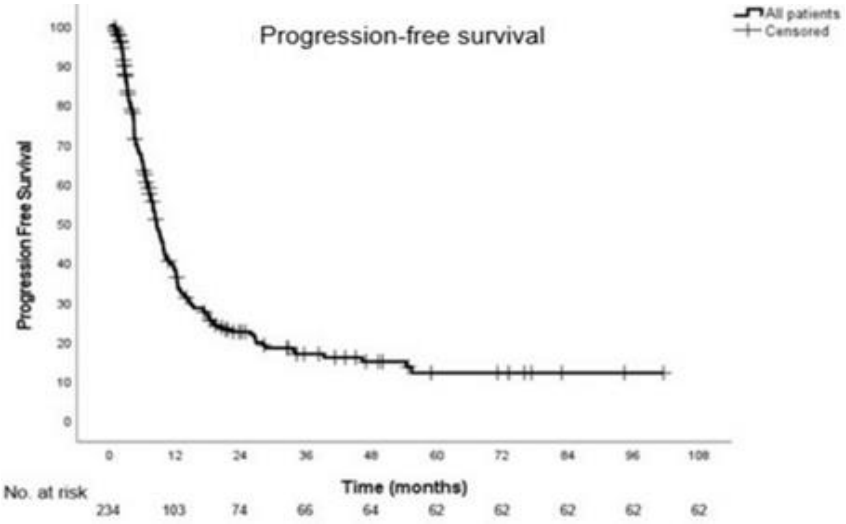
Characteristic	p-value	D: Both cachexia and sarcopenia (n = 21)	C: Sarcopenia without cachexia (n = 34)	B: Cachexia without sarcopenia (n = 46)	A: Neither cachexia nor sarcopenia (n = 133)	Overall cohort (n = 234)
Age at diagnosis, median (range), years	0.69	66 (50–85)	65 (48–88)	67 (49–85)	68 (39–89)	67 (39–89)
Sex, n (%)	0.82					
Male		10 (52.4)	20 (58.8)	25 (54.3)	68 (51.1)	123 (52.6)
Female		11 (47.6)	14 (41.2)	21 (45.7)	65 (48.9)	111 (47.4)

WHO performance status, n (%)	0.001					
0		2 (9.5)	16 (47.1)	12 (26.1)	72 (54.1)	102 (43.6)
1		16 (76.2)	15 (44.1)	26 (56.5)	51 (38.3)	108 (46.2)
2		3 (14.3)	2 (5.9)	6 (13.0)	10 (7.5)	21 (9.0)
3*		0 (0)	1 (2.9)	2 (4.3)	0 (0)	3 (1.3)
Body mass index, median (range), kg/m²	< 0.001	21.1 (15.8–31.2)	24.5 (16.5–41.4)	23.0 (16.6–35.9)	26.4 (18.4–42.1)	25.0 (15.8–42.1)
Weight loss during the 6 months before diagnosis, median (range), kg	< 0.001	9 (1–25)	0 (0–9)	7.3 (2–25)	0 (0–5)	0 (0–25)
Psoas muscle index, median (range), mm²/m²	< 0.001	3.95 (2.13–5.89)	4.21 (1.50–5.94)	6.67 (3.78–14.58)	7.05 (3.90–12.49)	6.32 (1.50–14.58)
LDH, median (range)	0.82	201 (151–415)	211 (122–406)	196 (132–499)	208 (120–699)	208 (120–699)
CRP, median (range), mg/L	0.14	22 (1–217)	13 (1–164)	14 (1–268)	12 (1–174)	13 (1–268)
Serum albumin, median (range), g/dL	0.005	36.0 (21.0–45.4)	39.0 (29.5–49.0)	37.8 (22.1–47.0)	39.7 (21.2–53.0)	39.0 (21.0–53.0)
Serum total protein, median (range), g/dL	0.26	76.1 (76.1–76.1)	67.0 (57.0–71.0)	73.7 (67.0–81.0)	69.1 (57.0–76.0)	70.4 (57.0–81.0)
Smoking status, n (%)	0.02					
Current smoker		12 (57.1)	17 (50.0)	28 (60.9)	44 (33.1)	101 (43.2)
Former smoker		8 (38.1)	16 (47.1)	15 (32.6)	79 (59.4)	118 (50.4)
Never smoker		1 (4.8)	1 (2.9)	1 (2.2)	9 (6.7)	12 (5.1)
Unknown		0 (0)	0 (0)	2 (4.3)	1 (0.8)	3 (1.3)
NSCLC histological subtype, n (%)	0.83					
Non-squamous		18 (85.7)	27 (79.4)	36 (78.3)	102 (76.6)	183 (78.2)
Squamous		3 (14.3)	7 (20.6)	10 (21.7)	31 (23.3)	51 (21.8)
PD-L1 expression status, n (%)	0.57					
Positive (≥50%)		8 (38.1)	14 (41.2)	12 (26.1)	34 (25.6)	68 (29.1)
Positive (1–49%)		4 (19.0)	7 (20.6)	6 (13.0)	28 (21.1)	45 (19.2)
Negative (<1%)		4 (19.0)	3 (8.8)	8 (17.4)	24 (18.0)	39 (16.7)
Unknown		5 (23.9)	10 (29.4)	20 (43.5)	47 (35.3)	82 (35.0)

