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Research Paper

Computed tomography-determined high visceral adipose tissue and sarcopenic obesity and their associations with survival in vulnerable or frail older adults with cancer considered for systemic anticancer treatment

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ABSTRACT

Introduction: Treatment decisions are challenging in older adults with solid tumors. Geriatric 8 (G8)-screening and comprehensive geriatric assessment (CGA) are important but additional methods are needed. We examined the association of computed tomography (CT)-derived high visceral adipose tissue index (VATI) with or without low skeletal muscle index (SMI) on three-month and overall survival (OS).

Materials and Methods: Vulnerability was evaluated with G8 in patients ≥75 years referred for systemic anticancer treatment. Vulnerable/frail patients (G8 ≤ 14) received CGA and were included. VATI and SMI were retrospectively measured from CT scans. We examined associations between high VATI with or without low SMI and three-month and OS with Cox regression models and Kaplan-Meier estimation.

Results: Seventy-nine patients with median age of 80 (range 75–91) years were evaluated. In the palliative-intent group (n = 58), three-month OS rates were 88 % and 58 % in the normal and high VATI groups, respectively (hazard ratio 4.3; 95 % confidence interval 1.3–14), and 88 % vs. 47 % in group without and with 'high VATI+low SMI', respectively (5.5; 1.9–17). The median OS was 12.7 vs. 9.5 months in normal VATI/SMI and 'high VATI+low SMI' (1.9; 1.1–3.2), respectively. In Cox multivariable models with established predictive factors (ECOG PS, Clinical Frailty Scale, and sex), only high VATI (4.9; 1.0–24) or 'high VATI+low SMI' (8.9; 1.7–46) remained significant predictors of three-month OS.

Discussion: High VATI with or without low SMI were associated with impaired three-month OS in the palliative-intent group and with OS in the whole cohort independently of oncologic and geriatric functional status measures; thus, they may aid in treatment decision-making.

1. Introduction

As the population ages, the number of older adults with cancer increases [1]. A significant proportion of older adults are unfit for oncological treatment due to aging-related conditions. Multimorbidity, cachexia, and geriatric syndromes, such as frailty, malnutrition, and sarcopenia, increase the likelihood of impaired survival, even in patients without cancer [2,3]. Furthermore, older patients may be more

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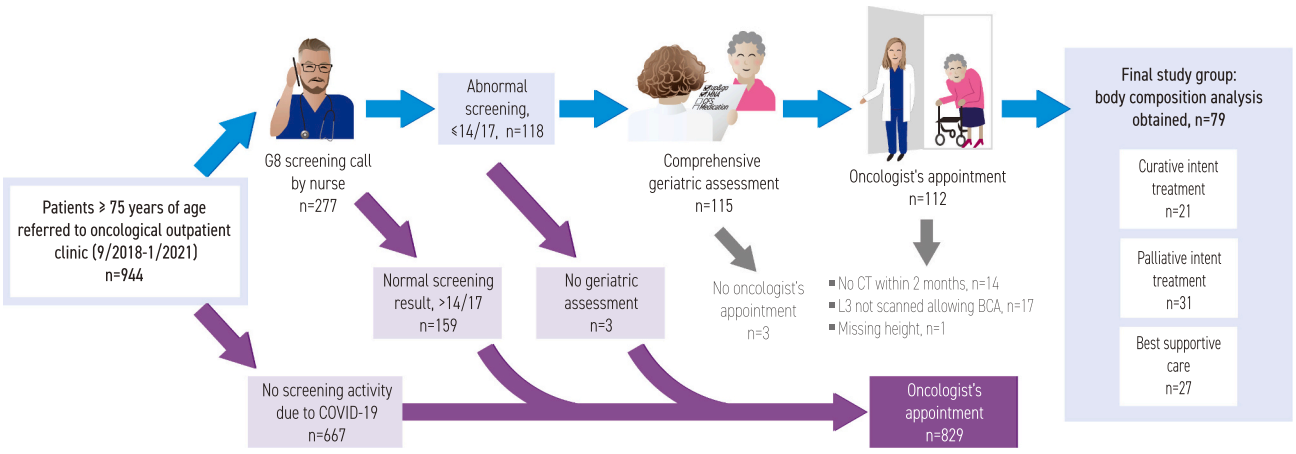

Fig. 1. Flowchart for ≥75-year-old patients with solid cancers at the geriatric oncology unit at Tampere University Hospital.

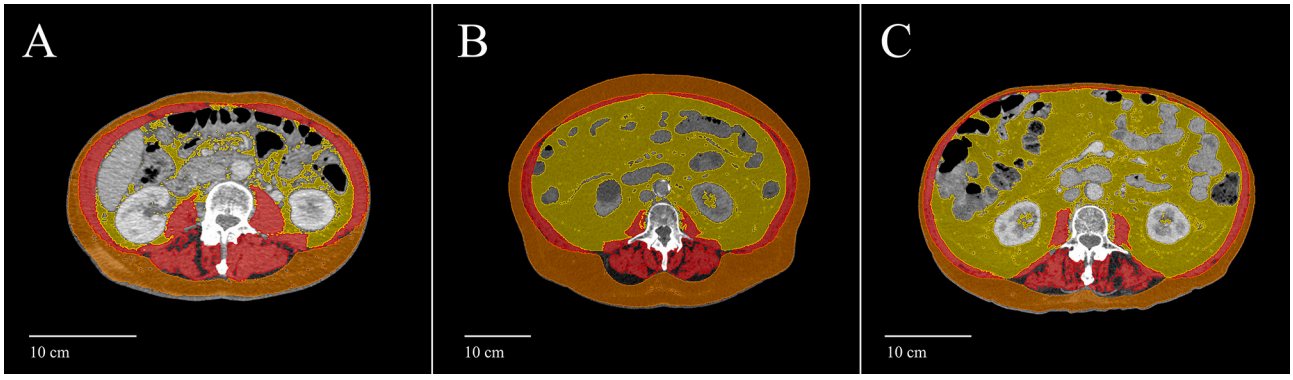

Fig. 2. Body composition from the level of the third lumbar vertebra with muscle tissue in red, visceral adipose tissue in yellow (VAT), and subcutaneous adipose tissue in orange (SAT). Patient A (female aged 76 years) had normal body composition with a normal VAT index (VATI) of 40.5 cm^2/m^2 and a normal skeletal muscle index (SMI) of 38.4 cm^2/m^2. Patient B (male aged 77 years) had a high VATI of 184 cm^2/m^2 and a normal SMI of 53.8 cm^2/m^2. Patient C (male aged 81 years) had high VATI of 139 cm^2/m^2 and a low SMI of 34.8 cm^2/m^2. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

susceptible to treatment-related toxicities than younger patients [1,4]. On the other hand, there can be vast biological differences between patients who are chronologically the same age [5]. Indeed, the decision to initiate or refrain from initiating active oncological treatments may be challenging in older adults as treatments should not be initiated when a patient has a short life expectancy (<3 months), an exclusion criteria in oncological studies [6].

