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research article

Influence of nutritional status and body composition on postoperative events and outcome in patients treated for primary localized retroperitoneal sarcoma

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Background. Retroperitoneal sarcomas (RPS) are rare tumours of mesenchymal origin, commonly presented as a large tumour mass at time of diagnosis. We investigated the impact of body composition on outcome in patients operated on for primary localized RPS.

Patients and methods. We retrospectively analysed data for all patients operated on for primary RPS at our institution between 1999 and 2020. Preoperative skeletal muscle area (SMA), visceral and subcutaneous adipose tissue area (VAT and SAT) and muscle radiation attenuation (MRA) were calculated using computed tomography scans at the level of third lumbar vertebra. European Working Group on Sarcopenia in Older People (EWGSOP2) criteria were applied to define myopenia. Using maximum log-rank statistic method we determined the optimal cut-off values of body composition parameters. Myosteatosis was defined based on determined MRA cut-offs.

Results. In total 58 patient were eligible for the study. With a median follow-up of 116 months, the estimated 5-year overall survival (OS) and local-recurrence free survival (LRFS) were 66.8% and 77.6%, respectively. Patients with myopenia had significantly lower 5-year OS compared to non-myopenic ($p = 0.009$). Skeletal muscle index and subcutaneous adipose tissue index predicted LRFS on univariate analysis ($p = 0.052$ and $p = 0.039$, respectively). In multivariate analysis high visceral-to-subcutaneous adipose tissue area ratio (VSR) independently predicted higher postoperative complication rate (89.2% vs. 10.8%, $p = 0.008$). Myosteatosis was associated with higher postoperative morbidity.

Conclusions. Myopenia affected survival, but not postoperative outcome in RPS. Visceral obesity, VSR (> 0.26) and myosteatosis were associated with higher postoperative morbidity. VSR was better prognostic factor than VAT in RPS.

Key words: body composition; myopenia; cancer cachexia; myosteatosis; obesity; retroperitoneal sarcoma

Introduction

Retroperitoneal sarcomas (RPS) are soft tissue tumours of mesenchymal origin accounting for approximately 15% of all sarcomas and less than 1% of all tumour malignancy.[1-3] Most patients develop large tumour mass before diagnosis is clinically confirmed. Imaging techniques, CT and MRI

are primarily used in clinical evaluation of RPS.[1,4] Surgical resection with removal of all gross disease is the cornerstone of curative therapy and optimal results are achieved with *en bloc* resection at the time of primary presentation.[4,5] The role of radiation therapy and chemotherapy in management of RPS is still under investigation. Following the STRASS trial and STREXIT study, it seems that preoperative radiotherapy might influence the local control in liposarcoma (LPS) patients, while the evaluation of chemotherapy remains ongoing for high-grade LPS and leiomyosarcoma.[6-8] There are no currently available data supporting the use of routine neoadjuvant or adjuvant chemotherapy for these patients.[1] Optimal management is achieved in specialized sarcoma centres[4,9] with multidisciplinary approach.[10-13] Institute of Oncology Ljubljana is the only referral sarcoma centre in Slovenia.[14]

Body composition changes are related to nutrition status and associated with perioperative outcome and influence management of surgical oncology patients.[15] Ongoing catabolic processes, systemic inflammation, as well as decreased protein synthesis, as part of often presented cancer-associated cachexia, together contribute to loss of lean body mass and pose a risk of malnutrition in sarcoma patients.[16-18] Sarcopenia is a clinical syndrome in which involuntary loss of skeletal muscle mass and function is progressive and generalized, together or without increased fat mass.[19,20] Another clinically important body composition abnormality, myosteatosis, is characterized by excess accumulation of adipose tissue within muscle, resulting in impaired muscle strength and physical ability, as well as increased frailty.[21,22] Recent studies demonstrated that both sarcopenia and myosteatosis pose a greater risk for postoperative complications and decrease overall survival (OS) in a variety of different cancers, including soft tissue sarcomas.[22-27] Visceral obesity (VO) is the fat accumulation in visceral adipose tissue and serves as a clinical marker for adiposopathy.[28] Number of recent studies reported that VO is more reliable clinical marker for predicting outcome than traditional view on obesity defined by BMI.[29-33] The useful predictor of VO is visceral-to-subcutaneous adipose tissue area ratio (VSR), and high VSR is associated with poor oncologic outcome.[34-37] Also, another body composition abnormality, the new concept of sarcopenic obesity (SO), a combination of excess adiposity and sarcopenia, seems to have powerful negative prognostic impact in oncology treatment and is gaining increased attention in cancer research.[38,39] Loss of muscle mass or myopenia is a critical determinant of sarcopenia.