Abbreviations: WHO-PS—World Health Organization Performance Score; BMI—body mass index; PMI—Psoas muscle index; CRP—C-reactive protein; PD-L1—programmed death ligand 1; ALK—anaplastic lymphoma kinase; EGFR—epidermal growth factor receptor; ICI—immune checkpoint inhibitor; TKI—tyrosine kinase inhibitor; RECIST 1.1—response evaluation criteria in solid tumors 1.1; CR—complete response; PR—partial response; SD—stable disease; PD—progressive disease. *Three patients had a WHO-PS of 3 due to symptomatic cerebral edema, but their clinical condition rapidly improved after treatment, and they were deemed candidates for LRT by the MDT. **TNM staging is based on TNM 8 (AJCC). If staging was based on TNM 7 in the MDT, it is recalculated into TNM 8.

Survival analysis

Across the full study population, the median follow-up period extended to 49.7 months (95% CI, 42.4–57.1). Median progression-free survival (PFS) was recorded as 8.6 months (95% CI, 7.2–9.9), and median overall survival (OS) was 17.3 months (95% CI, 13.9–20.7) **(Figure 2)**.



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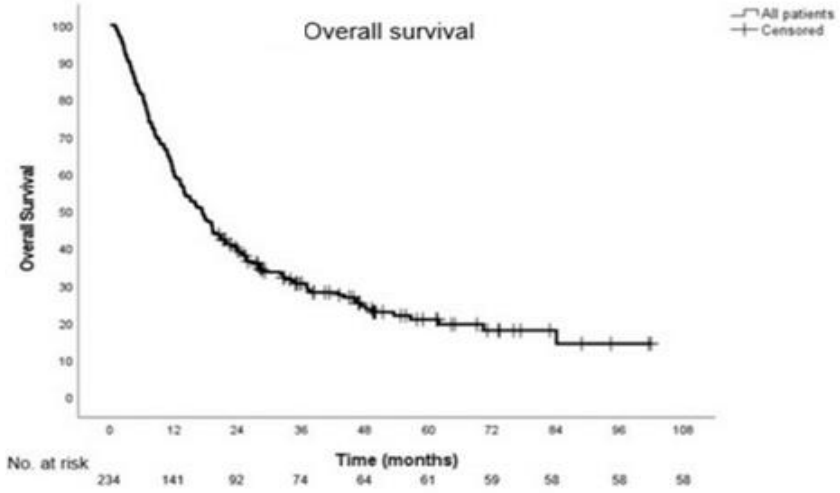
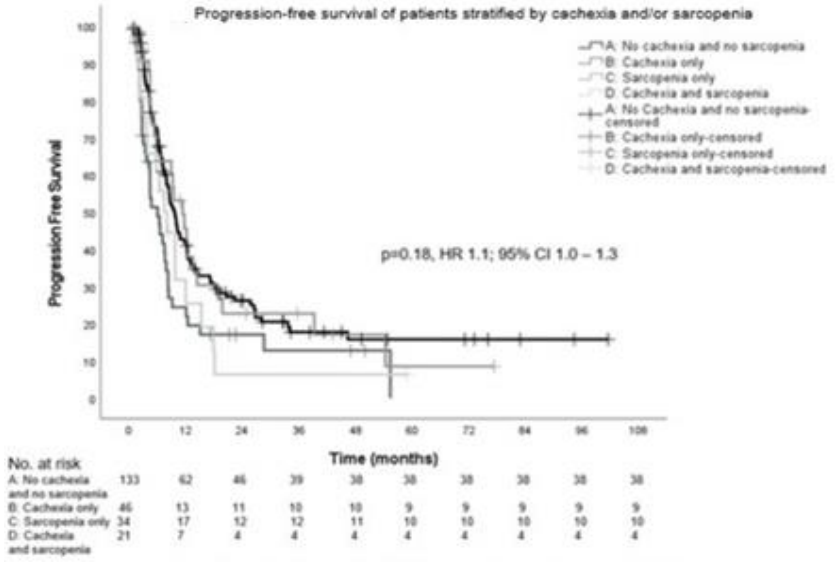


b)

Figure 2. Progression-free survival (a) and overall survival (b) in all patients.

Follow-up durations were comparable across Groups A, B, C, and D at 49.7 (95% CI, 39.9–59.6), 47.0 (95% CI, 42.2–51.8), 43.1 (95% CI, 29.1–57.2), and 57.8 months (95% CI, 37.6–77.9), respectively (p = 0.92). Progression events occurred in 95 (71.4%), 37 (80.4%), 24 (70.6%), and 17 (81.0%) individuals within these respective groups. Mortality was observed in 96 (72.2%), 39 (84.8%), 26 (76.5%), and 15 (71.4%) patients.