Screening for vulnerability and frailty to assess risk of adverse outcomes before deciding to proceed to oncological treatments with tools like the Geriatric 8 (G8) is the gold standard for identifying older patients with cancer who would benefit from comprehensive geriatric assessment (CGA) [7,8]. Imaging-based evaluation of body composition has shown promise as a novel method for identifying muscle wasting in patients with cancer [9] and is regarded as the gold standard in assessing muscle mass [10]. Indeed, imaging-based loss of muscle mass, a surrogate for sarcopenia, is associated with impaired survival outcomes in patients with cancer [11,12]. Unlike the traditional methods for body composition assessment (e.g., body mass index [BMI]), bioimpedance analysis, and dual energy X-ray absorptiometry), cross-sectional imaging can differentiate between adipose tissue compartments. Adipose tissue can be divided into visceral adipose tissue (VAT) and subcutaneous adipose tissue. A growing body of evidence has highlighted the importance of VAT for outcome prediction [9]. Several cut-offs for "high" and "normal" imaging-determined VAT have been proposed in the literature [13,14] but none specifically for older adults [15].

The effect of low muscle mass and impaired muscle function combined with high visceral adiposity, i.e., sarcopenic obesity, has been studied in older adults without cancer, showing increased risk of falls, osteoporosis, metabolic syndrome, cardiovascular disease, and mortality [16–18]. Sarcopenic obesity has been linked to poor prognosis in adults with solid tumors [11,12,19]. To the best of our knowledge, the association between sarcopenic obesity and prognosis has not been studied in vulnerable older adults with cancer.

The aim of this study was to examine whether optimized CT-derived high visceral adipose tissue index (VATI) with or without low skeletal muscle index (SMI) were associated with three-month and overall survival in vulnerable ≥75-year-old patients with solid cancer considered for systemic anticancer treatment, and thus guide treatment decision-making.

2. Materials and Methods

2.1. Study Aim, Design, and Setting

The data were collected retrospectively and consisted of patients aged ≥75 years considered for systemic anticancer therapy at the Geriatric Oncology Unit at the Department of Oncology, Tampere University Hospital, from September 2018 to January 2021, with exception of the COVID-19 period between March 18 and September 2, 2020, when the Geriatric Oncology Unit was closed. A trained oncology nurse conducted G8 screening by phone for all patients ≥75 years of age referred to the oncology outpatient clinic for consideration of systemic

Table 1
Patient characteristics in palliative- and curative-intent subgroups.

	All	Palliative-intent group		Curative-intent group		OR[a] (95 % CI[b],[c])
	N = 79	*n* = 59	73 %	n = 21	27 %	
Age						
<80 years	38	28	74 %	10	26 %	1
≥80 years	41	30	73 %	11	27 %	0.97 (0.4–2.6)
Sex						
Female	37	28	76 %	9	24 %	1
Male	42	30	71 %	12	29 %	1.24 (0.5–3.4)
Tumor site						
Colorectal	25	12	48 %	13	52 %	0.46 (0.0–5.7)
Pancreatic	20	17	85 %	3	15 %	2.84 (0.2–42)
Esophago-gastric	9	5	56 %	4	44 %	0.63 (0.0–9.7)
Genitourinary	7	7	100 %	0	0 %	–
Liver and biliary	7	7	100 %	0	0 %	–
Breast	4	4	100 %	0	0 %	–
Lung	4	4	100 %	0	0 %	–
Other[c]	3	2	67 %	1	33 %	–
Tumor stage						
Localized	13	0	0 %	13	100 %	–
Locally advanced	18	13	72 %	5	28 %	0.17 (0.0–0.8)*
Metastatic	48	45	93 %	3	6 %	–
Oncological treatment						
Combination systemic anticancer therapy	18	16	89 %	2	11 %	1
Single systemic anticancer therapy	16	8	50 %	8	50 %	8.00 (1.37–47)*
Endocrine therapy	6	6	100 %	0	0 %	–
Stereotactic body radiotherapy	1	1	100 %	0	0 %	–
Follow-up or best supportive care	38	27	71 %	11	29 %	3.26 (0.64–17)
ECOG PS[d]						
0 to 2	52	37	71 %	15	29 %	1
3 to 4	21	15	71 %	6	29 %	0.99 (0.3–3.0)
Not available	6	6	100 %	0	0 %	–
FRAIL scale[e]						
0 to 2	47	28	74 %	10	26 %	1
3 to 5	23	16	70 %	7	30 %	1.23 (0.4–3.8)
Not available	9	14	78 %	4	22 %	–
Clinical Frailty Scale						
1 to 4	48	35	73 %	13	27 %	1
5 to 9	25	20	80 %	5	20 %	0.67 (0.2–2.2)
Not available	6	3	50 %	3	50 %	–
MNA-SF[f]						
Normal/risk	38	28	74 %	10	26 %	1
Malnutrition	37	28	76 %	9	24 %	0.90 (0.3–2.6)
Not available	4	2	50 %	2	50 %	–
GLIM[g]						
Normal	30	19	63 %	11	37 %	1
Malnutrition	44	34	77 %	10	23 %	0.51 (0.2–1.4)
Not available	5	5	100 %	0	0 %	–
BMI[h]						
≥22 kg/m^2	60	42	70 %	18	30 %	1
<22 kg/m^2	19	16	84 %	3	16 %	0.44 (0.1–1.7)

[a] Odds ratio.
[b] Confidence interval.
[c] Other cancers included 1 small bowel cancer, 1 sarcoma of the lower limb, and 1 thymic carcinoma.
[d] Eastern Cooperative Oncology Group performance status.
[e] Fatigue, resistance, ambulation, illnesses, and loss of weight.
[f] Mini Nutritional Assessment – Short Form.
[g] Global Leadership Initiative on Malnutrition classification.
[h] Body mass index.
* Indicates statistical significance ($p \leq 0.05$).

anticancer treatment (Fig. 1). Frail older adults considered unfit for systemic therapy were referred directly to the palliative unit with a transfer option to oncology if they were fit for treatment. The G8 screen consisted of eight questions with a maximum of 17 points. Patients who received ≤14 points were considered at risk for being vulnerable or possibly frail (denoted as "vulnerable" hereafter) [20]. Vulnerable patients were further evaluated with CGA according to principles in previous studies [8,21,22] performed by a trained nurse and a geriatrician (mostly HK). In this study, CGA was performed before the oncologist's appointment as a basis for an individualized treatment plan, accounting for the patients' physical, cognitive, and psychosocial resilience. Patients who received >14 points were considered fit and underwent routine treatment without CGA and were not included in this study.

To be included, the patients' clinical information and an appropriate CT scan had to be available. The scan had to fulfill the following criteria: The midpoint level of the third lumbar vertebra (L3) had to be visible to allow body composition analysis and had to be performed no more than two months prior to CGA and thus the initiation of systemic oncological treatment.