CT has been shown to be a precise and feasible method to evaluate body composition parameters.[40-43] There is a lack of literature data regarding the impact of body composition on postoperative and oncologic outcome in patients operated on for primary RPS.

The aim of our study is to investigate the impact of low muscle mass or myopenia, myosteatosis, visceral obesity and cancer cachexia on OS, local recurrence-free survival (LRFS) and postoperative morbidity in patients operated for primary localized RPS. Additionally, we aimed to investigate the predictive value of preoperative body composition parameters for OS, LRFS and postoperative morbidity.

Patients and methods

Study design and population

Retrospective study was conducted on patients operated on for primary RPS at Department of Surgical Oncology at the Institute of Oncology Ljubljana between September 1999 and June 2020 (Figure 1). A total of 58 patients met the inclusion criteria, 24 females (41.4%) and 34 males (58.6%). The Slovenian National Medical Ethical Committee (decision number: 0120-530/2020/3), Institutional Review Board (ERID-KSOPKR-0081/2020) and Institutional Ethical Committee (ERIDEK-0079/2020) approved the study. Due to the retrospective nature of the study the need to obtain informed consent from participants was waived.

Clinical data collection

Patient's histories including anesthesiologic preoperative reports, operative reports, hospital records, and follow-up data were reviewed. Clinical and pathological data were collected (Figure 1). Postoperative complications were evaluated in accordance with Clavien–Dindo classification.[44] Tumour features of interest were as follows: histopathological diagnosis, stage (according to American Joint Committee on Cancer [AJCC] 8th Edition), grade (according to National Federation of Centers for the Fight Against Cancer grading system)[45] and tumour size (largest diameter value). Resection quality was recorded as either complete (R0), incomplete (R1) with microscopic involvement of resection margins or macroscopic residual tumour (R2).

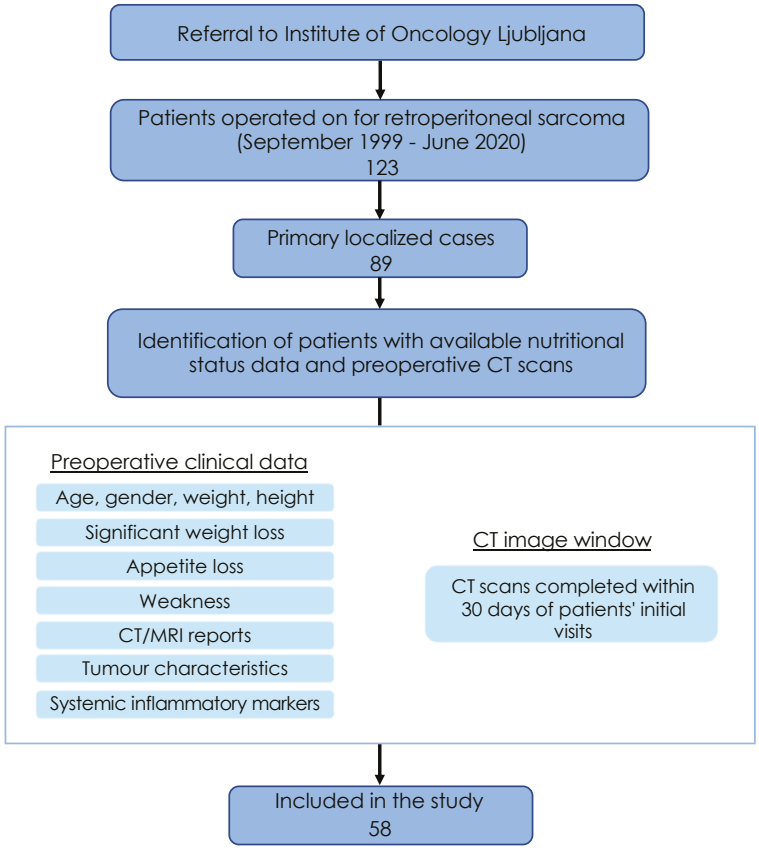


FIGURE 1. Patients' flow diagram. Out of 123 patients, 58 (47.1%) with primary localized retrperitoneal sarcomas (RPS) were included in the study and 65 were excluded. 34 (27.6%) were excluded as they presented as primary metastatic cases (6), locally recurrent cases (14) or cases with residual disease after operation elsewhere (14), and 31 patients (25.2%) were excluded as they had CT performed > 30 days from initial assessment or CT image was not technically adequate for analysis