No statistically significant differences in median PFS were detected between groups: 9.7 months (95% CI, 8.2–11.1) for Group A, 6.1 months (95% CI, 3.4–8.7) for Group B, 11.4 months (95% CI, 7.8–15.0) for Group C, and 8.1 months (95% CI, 4.9–11.2) for Group D (P = 0.18, hazard ratio (HR): 1.1; 95% CI, 1.0–1.3) **(Figure 3a)**.



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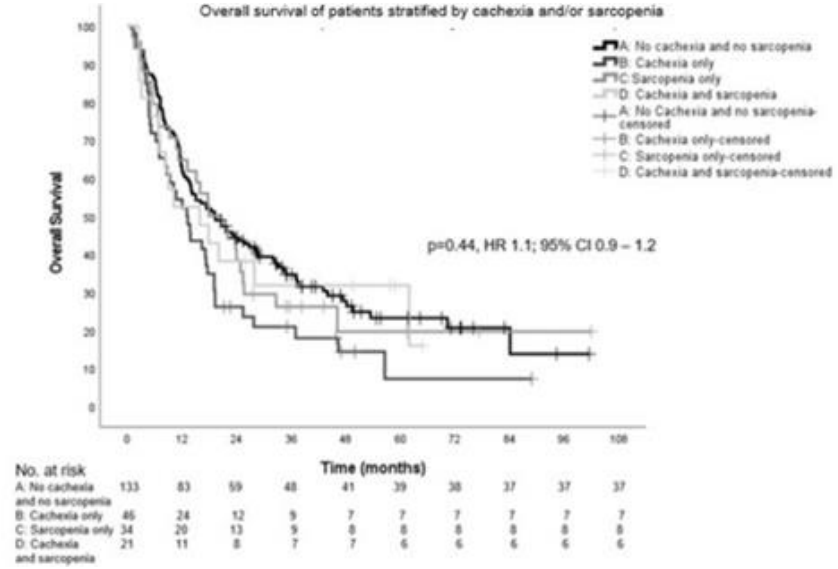


b)

Figure 3. Progression-free survival (a) and overall survival (b) among patients intended for locoregional therapy (LRT), categorized by the presence or absence of cachexia and/or sarcopenia.

Median overall survival showed no statistically significant differences between the groups: 19.3 (95% CI, 12.3–26.2), 13.1 (95% CI, 9.0–17.2), 17.9 (95% CI, 9.2–26.6), and 15.9 months (95% CI, 2.7–29.1), respectively (P = 0.44, HR: 1.1; 95% CI, 0.9–1.2) **(Figure 3b)**.

Additional evaluation focused on patients who ultimately underwent LRT after responding to initial systemic treatment.

Within the studied population, only 60.5% of individuals progressed to LRT after receiving induction systemic therapy. This proportion was lower than the 64.7% observed in group A (patients without cachexia or sarcopenia). Patients with cachexia alone (56.5%), sarcopenia alone (55.9%), and concurrent cachexia plus sarcopenia (52.4%) were less likely to proceed to LRT, although the observed differences lacked statistical significance.

Median progression-free survival likewise demonstrated no significant variation across groups: 12.3 (95% CI, 10.1–14.6), 7.6 (95% CI, 5.5–9.7), 13.6 (95% CI, 10.8–

16.3), and 9.8 months (95% CI, 7.3–12.3), respectively (P = 0.14, HR: 1.2; 95% CI, 1.0–1.4) **(Figure 4a)**.