2.2. Ethics Statement

This retrospective study was approved by the local institutional review board of Tampere University Hospital (R19628S), which also waived the need for written informed consent. Ethics committee evaluation and the collection of written informed consents are not needed for register-based studies in Finland.

2.3. Adipose Tissue Measurements and Indexes

One reader (AT) manually performed body composition analysis with 3D Slicer (Version 4.11, available at https://www.slicer.org/). The reader was trained and supervised by an experienced body composition analyst (OA) without access to survival data. A training sample was checked for accuracy during the training process. VAT mass was measured from the axial slice at the midpoint of the L3 level. Slice volumes were divided by slice thicknesses (0.45–3.00 mm) to calculate areas. The Hounsfield unit (HU) range for VAT was set from −190 to −30 [23], irrespective of scan phase or the use of an iodine-based contrast agent. Manual correction of the area was performed to account for the variability in tissue HUs and morphology. Thus, the VAT area was obtained, and the VAT index was calculated as follows: VATI = VAT area/(patient height)^2.

We used cut-offs from the literature on VATI by Van Dijk et al. [13] and VAT area by Doyle et al. [14] to determine their performance in this study sample. Sex-specific cut-offs for three-month survival for high and normal VATI were obtained using receiver operating characteristics. We selected the cut-offs with the highest Youden's index values (sensitivity + specificity −1) [24].

We have previously reported the cut-offs for three-month survival and the results of low muscle mass with skeletal muscle index (SMI) in this cohort [23]. SMI cut-offs determined with Youden's index for this cohort were 48.8 cm^2/m^2 for males and 33.4 cm^2/m^2 for females (Fig. 2).

We used criteria for sarcopenic obesity established by Prado et al.

Table 2
Associations between Youden's index -defined high visceral adipose tissue index (VATI) and patient characteristics in palliative- and curative-intent subgroups.

		Palliative-intent group				OR[a] (95 % CI[b])	Curative-inten group				OR[a] (95 % CI[b])
		VATI (Youden)					VATI (Youden)				
		Normal		High			Normal		High		
		n = 34	59 %	*n* = 24	41 %		*n* = 12	57 %	*n* = 9	43 %	
Age	<80 years	16	57 %	12	43 %	1	5	50 %	5	50 %	1
	≥80 years	18	60 %	12	40 %	0.89 (0.3–2.5)	7	64 %	4	36 %	0.57 (0.1–3.3)
Sex	Female	19	68 %	9	32 %	1	9	100 %	0	0 %	1
	Male	15	50 %	15	50 %	2.11 (0.7–6.1)	3	25 %	9	75 %	N/A
Tumor site	Upper GI	18	60 %	12	40 %	1	4	57 %	3	43 %	1
	Lower GI	6	50 %	6	50 %	1.50 (0.4–5.8)	7	54 %	6	46 %	1.14 (0.2–7.3)
	Other[c]	10	63 %	6	38 %	0.90 (0.3–3.1)	1	100 %	0	0 %	N/A
Tumor stage	Local	0	0 %	0	0 %	1	7	54 %	6	46 %	1
	Metastatic or locally advanced	34	59 %	24	41 %	N/A	5	63 %	3	38 %	0.70 (0.1–4.2)
Oncological treatments	Combination systemic anticancer therapy	12	75 %	4	25 %	1	0	0 %	2	100 %	–
	Single systemic anticancer therapy	5	63 %	3	38 %	1.80 (0.29–11)	5	63 %	3	38 %	–
	Endocrine therapy	3	50 %	3	50 %	3.00 (0.42–21)	0	0 %	0	0 %	–
	Stereotactic body radiotherapy	0	0 %	1	100 %	–	0	0 %	0	0 %	–
	Follow-up or best supportive care	14	52 %	13	48 %		7	64 %	4	36 %	0.57 (0.1–3.3)
ECOG PS[d]	0 to 2	23	62 %	14	38 %	1	7	47 %	8	53 %	1
	3 to 4	7	47 %	8	53 %	1.88 (0.6–6.3)	5	83 %	1	17 %	0.18 (0.0–1.8)
	Not available	4	67 %	2	33 %		0	0 %	0	0 %	
ADL[e]	Normal	24	69 %	11	31 %	1	7	44 %	9	56 %	1
	Impaired	8	42 %	11	58 %	3.00 (0.9–9.5)	5	100 %	0	0 %	N/A
	Not available	2	50 %	2	50 %		0	0 %	0	0 %	
IADL[f]	Normal	18	82 %	4	18 %	1	3	30 %	7	70 %	1
	Impaired	13	42 %	18	58 %	6.23 (1.7–23)*	9	82 %	2	18 %	0.10 (0.0–0.7)*
	Not available	3	60 %	2	40 %		0	0 %	0	0 %	
FRAIL Scale[g]	0 to 2	22	65 %	12	35 %	1	6	46 %	7	54 %	1
	3 to 5	9	56 %	7	44 %	1.43 (0.4–4.7)	6	86 %	1	14 %	0.14 (0.0–1.5)
	Not available	3	38 %	5	63 %		0	0 %	1	100 %	
Clinical Frailty Scale	1 to 4	22	63 %	13	37 %	1	6	46 %	7	54 %	1
	5 to 9	10	50 %	10	50 %	1.69 (0.6–5.2)	5	100 %	0	0 %	1
	Not available	2	67 %	1	33 %		1	33 %	2	67 %	N/A
MNA-SF[h]	Normal/risk	12	43 %	16	57 %	1	3	30 %	7	70 %	1
	Malnutrition	20	71 %	8	29 %	0.30 (0.1–0.9)*	7	78 %	2	22 %	0.12 (0.0–1.0)*
	Not available	2	100 %	0	0 %		2	100 %	0	0 %	
GLIM[i]	Normal	11	58 %	8	42 %	1	5	46 %	6	55 %	1
	Malnutrition	20	59 %	14	41 %	0.96 (1.0–3.0)	7	70 %	3	30 %	0.36 (0.1–2.2)
	Not available	3	60 %	2	40 %		0	0 %	0	0 %	
BMI[j]	≥22 kg/m^2	18	43 %	24	57 %	1	9	50 %	9	50 %	1
	<22 kg/m^2	16	100 %	0	0 %	N/A	3	100 %	0	0 %	N/A
	Normal	18	69 %	8	31 %	1	3	33 %	6	67 %	1
Sit-to-stand	Impaired	6	60 %	4	40 %	1.50 (0.3–6.8)	5	83 %	1	17 %	0.10 (0.0–1.3)
	Not available	10	46 %	12	55 %		4	67 %	2	33 %	
Hand grip strength	Normal	22	61 %	14	39 %	1	8	67 %	4	33 %	1
	Impaired	6	46 %	7	54 %	1.83 (0.5–6.6)	4	50 %	4	50 %	2.00 (0.3–13)
	Not available	6	67 %	3	33 %		0	0 %	1	100 %	
CRP[k]	<10 mg/L	18	72 %	7	28 %	1	6	55 %	5	46 %	1
	≥10 mg/L	12	48 %	13	52 %	2.79 (0.9–9.0)	3	75 %	1	25 %	0.40 (0.0–5.2)
	Not available	4	50 %	4	50 %		3	50 %	3	50 %	
Hemoglobin	≥110 g/L	25	63 %	15	38 %	1	8	57 %	6	43 %	1
	<110 g/L	8	50 %	8	50 %	1.67 (0.5–5.4)	3	50 %	3	50 %	1.33 (0.2–9.1)
	Not available	1	50 %	1	50 %		1	100 %	0	0 %	
Creatinine	Normal	24	65 %	13	35 %	1	9	69 %	4	31 %	1
	Impaired[l]	9	47 %	10	53 %	2.05 (0.7–6.3)	2	33 %	4	67 %	4.50 (0.6–36)
	Not available	1	50 %	1	50 %		1	50 %	1	50 %	
Albumin	≥30 g/L	21	75 %	7	25 %	1	5	42 %	7	58 %	1