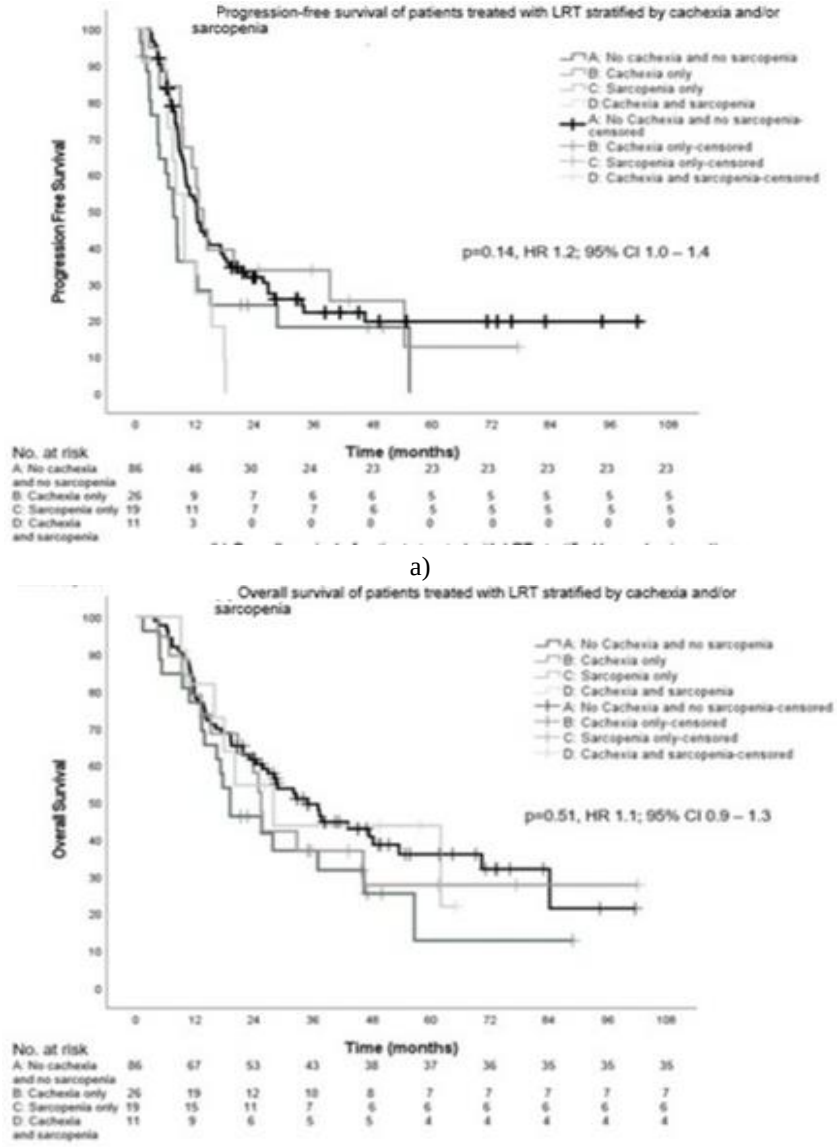
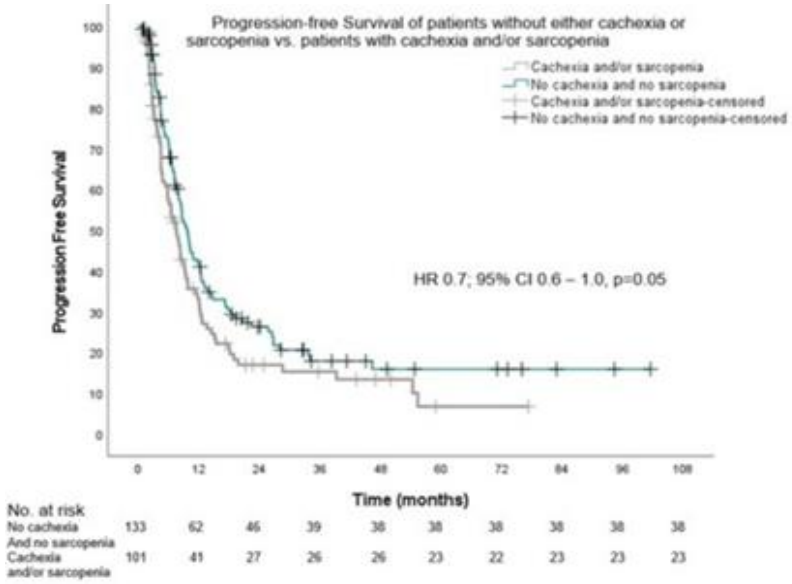


Figure 4. Progression-free survival (a) and overall survival (b) for patients who completed LRT, stratified according to cachexia and sarcopenia.

Although group A exhibited numerically superior median overall survival, no statistically meaningful differences emerged between the groups: 34.9 (95% CI, 25.3–44.4), 19.1 (95% CI, 9.3–28.9), 25.4 (95% CI, 22.8–28.0), and 27.9 months (95% CI, 12.7–43.1), respectively (P = 0.51, HR: 1.1; 95% CI, 0.9–1.3) **(Figure 4b)**.

In a separate comparison, outcomes were assessed between group A (no cachexia and no sarcopenia) and the combined cohort of patients with cachexia and/or sarcopenia (groups B, C, and D). A non-significant trend toward extended progression-free survival was noted in group A, with median PFS of 9.7 months (95% CI, 8.2–11.1) versus 7.5 months (95% CI, 5.9–9.2) in the other groups (HR 0.7, 95% CI 0.6–1.0, P = 0.05). Median

overall survival did not differ substantially: 19.3 months (95% CI, 12.3–26.2) versus 15.9 months (95% CI, 11.9–19.9) (HR: 0.8, 95% CI, 0.6–1.1, P = 0.10), respectively **(Figure 5)**.



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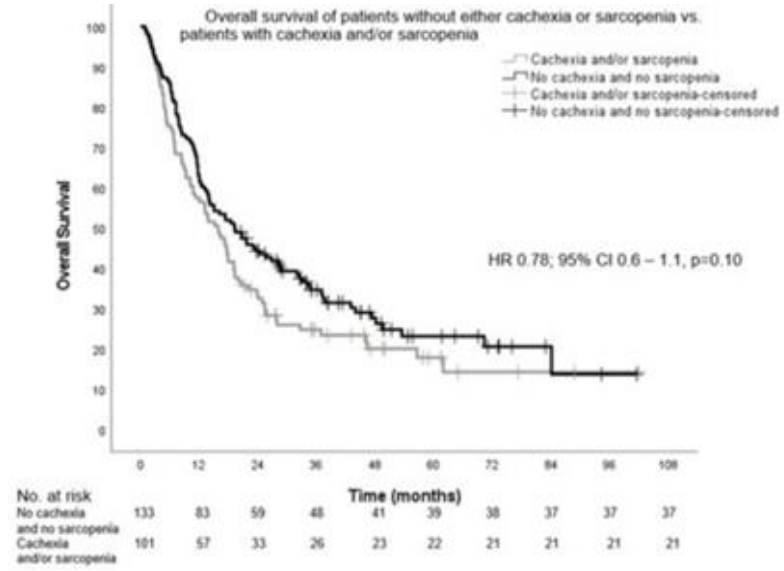

b)

Figure 5. Progression-free survival (a) and overall survival comparing patients free of both cachexia and sarcopenia (b) with those exhibiting cachexia and/or sarcopenia.