(*continued on next page*)

Table 2 (*continued*)

		Palliative-intent group				OR[a] (95 % CI[b])	Curative-inten group				OR[a] (95 % CI[b])
		VATI (Youden)					VATI (Youden)				
		Normal		High			Normal		High		
		n = 34	59 %	*n* = 24	41 %		*n* = 12	57 %	*n* = 9	43 %	
	<30 g/L	6	43 %	8	57 %	4.00 (1.0–16)*	3	100 %	0	0 %	N/A
	Not available	7	44 %	9	56 %		4	67 %	2	33 %	
mGPS[m]	0 to 1	21	68 %	10	32 %	1	7	58 %	5	42 %	1
	2	9	47 %	10	53 %	2.33 (0.7–7.5)	2	67 %	1	33 %	0.70 (0.0–10)
	Not available	4	50 %	4	50 %		3	50 %	3	50 %	

[a] Odds ratio.
[b] Confidence interval.
[c] Other cancers included 7 genitourinary cancers, 4 breast cancers, 4 lung cancers, 1 sarcoma of the lower limb, and 1 thymic carcinoma.
[d] Eastern Cooperative Oncology Group performance status.
[e] Assisted daily living.
[f] Instrumental assisted daily living.
[g] Fatigue, resistance, ambulation, illnesses, and loss of weight.
[h] Mini Nutritional Assessment-Short Form.
[i] Global Leadership Initiative on Malnutrition classification.
[j] Body mass index.
[k] C-reactive protein.
[l] >100 μmol/L for males and > 90 μmol/L for females.
[m] Modified Glasgow prognostic score; percentages are based on rows.
* Indicates statistical significance ($p \leq 0.05$).

Table 3
Associations between Youden's index -defined high visceral adipose tissue index (VATI) / low skeletal muscle index (SMI) and patient characteristics per palliative- and curative intent subgroups.

		Palliative-intent group				OR[a] (95 % CI[b])	Curative treatment				OR[a] (95 % CI[b])
		Normal VATI/ SMI		High VATI+low SMI			Normal VATI/ SMI		High VATI+low SMI		
		n = 42	72 %	*n* = 16	28 %		*n* = 17	81 %	*n* = 4	19 %	
Age	<80 years	19	68 %	9	32 %	1	9	90 %	1	10 %	1
	≥80 years	23	77 %	7	23 %	0.55 (0.2–1.7)	8	73 %	3	27 %	3.38 (0.3–39)
Sex	Female	25	89 %	3	11 %	1	9	100 %	0	0 %	1
	Male	17	57 %	13	43 %	7.29 (1.8–30)*	8	67 %	4	33 %	N/A
Tumor site	Upper GI	19	63 %	11	37 %	1	7	100 %	0	0 %	1
	Lower GI	9	75 %	3	25 %	0.58 (0.1–2.6)	9	90 %	1	10 %	N/A
	Other[c]	13	81 %	3	19 %	0.40 (0.1–1.7)	1	100 %	0	0 %	N/A
Tumor stage	Local	0	0 %	0	0 %	1	10	77 %	3	23 %	1
	Metastatic or locally advanced	42	72 %	16	28 %	N/A	7	88 %	1	13 %	0.48 (0.0–5.6)
Oncological treatments	Combination systemic anticancer therapy	13	81 %	3	19 %	1	2	100 %	0	0 %	1
	Single systemic anticancer therapy	6	75 %	2	25 %	1.44 (0.19–11)	7	88 %	1	13 %	–
	Endocrine therapy	5	83 %	1	17 %	0.87 (0.07–10)	0	0 %	0	0 %	–
	Stereotactic body radiotherapy	1	100 %	0	0 %	–	0	0 %	0	0 %	–
	Follow-up or best supportive care	16	59 %	11	41 %	2.87 (0.9–9.3)	8	73 %	3	27 %	3.38 (0.3–39)
ECOG PS[d]	0 to 2	28	76 %	9	24 %	1	12	80 %	3	20 %	1
	3 to 4	10	67 %	5	33 %	1.35 (0.4–4.9)	5	83 %	1	17 %	0.80 (0.1–9.7)
	Not available	4	67 %	2	33 %		0	0 %	0	0 %	
ADL[e]	Normal	28	80 %	7	20 %	1	12	75 %	4	25 %	1
	Impaired	11	58 %	8	42 %	2.46 (0.7–8.2)	5	100 %	0	0 %	N/A
	Not available	3	75 %	1	25 %		0	0 %	0	0 %	
IADL[f]	Normal	20	91 %	2	9 %	1	8	80 %	2	20 %	1
	Impaired	18	58 %	13	42 %	4.57 (1.1–19)*	9	82 %	2	18 %	0.90 (0.1–7.9)
	Not available	4	80 %	1	20 %		0	0 %	0	0 %	
FRAIL Scale[g]	0 to 2	28	82 %	6	18 %	1	11	85 %	2	15 %	1
	3 to 5	10	63 %	6	38 %	2.31 (0.6–8.6)	6	86 %	1	14 %	0.92 (0.1–12)
	Not available	4	50 %	4	50 %		0	0 %	1	100 %	
Clinical Frailty Scale	1 to 4	26	74 %	9	26 %	1	10	77 %	3	23 %	1
	5 to 9	14	70 %	6	30 %	1.07 (0.3–3.6)	5	100 %	0	0 %	N/A
	Not available	2	67 %	1	33 %		2	67 %	1	33 %	
MNA-SF[h]	Normal/risk	18	64 %	10	36 %	1	8	80 %	2	20 %	1
	Malnutrition	22	79 %	6	21 %	0.42 (0.1–1.4)	7	78 %	2	22 %	1.14 (0.1–10)
	Not available	2	100 %	0	0 %		2	100 %	0	0 %	
GLIM[i]	Normal	17	90 %	2	11 %	1	9	82 %	2	18 %	1
	Malnutrition	22	65 %	12	35 %	5.26 (1.0–27)*	8	80 %	2	20 %	1.13 (0.1–10)
	Not available	3	60 %	2	40 %		0	0 %	0	0 %	

(*continued on next page*)

Table 3 (*continued*)

		Palliative-intent group				OR[a] (95 % CI[b])	Curative treatment				OR[a] (95 % CI[b])
		Normal VATI/SMI		High VATI+low SMI			Normal VATI/SMI		High VATI+low SMI		
		n = 42	72 %	*n* = 16	28 %		*n* = 17	81 %	*n* = 4	19 %	
BMI[j]	≥22 kg/m^2	26	62 %	16	38 %	1	14	78 %	4	22 %	1
	<22 kg/m^2	16	100 %	0	0 %	N/A	3	100 %	0	0 %	N/A
Sit-to-stand	Normal	21	81 %	5	19 %	1	5	56 %	4	44 %	1
	Impaired	6	60 %	4	40 %	4.20 (0.9–20)	6	100 %	0	0 %	N/A
	Not available	15	68 %	7	32 %		6	100 %	0	0 %	
Hand grip strength	Normal	28	78 %	8	22 %	1	11	92 %	1	8 %	1
	Impaired	6	46 %	7	54 %	3.50 (0.9–13)	5	63 %	3	38 %	6.60 (0.5–80)
	Not available	8	89 %	1	11 %		1	100 %	0	0 %	
CRP[k]	<10 mg/L	23	92 %	2	8 %	1	9	82 %	2	18 %	1
	≥10 mg/L	15	60 %	10	40 %	4.90 (1.2–21)*	3	75 %	1	25 %	1.50 (0.1–23)
	Not available	4	50 %	4	50 %		5	83 %	1	17 %	
Hemoglobin	≥110 g/L	30	75 %	10	25 %	1	12	86 %	2	14 %	1
	<110 g/L	11	69 %	5	31 %	1.20 (0.3–4.2)	4	67 %	2	33 %	3.00 (0.3–29)
	Not available	1	50 %	1	50 %		1	100 %	0	0 %	
Creatinine	Normal	28	76 %	9	24 %	1	10	77 %	3	23 %	1
	Impaired[l]	13	68 %	6	32 %	1.25 (0.4–4.2)	6	100 %	0	0 %	N/A
	Not available	1	50 %	1	50 %		1	50 %	1	50 %	
Albumin	≥30 g/L	25	89 %	3	11 %	1	9	75 %	3	25 %	1
	<30 g/L	7	50 %	7	50 %	6.00 (1.4–27)*	3	100 %	0	0 %	N/A
	Not available	10	63 %	6	38 %		5	83 %	1	17 %	
mGPS[m]	0 to 1	26	84 %	5	16 %	1	10	83 %	2	17 %	1
	2	11	58 %	8	42 %	3.78 (1.0–14)*	2	67 %	1	33 %	2.50 (0.1–43)
	Not available	4	50 %	4	50 %		5	83 %	1	17 %	

[a] Odds ratio.
[b] Confidence interval.
[c] Other cancers included 7 genitourinary cancers, 4 breast cancers, 4 lung cancers, 1 sarcoma of the lower limb, and 1 thymic carcinoma.
[d] Eastern Cooperative Oncology Group performance status.
[e] Assisted daily living.
[f] Instrumental assisted daily living.
[g] Fatigue, resistance, ambulation, illnesses, and loss of weight.
[h] Mini Nutritional Assessment-Short Form.
[i] Global Leadership Initiative on Malnutrition classification.
[j] Body mass index.
[k] C-reactive protein.
[l] >100 μmol/L for males and > 90 μmol/L for females.
[m] Modified Glasgow prognostic score; percentages are based on rows.
* Indicates statistical significance ($p \leq 0.05$).

(BMI >30 kg/m^2 and SMI <52.4 cm^2/m^2 for males or < 38.5 cm^2/m^2 for females) [11]. We also defined a proxy for 'sarcopenic obesity' in our material by combining high Youden's index-defined VATI with Youden's index-defined low SMI, (denoted 'high VATI+low SMI').

2.4. Clinical Data Acquisition

Patients' age, sex, clinical information, dates for the CT scan, visits to the geriatrician and oncologist, and information of death or last date of follow-up were collected from the hospital's electronic patient records. The primary tumor site, stage (localized vs. locally advanced inoperable or metastatic), and treatment-intent were recorded. For the analysis,

Table 4
Univariable and multivariate Cox regression analyses between visceral adipose tissue index (VATI) and 3-month overall survival among palliative-intent patients.

	Number of patients in analysis		Univariate	Multivariable
	Univariate	Multivariable	HR[a] (95 % CI[b])	HR[a] (95 % CI[b])
Sex				
Female	28	25	1	1
Male	30	26	1.68 (0.56–5.02)	1.46 (0.38–5.94)
ECOG PS[c]				
0 to 2	37	36	1	1
3 to 4	15	15	3.01 (0.87–10.4)	1.77 (0.46–6.76)
Clinical Frailty Scale				
1 to 4	35	33	1	1
5 to 9	20	18	3.35 (1.09–10.3)*	2.11 (0.54–8.26)
VATI (Youden)[d]				
Normal	34	29	1	1
High	24	22	4.28 (1.34–13.7)*	4.94 (1.02–23.9)*

[a] Hazard ratio.
[b] Confidence interval.
[c] Eastern Cooperative Oncology Group performance status.
[d] 69.3 cm^2/m^2 for males and 61.4 cm^2/m^2 for females.
* Indicates statistical significance ($p \leq 0.05$).

patients were further divided into curative- and palliative-intent treatment groups. Patients in the curative-intent group underwent surgical resection and either received neoadjuvant and/or adjuvant treatment or no additional oncological treatment. Patients in the palliative-intent group were given active oncological treatment or best supportive care only. Treatment decisions by oncologists (mostly KL) were guided by the CGA.

The Eastern Cooperative Oncology Group performance status (ECOG PS) was recorded at the oncologist's visit [25]. The FRAIL scale [26], the Clinical Frailty Scale [27], activities of daily living (ADL), instrumental activities of daily living (IADL) [28], hand-grip strength, and sit-to-stand tests were recorded at the CGA. Nutritional status was assessed with the Mini Nutritional Assessment – Short Form (MNA-SF) [29] at the CGA. The Global Leadership Initiative on Malnutrition (GLIM) classification was calculated retrospectively [30], for which the phenotypic criteria included weight loss of >5 % per six months, BMI <22 kg/m^2, or impaired hand-grip strength with cut-offs, as in the work of Aromaa et al. [31]; etiologic criteria were serum albumin <35 g/L or C-reactive protein (CRP) >10 mg/L [32]. The modified Glasgow prognostic score was also determined retrospectively and was considered impaired when a score of 2 occurred (albumin <35 g/L and CRP ≥10 g/L) [32].