To explore potential associations, univariate and multivariate logistic regression models were applied to examine the impact of cachexia and sarcopenia on survival, initially across the complete study population and subsequently restricted to individuals who received LRT after induction therapy. In the full cohort, univariate analysis showed that older age at diagnosis (≥75 years) and male sex were associated with poorer survival. In contrast, squamous cell histology was associated with more favorable outcomes. Multivariate analysis retained only older age at diagnosis as a significant predictor of reduced survival **(Table 3)**.

Table 3. Logistic regression evaluating predictors of one-year overall survival in the entire patient population.

Characteristic	Category/Comparison	P-value	Multivariate analysis: hazard ratio (95% CI)	P-value	Univariate analysis: hazard ratio (95% CI)
Age (reference: < 75 years)	≥ 75 years	0.03	2.1 (1.1–4.3)	0.005	2.5 (1.3–4.9)
Gender (reference: male)	Female	0.07	0.6 (0.3–1.0)	0.02	0.5 (0.3–0.9)
WHO performance status (reference: 0–1)	2–3	0.24	1.7 (0.7–4.2)	0.12	2.0 (0.8–4.6)
Smoking status (reference: never)	Former smoker	—	—	0.50	1.5 (0.5–5.0)
	Current smoker	—	—	0.37	1.7 (0.5–5.7)
Histological subtype (reference: non-squamous)	Squamous	0.09	0.6 (0.3–1.1)	0.01	0.4 (0.2–0.8)
Body mass index (reference: < 25 kg/m²)	≥ 25 kg/m²	—	—	0.49	1.2 (0.7–2.0)
Cachexia	Present vs. absent	0.15	0.6 (0.4–1.2)	0.17	0.7 (0.4–1.2)
Sarcopenia	≥ 6.05 mm²/m² for men and ≥ 4.20 mm²/m² for women	0.92	1.0 (0.5–1.8)	0.91	1.0 (0.5–1.8)
Serum albumin (reference: < 40 g/L)	≥ 40 g/L	—	—	0.55	0.8 (0.5–1.5)
Serum CRP (reference: ≤ 5 mg/L)	> 5 mg/L	—	—	0.09	1.8 (0.9–3.5)
Serum LDH (reference: < 248)	≥ 248	—	—	0.59	1.2 (0.7–2.1)
Actionable driver mutation (reference: yes)*	No actionable driver mutation	—	—	0.64	0.8 (0.3–2.1)

Abbreviations: ref—reference; WHO-PS—World Health Organization Performance Score; BMI—body mass index; CRP—C-reactive protein; LDH—lactate dehydrogenase; *—actionable: ALK, BRAF V600, EGFR, ROS1, RET. KRAS (G12C) was not actionable at the time of patient inclusion.

Regarding progression-free survival, univariate analysis identified male gender and elevated CRP as factors associated with worse outcomes. Multivariate modeling confirmed high CRP as an independent predictor of inferior PFS **(Table 4)**.

Table 4. Logistic regression evaluating predictors of one-year progression-free survival in the entire patient population.

Characteristic	Category/Comparison	P-value	Multivariate analysis: hazard ratio (95% CI)	P-value	Univariate analysis: hazard ratio (95% CI)
Age (reference: < 75 years)	≥ 75 years	0.17	1.9 (0.8–5.1)	0.16	1.7 (0.8–3.6)
Gender (reference: male)	Female	0.13	0.6 (0.3–1.2)	0.04	0.6 (0.3–0.9)
WHO performance status (reference: 0–1)	2–3	0.25	2.5 (0.5–12.0)	0.10	2.6 (0.8–7.8)
Smoking status (reference: never smoker)	Former smoker	—	—	0.28	2.4 (0.5–11.4)
	Current smoker	—	—	0.25	2.6 (0.6–12.2)
Histological subtype (reference: non-squamous)	Squamous	—	—	0.91	1.0 (0.5–1.9)
Body mass index (reference: < 25 kg/m²)	≥ 25 kg/m²	—	—	0.43	1.3 (0.7–2.2)
Cachexia	Present vs. absent	0.05	0.4 (0.2–1.0)	0.05	0.5 (0.2–1.0)
Sarcopenia	≥ 6.05 mm²/m² for men and ≥ 4.20 mm²/m² for women	0.58	1.3 (0.6–2.8)	0.84	0.9 (0.5–1.8)
Serum albumin (reference: < 40 g/L)	≥ 40 g/L	—	—	0.56	0.83 (0.5–1.6)
Serum CRP (reference: ≤ 5 mg/L)	> 5 mg/L	0.008	3.6 (1.3–5.2)	0.003	2.8 (1.4–5.4)
Serum LDH (reference: < 248)	≥ 248	—	—	0.94	1.0 (0.5–1.8)