2.5. Statistical Analyses

Patient demographics are presented as absolute values and percentages or as medians and ranges. Body composition analysis metrics are presented as means ± standard deviations (SDs). Logistic regression with odds ratios (ORs) and 95 % confidence intervals (CIs) were used to examine differences between the body composition measurements and baseline characteristics. The association between VATI with or without SMI and OS was examined using the Kaplan–Meier estimation and Cox regression models with hazard ratios (HRs). OS was calculated from the oncologist's visit until the end of follow-up (May 27, 2023) or death. Three-month OS was analyzed in the palliative-intent group, whereas OS was analyzed in all patients and subgroups. Variables that predicted OS in univariate analyses and established factors (ECOG PS, Clinical Frailty Scale, sex) were included in preplanned multivariable analyses. All *p*-values were two-sided and were considered significant when $p \leq 0.05$. Data were analyzed with IBM SPSS Statistics for Windows (2020, Version 27.0.0.1, IBM Corporation, Armonk, USA).

3. Results

3.1. Patient Characteristics

A total of 79 patients met the inclusion criteria (Fig. 1), 42 of whom were male (median age 80 years; range 75–89) and 37 female (80; 75–91). Most patients (82 %) had gastrointestinal cancers (Table 1). The distribution of cancers was representative of Finnish older adults with solid tumors referred for systemic anticancer treatment. Forty-eight (61 %) patients had metastatic, 18 (23 %) locally advanced, and 13 (17 %) local cancers (Table 1).

Patients in the palliative-intent treatment group ($n = 58$) received either active oncological treatment ($n = 31$, 53 %; for details, see Table 1) or best supportive care only ($n = 27$, 47 %). In the palliative-intent group, 45 patients had metastatic disease and 13 had locally advanced inoperable disease. Patients in the curative intent group ($n = 21$) underwent surgical resection and received neoadjuvant and/or adjuvant treatment ($n = 10$, 48 %), or no additional oncological treatment ($n = 11$, 52 %). No significant differences in patient characteristics or in oncological treatment intensity were noted between patients in the palliative-intent and curative-intent groups.

3.2. Body Composition

Males had higher BMI (mean 25.5 ± SD 4.4 kg/m^2 vs. 24.2 ± 4.2 kg/m^2) than females. In the palliative-intent group, the mean BMIs for males and females were 25.1 ± 4.0 kg/m^2 and 24.4 ± 4.3 kg/m^2, respectively. In the curative-intent group, the mean BMIs for males and females were 26.3 ± 5.5 kg/m^2 and 23.5 ± 3.9 kg/m^2, respectively.

Males had higher VATI (81 ± 46 cm^2/m^2 and 43 ± 28 cm^2/m^2) than females. In the palliative-intent group, the mean VATI values for males and females were 77.6 ± 42.8 cm^2/m^2 and 45.0 ± 30.2 cm^2/m^2, respectively. In the curative-intent group, the mean VATI values for males and females were 89.9 ± 52.6 cm^2/m^2 and 35.9 ± 20.1 cm^2/m^2, respectively.

The Youden's index-determined receiver operating characteristic (ROC) cut-off values for three-month survival rate for high VATI were 69.3 and 61.4 cm^2/m^2 for males and females, respectively (Supplementary Fig. 1). High VATI according to optimized criteria were seen in 42 % (33/79) of all and in 41 % (24/58) of patients treated with palliative-intent (Supplementary Table 1). High VATI according to criteria by Van Dijk et al. [13] were seen in 56 % of all and in 50 % of palliative-intent patients (Supplementary Table 1).

High VAT area by our optimized Youden's criteria and by Doyle et al. [14] appear in Supplementary Table 1.

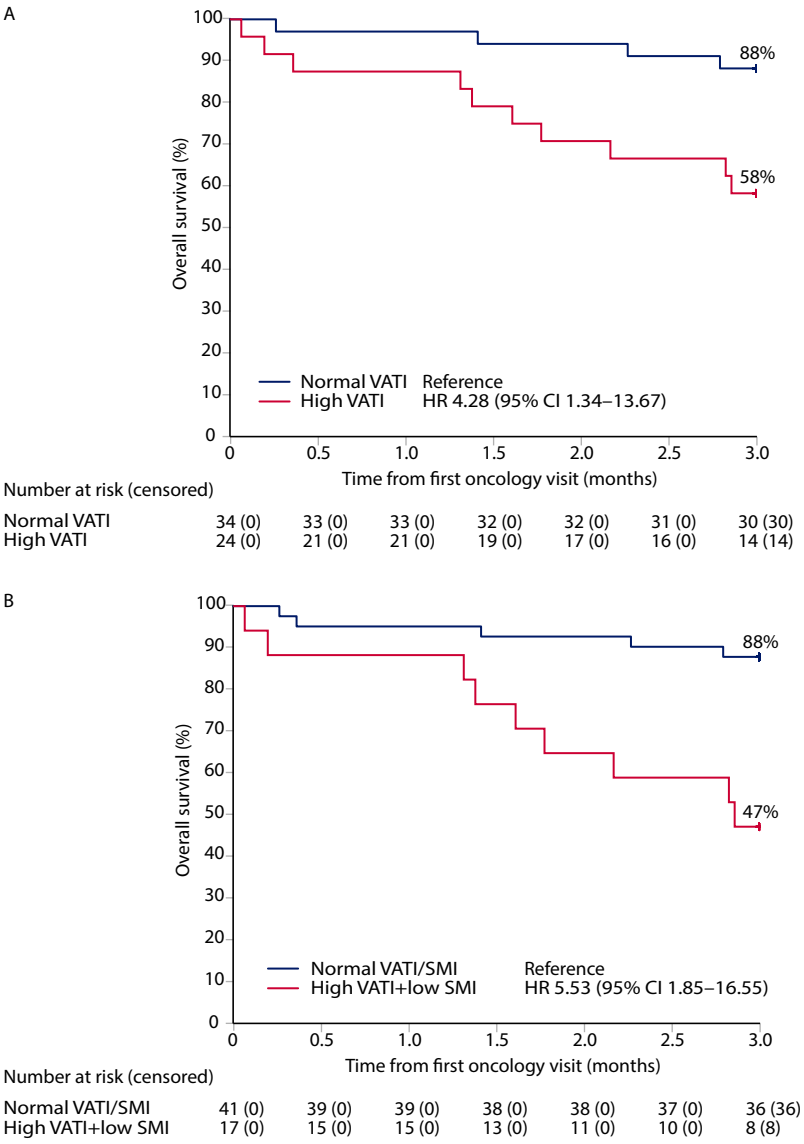

Fig. 3. Association between visceral adipose tissue index (VATI, panel A) or VATI combined with skeletal muscle index (VAT/SMI, panel B) and 3-month survival in the palliative-intent intent treatment group CI = confidence interval; HR = hazard ratio.

Table 5
Univariable and multivariate Cox regression analyses between visceral adipose tissue index (VATI)/low skeletal muscle index (SMI) and 3-month overall survival among palliative-intent patients.