Actionable driver mutation (reference: yes)*	No actionable driver mutation	—	—	0.36	0.6 (0.2–1.9)

Abbreviations: ref—reference; WHO-PS—World Health Organization Performance Score; BMI—body mass index; CRP—C-reactive protein; LDH—lactate dehydrogenase; *—actionable: ALK, BRAF V600, EGFR, ROS1, RET. KRAS (G12C) was not actionable at the time of patient inclusion.

Within the subgroup receiving LRT, treatment-related adverse events and best response to induction systemic therapy were additionally examined **(Tables 5 and 6)**. High CRP levels (> 5 mg/L) were significantly associated with shorter PFS in both univariate and multivariate analyses **(Table 6)**.

Table 5. Logistic regression evaluating predictors of one-year overall survival among patients who underwent LRT.

Characteristic	Category/Comparison	P-value	Multivariate analysis: hazard ratio (95% CI)	P-value	Univariate analysis: hazard ratio (95% CI)
Age (reference: < 75 years)	≥ 75 years	0.87	0.8 (0.2–3.4)	0.45	1.5 (0.5–4.2)
Gender (reference: male)	Female	0.29	1.7 (0.6–4.5)	0.09	0.5 (0.3–1.2)
WHO performance status (reference: 0–1)	2	0.82	0.8 (0.1–5.0)	0.93	1.1 (0.2–5.4)
Smoking status (reference: never smoker)	Former smoker	—	—	0.86	0.8 (0.1–7.9)
	Current smoker	—	—	0.98	1.0 (0.1–10.0)
Histological subtype (reference: non-squamous)	Squamous	0.11	2.4 (0.8–7.0)	0.02	0.3 (0.1–0.8)
Body mass index (reference: < 25 kg/m²)	≥ 25 kg/m²	—	—	0.09	2.1 (0.9–4.7)
Cachexia	Present vs. absent	0.67	1.3 (0.4–3.7)	0.93	1.0 (0.4–2.4)
Sarcopenia	≥ 6.05 mm²/m² for men and ≥ 4.20 mm²/m² for women	0.55	0.7 (0.2–2.5)	0.87	1.1 (0.4–2.9)
Serum albumin (reference: < 40 g/L)	≥ 40 g/L	—	—	0.29	1.7 (0.7–4.1)
Serum CRP (reference: ≤ 5 mg/L)	> 5 mg/L	0.40	0.6 (0.2–1.9)	0.25	1.9 (0.6–5.6)
Serum LDH (reference: < 248)	≥ 248	—	—	0.58	1.3 (0.5–3.1)
Treatment-related adverse events (TRAE) (reference: toxicity ≤ 2)	Toxicity grade ≥ 3	—	—	0.32	1.5 (0.7–3.4)
Best response to induction systemic therapy (reference: CR and PR)	Stable disease (SD) and progressive disease (PD)	—	—	0.06	2.2 (0.9–5.1)
Actionable driver mutation (reference: yes)*	No actionable driver mutation	—	—	0.87	0.89 (0.3–3.5)

Abbreviations: ref—reference; WHO-PS—World Health Organization Performance Score; BMI—body mass index; CRP—C-reactive protein; LDH—lactate dehydrogenase; TRAE—treatment-related adverse events; CR—complete response; PR—partial response; SD—stable disease; PD—progressive disease; —actionable: ALK, BRAF V600, EGFR, ROS1, RET. KRAS (G12C) was not actionable at the time of patient inclusion.

Table 6. Logistic regression evaluating predictors of one-year progression-free survival among patients who underwent LRT.

Characteristic	Category/Comparison	P-value	Multivariate analysis: hazard ratio (95% CI)	P-value	Univariate analysis: hazard ratio (95% CI)
Age (reference: < 75 years)	≥ 75 years	0.84	1.1 (0.3–3.9)	0.77	0.9 (0.4–2.2)
Gender (reference: male)	Female	0.75	1.2 (0.5–2.7)	0.35	0.7 (0.4–1.4)
WHO performance status (reference: 0–1)	2	0.50	0.6 (0.1–3.0)	0.14	3.4 (0.7–16.7)
Smoking status (reference: never smoker)	Former smoker	—	—	0.71	1.4 (0.2–9.0)