	Number of non–curative patients in analysis		Univariate	Multivariable
	Univariate	Multivariable	HR[a] (95 % CI[b])	HR[a] (95 % CI[b])
Sex				
Female	28	25	1	1
Male	30	26	1.68 (0.56–5.02)	0.63 (0.12–3.31)
ECOG PS[c]				
0 to 2	37	36	1	1
3 to 4	15	15	3.01 (0.87–10.4)	2.06 (0.57–7.49)
Clinical Frailty Scale				
1 to 4	35	33	1	1
5 to 9	20	18	3.35 (1.09–10.3)*	2.66 (0.71–10.0)
VATI and SMI (Youden)[d]				
Normal VATI/SMI	41	36	1	1
High VATI+Low SMI	17	15	5.53 (1.85–16.6)*	8.91 (1.72–46.3)*

[a] Hazard ratio.
[b] Confidence interval.
[c] Eastern Cooperative Oncology Group performance status.
[d] VATI cut-offs were 69.3 cm^2/m^2 for males and 61.4 cm^2/m^2 for females and SMI cut-offs were 48.8 cm^2/m^2 for males and 33.4 cm^2/m^2 for females.
* Indicates statistical significance ($p \leq 0.05$).

High VATI+low SMI was seen in 27 % of all patients and in 29 % of patients in the palliative-intent group. Sarcopenic obesity using the criteria of Prado et al. [11] was seen in 5 % of all patients and in 7 % of the patients in the palliative-intent group.

3.3. Associations between VATI with or without SMI and Clinical Characteristics

High VATI was associated with less malnutrition according to the MNA-SF irrespective of the treatment intent (OR 0.12 and 0.30) and with impaired IADL in the palliative-intent group (OR 6; Table 2).

High VATI+low SMI was associated with male sex (OR 7), impaired IADL (OR 5), less malnutrition according to GLIM (OR 5), elevated CRP (OR 5), low albumin (OR 6), and impaired modified Glasgow prognostic score (OR 4) in the palliative-intent treatment group (Table 3).

3.4. Associations between VATI with or without SMI and Three-Month OS in the Palliative-Intent Treatment Group

In univariate models, the three-month OS rates were 88 % and 58 % in the normal and high VATI groups, respectively, using Youden's index-defined cut-offs (HR 4.28; 95 % CI 1.3–14) (Table 4 and Fig. 3A). Cut-offs from the literature for VATI by Doyle et al. [14] and for VAT area by van Dijk et al. [13] did not differentiate patients by three-month OS (Supplementary Table 1).

Patients with normal VATI/SMI vs. high VATI+low SMI had three-month OS rates of 88 % and 47 % (5.5; 1.9–17), respectively (Fig. 3B). Cut-offs by Prado et al. [11] did not differentiate patients in terms of three-month OS (Supplementary Table 1).

In a multivariable Cox regression model adjusted for pre-established prognostic factors, ECOG PS, the Clinical Frailty Scale, and sex, high VATI was a significant independent predictor of three-month OS (4.9; 1.0–24; Table 4). Additionally, high VATI+low SMI was significant in another adjusted multivariable model (8.9; 1.7–46; Table 5).

3.5. Long-Term Overall Survival

The median OS in the whole cohort ($N = 79$ patients) was 12.7 months vs. 10.5 months for those with normal and high VATI (1.21; 0.7–2.0; Fig. 4A), and 12.7 months vs. 9.6 months for those with normal VATI/SMI and high VATI+low SMI (1.86; 1.1–3.2; Fig. 4B), respectively.

The OS in the palliative-intent group did not differ significantly between those with normal vs. high VATI with medians of 9.9 vs. 5.9 months, respectively (1.38; 0.80–2.4; Fig. 4C). The median OS in the palliative-intent group was 9.9 months vs. 2.7 months in normal VATI/SMI and high VATI+low SMI groups, respectively (1.82; 1.0–3.3; Fig. 4E).

The OS for patients with normal vs. high VATI showed no significant differences in the curative group (Fig. 4D). The 24-month OS rates for patients in the curative group with normal VATI/SMI and with high VATI+low SMI were 71 % and 50 %, respectively (1.0; 0.22–4.7, Fig. 4F).

4. Discussion

Our cohort represents a rarely studied, real-life, vulnerable/frail patient population referred to a geriatric oncology unit where geriatric assessment is routine in patients with G8 $\leq$ 14/17. The findings of this study suggest that CT-determined VATI alone or, particularly, combined with low SMI are useful measures in predicting three-month survival, thus recommending refraining from active oncological treatment in vulnerable older adults with solid cancers being treated with palliative intent. These associations remained significant irrespective of oncological and geriatric functional status measures (ECOG PS and Clinical Frailty Scale, respectively). In all patients, OS was shorter for patients with high VATI+low SMI.

Our results are consistent with previous evidence suggesting that VAT has an adverse effect on survival in colorectal [33], pancreatic [13], and gastric [34] cancers, the most prevalent cancers in this study. Indeed, VAT causes metabolic disturbances including insulin resistance, faulty adipokine secretion, and chronic inflammation [35,36], which may induce carcinogenesis [37,38] and contribute to cancer cachexia, common in older adults with end-stage diseases [39]. However, there is also conflicting evidence on the role of VAT [15] in cancer mortality. High VAT has been associated with better overall and progression-free survival in hematological cancers [40] and with better cause-specific survival in renal cell cancer [41]. Some have suggested that VAT produces factors that inhibit tumor growth and improve treatment response [40].

In this study, we defined optimized VAT cut-off values for three-month OS in a cohort of older adult patients with cancer because there were no well-suited cut-offs available to achieve this aim. Several cut-offs for high visceral adiposity have been proposed in the literature for different cancer types, patient populations, endpoints, and study settings [15]. For example, Doyle et al. [14] proposed cut-offs for VAT area, and van Dijk et al. [13] proposed cut-offs for VATI for younger and fitter cohorts and did not differentiate patients with respect to three-

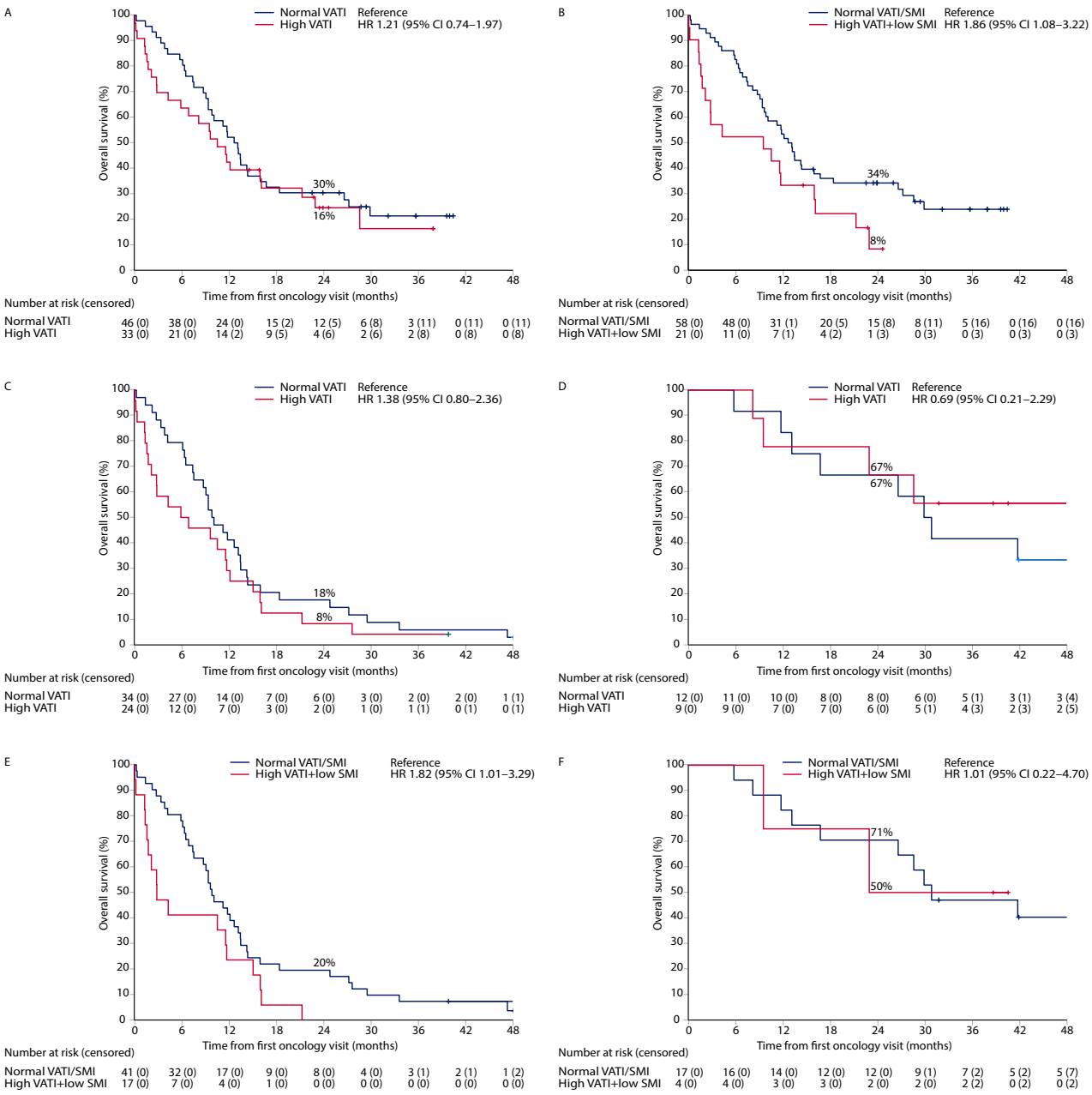

Fig. 4. Association between visceral adipose tissue index (VATI, panel A, C, and D) or VATI combined with skeletal muscle index (VATI/SMI, Panel B, E, and F) and overall survival in in the whole cohort (Panels A and B), palliative-intent (Panels C and E), and curative-intent groups (Panels D and F) CI = confidence interval; HR = hazard ratio.

month survival in this cohort.

In this cohort, high VATI combined with low SMI, a proxy for sarcopenic obesity in older adults, was associated with worse three-month and long-term OS than high visceral adiposity alone. This aligns with studies in older adults without cancer where sarcopenic obesity showed an increased risk of falls, osteoporosis, metabolic syndrome, cardiovascular disease, and mortality [16–18]. This finding supports previous studies of patients with cancers of the respiratory and gastrointestinal tract [11,12,19], which were represented in this study. The combination of high VATI+low SMI in this cohort is probably multifactorial and likely to emerge in older adults as a combination of sarcopenia, cancer cachexia, malnutrition, and frailty [42]. In line with these findings, high VATI with or without low SMI is associated with malnutrition, male sex, impaired IADL, elevated CRP, and hypoalbuminemia.

All patients in this cohort can be considered vulnerable and some even frail according to the definition by the International Society of Geriatric Oncology [43], since fit patients suitable for normal intensive therapy were excluded by G8 > 14. From a clinician's perspective, this cohort was an extremely difficult patient group. These patients might tolerate active oncological treatment but probably require reduced treatment intensity [21,22]. Most patients (78 %) in this study had gastrointestinal cancer, where the gold standard treatment consists of combination chemotherapy with or without biologics, making treatment tolerability assessment and selection even more challenging. All patients in this cohort were thoroughly evaluated for treatability with CGA, which is recommended for older adults [8] yet rarely available. Furthermore, 52 % of all patients received oncological treatment, whereas 47 % of patients who received palliative-intent care were considered too frail or declined oncological treatment. To make ethical treatment decisions, oncologists need additional tools for the evaluation

of treatability, which could include VATI, especially combined with SMI, if validated in a larger, more uniform patient series.

The strength of this study is that it is a real-life application of body composition analysis in a cohort of rarely studied yet common, clinically challenging patient population. However, there are limitations to this study. First, this study included a small retrospective patient cohort with different types of primary tumors, tumor stages, and oncological treatments. Second, the small number of patients in the curative treatment group resulted in low power, thus the survival trends should be interpreted with caution. Third, we studied only the most vulnerable patients, so the results are not generalizable to all older adults with solid tumors. Further research on the effect of VAT and SMI on survival in older adults with cancer, regardless of G8 score, is warranted. The associations of adipose tissue density measured with standardized CT-imaging methodologies and survival also warrant research in older adult patient cohorts. Furthermore, our cut-off values require validation in larger homogenous patient populations.

In conclusion, CT-determined high visceral adiposity and low skeletal muscle mass are associated with impaired three-month OS in vulnerable older adults with incurable cancer, independent of geriatric and oncological functional assessments. High visceral adiposity combined with low skeletal muscle mass was a stronger predictor of impaired survival than visceral adiposity alone. Routinely performed CT studies can be used to identify patients with impaired body composition and guide treatment decisions between allocating to or refraining from active oncological treatment.

CRediT authorship contribution statement

Antti Tolonen: Conceptualization, Methodology, Software, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization. **Kaisa Lehtomäki:** Conceptualization, Validation, Investigation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Hanna Kerminen:** Conceptualization, Validation, Formal analysis, Investigation, Resources, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Heini Huhtala:** Methodology. **Maarit Bärlund:** Conceptualization, Validation, Resources, Data curation, Writing – original draft, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Pia Österlund:** Conceptualization, Methodology, Validation, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition. **Otso Arponen:** Conceptualization, Methodology, Software, Validation, Formal analysis, Resources, Data curation, Writing – original draft, Writing – review & editing, Visualization, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest. The funders had no role in the design of the study, in the collection, analyses or interpretation of data, in the writing of the manuscript, or in the decision to publish the results. Additionally, O.A. received grants from the Osk. Huttunen Foundation, Sigrid Jusélius Foundation, Relander Foundation, Finnish Medical Foundation, Cancer Foundation Finland, and Orion Research Foundation.

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Appendix A. Supplementary Data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jgo.2024.102171.

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