	Current smoker	—	—	0.82	1.2 (0.2–7.9)
Histological subtype (reference: non-squamous)	Squamous	—	—	0.90	1.1 (0.5–2.4)
Body mass index (reference: < 25 kg/m²)	≥ 25 kg/m²	—	—	0.82	1.0 (0.9–1.1)
Cachexia	Present vs. absent	0.05	2.7 (1.0–6.9)	0.09	0.5 (0.2–1.1)
Sarcopenia	≥ 6.05 mm²/m² for men and ≥ 4.20 mm²/m² for women	0.13	0.4 (0.2–1.3)	0.73	1.2 (0.5–2.6)
Serum albumin (reference: < 40 g/L)	≥ 40 g/L	—	—	0.63	1.2 (0.6–2.5)
Serum CRP (reference: ≤ 5 mg/L)	> 5 mg/L	0.02	0.4 (0.1–0.9)	0.02	2.8 (1.2–6.7)
Serum LDH (reference: < 248)	≥ 248	—	—	0.61	1.2 (0.6–2.5)
Treatment-related adverse events (TRAE) (reference: toxicity ≤ 2)	Toxicity grade ≥ 3	—	—	0.99	1.0 (0.5–2.0)
Best response to induction systemic therapy (reference: CR and PR)	Stable disease (SD) and progressive disease (PD)	—	—	0.26	1.5 (0.7–3.1)
Actionable driver mutation (reference: yes)*	No actionable driver mutation	—	—	0.46	2.2 (0.3–18.6)

Abbreviations: ref—reference; WHO-PS—World Health Organization Performance Score; BMI—body mass index; CRP—C-reactive protein; LDH—lactate dehydrogenase; TRAE—treatment-related adverse events; CR—complete response; PR—partial response; SD—stable disease; PD—Progressive disease; —actionable: ALK, BRAF V600, EGFR, ROS1, RET. KRAS (G12C) was not actionable at the time of patient inclusion.

Safety profile

The four patient groups exhibited no meaningful differences in the distribution of toxicity grades.

Clinical practice guidelines recommend administering systemic therapy followed by locoregional therapy (LRT) to all detectable disease sites in patients with synchronous oligometastatic disease (sOMD) who respond to initial treatment [8-10]. However, baseline patient characteristics such as cachexia and sarcopenia can substantially modify disease trajectory in this setting. Although the effects of sarcopenia and cachexia have been extensively studied in individuals with limited-stage or metastatic non-small cell lung cancer (NSCLC), no prior reports have specifically addressed their relevance in sOMD. The current preliminary investigation therefore examined how sarcopenia and cachexia affect survival and toxicity in a cohort of comprehensively staged sOMD patients managed with an intention-to-treat strategy. For this purpose, participants were stratified into four subgroups reflecting every combination of cachexia and sarcopenia status. Despite the recognized overlap between sarcopenia and cachexia, these entities were analyzed independently, given that additional influences such as chronological age can contribute to sarcopenia development [34]. In addition, sarcopenia is often amenable to reversal, unlike cachexia, suggesting potentially distinct implications for long-term prognosis. Notably, even among patients with the most favorable baseline profile, fewer than two-thirds ultimately received LRT. This observation reinforces the importance of identifying robust pretreatment prognostic markers to optimize selection for LRT. Importantly, the presence of cachexia and/or sarcopenia alone should not exclude patients from potentially curative multimodal treatment. Consistent with this approach, although individuals with cachexia and/or sarcopenia displayed modestly reduced median PFS and OS, neither condition independently predicted survival in univariate or multivariate models. These data highlight the dominant role of other variables, particularly the quality of response to induction systemic therapy. A direct comparison between group A (no cachexia, no sarcopenia) and the combined cohort of groups B, C, and D (cachexia and/or sarcopenia) likewise failed to demonstrate statistically significant differences.

The limited prognostic weight of cachexia in sOMD may reflect the widespread adoption of immune checkpoint inhibitors (ICI) and tyrosine kinase inhibitors (TKI), both of which confer meaningful survival advantages [11, 13, 14]. Data concerning the interaction between cachexia and ICI effectiveness in advanced NSCLC remain heterogeneous, with no consensus yet established regarding a consistent association [19, 22, 23].

Similarly, multiple analyses of sarcopenia in advanced NSCLC patients treated with ICI or TKI have shown no substantial differences in survival according to sarcopenia presence [19, 38-42].

The present work appears to represent the first evaluation of prognostic markers in sOMD patients analyzed on an intention-to-treat basis. While neither cachexia nor sarcopenia emerged as independent predictors of survival, older age at diagnosis (≥ 75 years) was associated with significantly worse overall survival on multivariate testing. For progression-free survival, elevated CRP levels were identified as an independent risk factor for inferior outcome. Although cachexia and sarcopenia frequently coincide with elevated CRP and IL-6 levels [19], the prognostic significance of CRP is more likely due to its established association with adverse survival and reduced ICI efficacy, possibly through interference with antitumor immunity, as reported in several studies alongside LDH and IL-6 [43, 44].

When outcomes were compared between the broader intention-to-treat population planned for LRT and the subset who actually completed LRT, median PFS and OS were comparable between patients with and without cachexia/sarcopenia. These findings prompt further consideration of the extent to which cachexia and sarcopenia influence prognosis among individuals with good WHO-PS and suggest that this subgroup may still derive benefit from LRT **(Table 2)**. By contrast, cachexia tends to predominate in patients with compromised performance status, as it interferes with multiple aspects of physical function and daily activities. Prior literature has repeatedly linked cachexia with poorer PS, yet most available studies on cachexia and sarcopenia have focused on patients with preserved functional status [45, 46]. Future research should specifically address whether these conditions exert a stronger adverse prognostic effect in individuals presenting with reduced performance status.

Regarding the role of ICI in our cohort, individuals in the cachexia and sarcopenia group received a significantly higher proportion of immune checkpoint inhibitors (ICI) as induction systemic therapy. This imbalance may partly account for the comparatively favorable survival observed in this subgroup, despite the anticipated negative prognostic implications of cachexia and sarcopenia [11, 13]. As previously noted, evidence concerning the influence of cachexia and sarcopenia on the effectiveness of ICI and tyrosine kinase inhibitors (TKI) remains inconsistent, highlighting the need for larger-scale investigations involving more uniform patient populations. Serum albumin levels warrant consideration as a potential prognostic marker, given indications that hypoalbuminemia may signal worse outcomes during ICI treatment through its association with heightened systemic inflammation [47, 48]. This aspect holds particular relevance for patients with cachexia, in whom low serum albumin frequently reflects compromised nutritional status. Consequently, expanded studies examining the relationship between serum albumin concentrations and ICI efficacy are clearly justified.

However, because the study population was accrued between 2015 and 2021—partially preceding the broad implementation of ICI—only 15% of patients received immunotherapy and 10% were treated with TKI. This temporal context constitutes a notable limitation when extrapolating the findings to contemporary practice. In the current era, immunotherapy offers a generally well-tolerated option with substantial potential for durable tumor control in suitable candidates. Future investigations into the prognostic significance of cachexia and sarcopenia in NSCLC should therefore incorporate the full spectrum of modern treatment regimens. In particular, comparative analyses of survival outcomes among patients with cachexia and/or sarcopenia receiving chemotherapy versus immunotherapy are essential to align with present-day clinical realities.

Recent publications have indicated that cachexia and sarcopenia may heighten susceptibility to toxicity during chemotherapy [18, 49]. In contrast, data on their influence in patients managed with TKI or ICI have yielded variable findings [20, 42, 50]. The present analysis revealed comparable toxicity profiles regardless of cachexia or sarcopenia status at baseline, suggesting that an aggressive, radical-intent therapeutic approach remains a viable and safe consideration even in affected individuals.

To our knowledge, this study is the first to investigate the prognostic implications of cachexia and sarcopenia for survival in a large, well-characterized cohort of patients with synchronous oligometastatic NSCLC (sOMD) analyzed on an intention-to-treat basis.

Despite these strengths, several limitations should be acknowledged. Although the EORTC consensus definition was applied to ensure homogeneity of the oligometastatic population, detailed information on tumor burden (both primary and metastatic volumes) was unavailable. Assessment of volumetric parameters could serve as a valuable additional prognostic tool and merits evaluation in subsequent research. Furthermore,

although all patients shared an oligometastatic presentation and an intention-to-treat framework, heterogeneity existed regarding oncogenic drivers and specific treatment protocols, factors that may have influenced survival outcomes and represent a potential weakness. Additional constraints include the retrospective design and the absence of external validation for cachexia classification and sarcopenia measurement. The lack of international consensus on optimal assessment methods complicates direct comparisons across studies. In this analysis, psoas muscle index (PMI) served as a surrogate for sarcopenia rather than skeletal muscle index (SMI), and functional parameters such as muscle strength (e.g., handgrip strength) were not incorporated, in contrast to the EWGSOP recommendations [34]. Standardized cut-off values and assessment protocols for sarcopenia are still evolving; therefore, the sex-specific lower 25th percentile was employed as an unbiased threshold. Nevertheless, greater standardization and external validation will be necessary moving forward. The study cohort was also characterized by relatively preserved functional status, with 89.9% of patients having a WHO-PS of 0–1. This prevented evaluation of the relative impact of WHO-PS ≥2 compared with cachexia and sarcopenia, as reported in other series [22, 24]. Finally, response to induction systemic therapy, serum CRP concentration, and older age at diagnosis (≥75 years) emerged as potentially more useful prognostic indicators than cachexia or sarcopenia themselves. It may play a central role in identifying sOMD patients suitable for radical treatment. The relatively small sizes of the subgroups defined by cachexia and sarcopenia status further underscore the preliminary nature of the findings. Larger confirmatory studies are therefore required, although the intention-to-treat framework constitutes an important methodological strength despite the limited subgroup numbers.

Conclusion

In patients with synchronous oligometastatic NSCLC, neither cachexia nor sarcopenia—whether considered individually or in combination—was associated with reduced survival, regardless of whether locoregional therapy (LRT) was ultimately administered. Elevated CRP levels and older age at diagnosis (≥75 years) were linked to inferior survival. They may serve as practical prognostic tools to support clinical decision-making regarding the potential benefit of adding LRT. Prospective studies and further research are necessary to identify and validate additional biomarkers that can more precisely select patients who stand to gain the most from early integration of LRT within a homogeneous sOMD population.

Acknowledgments: None

Conflict of Interest: None

Financial Support: None

Ethics Statement: None

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