Body composition assessment

The assessment of body composition was conducted using images from CT scans taken within 30 days preoperatively at the level of the third lumbar vertebra using the "Automated Body Composition Analyzer using Computed tomography image Segmentation" (ABACS) software.[46] This method uses predefined CT Hounsfield units (HU) values to recognize different tissues. The CT HU thresholds were 29 to 150 for skeletal muscles, 190 to 30 for subcutaneous adipose tissue, and 150 to 50 for visceral adipose tissue. The following body composition parameters were measured: total cross-sectional skeletal muscle area (SMA, cm^2), subcutaneous adipose tissue area (SAT, cm^2) and visceral adipose tissue area (VAT, cm^2). After normalization by patient's height (m^2), we used these parameters as lumbar skeletal muscle index (SMI, cm^2/m^2), subcutaneous adipose tissue index (SATI, cm^2/m^2), and visceral adipose tissue index (VATI, cm^2/m^2). VSR was calculated by dividing VAT by SAT. To assess the muscle density and myosteatosis, skeletal muscle radiation attenuation (MRA) has also been recorded in HUs. All measurements were performed by experienced researcher, accredited for complex image analysis and segmentation techniques. Additionally, we used previously reported and validated equations to calculate appendicular skeletal muscle index (ASMI), lean body mass (LBM) and fat mass (FM)[26,29,43,47]:

ASMI (kg/m^2) = 0.11 x SMI (cm^2/m^2) + 1.17

LBM (kg) = 0.030 x Lean Tissue Area (cm^2) + 6.06

FM (kg) = 0.042 x Total Fat Area (cm^2) + 11.2

Based on a single abdominal CT image per patient, LBM and FM properly reflect appropriate dual-energy X-ray absorptiometry (DXA) derived whole-body fat-free mass (FFM) and whole-body fat mass (FM), respectively.

Assessment of myopenia, myopenic and visceral obesity, myosteatosis and cancer cachexia

Myopenia was defined based on the new recommendations of The European Working Group on Sarcopenia in Older People (EWGSOP2), as follows: SMI < 43 cm^2/m^2 for men with BMI < 25, SMI < 53 cm^2/m^2 for men with BMI ≥ 25, and SMI < 41 cm^2/m^2 for women.[48]

Muscle mass in patients with obesity was assessed according to The European Society for Clinical Nutrition and Metabolism (ESPEN) and the European Association for the Study of Obesity (EASO) consensus report for sarcopenic obesity.[39] Previously reported diagnostic criteria for visceral obesity were applied: VAT > 163.8 cm^2 for men and VAT > 80.1 cm^2 for women.[29,39,47]

Preoperative cancer cachexia was defined using Fearon *et al*. criteria.[49]

In order to establish optimal cut-off values for SMI, VATI, SATI, VSR and MRA which would best reflect our study cohort in relationship to defined outcome (maximum OS), we performed optimal stratification analysis based on maximally selected rank statistics using *maxstat* package implemented in R statistics.[50,51] This approach is widely used and validated in cancer patients.[26,52-55] The presence of myosteatosis was then confirmed based on established optimal threshold for MRA: < 35.88 HU in patients with a BMI ≥ 25 kg/m^2 and < 47.41 HU in those with a BMI < 25 kg/m^2.

TABLE 1. Clinical characteristics of study population

Clinical characteristic (N = 58)	Median (IQR); n (%)
Age, years	61.0 (46.0 – 67.0)
Gender	
Male	34 (58.6%)
Female	24 (41.4%)
ASA grade	
1	9 (16%)
2	30 (52%)
3	16 (28%)
4	3 (5.2%)
Baseline albumin, g/L	41.0 (34.2 – 45.0)
Baseline C-reactive protein, mg/L	13.5 (2.0 – 66.5)
Neutrophil-lymphocyte ratio	3.3 (2.1 – 4.7)
Body Mass Index, kg/m^2	26.0 (24.7 – 29.7)
Nutrition and body composition characteristics	
Nutritional team support before operation	28(48.3%)
Skeletal Muscle Area, cm^2	45.5 (115.9 – 170.1)
Visceral Fat Area, cm^2	104.5 (53.6 – 168.7)
Subcutaneous Adipose Tissue Area, cm^2	167.9 (127.9 – 231.6)
Total Fat Area, cm^2	23.6 (19.8 – 29.1)
Total Body Fat, %	30.6 (26.8 – 32.4)
Lean Body Mass, kg	52.7 (50.0 – 57.2)
Skeletal Muscle Index, cm^2/m^2	50.2 (44.0 – 55.6)
Appendicular Skeletal Muscle Index, cm^2/m^2	6.70 (6.00 – 7.3)
Myopenia based on estimated cut-off value for SMI[a]	18 (31.0%)
Myopenia based on EWGSOP2 criteria for SMI	19 (32.8%)
Cancer cachexia	13 (22.4%)
Visceral obesity	21 (36.2%)
Myopenic obesity	4 (6.9%)
Myosteatosis[a]	37 (63.7%)

Clinical characteristic (N = 58)	Median (IQR); n (%)
Pathologic characteristics and postoperative outcome data	
Postoperative (90 day) complication rate	37 (64%)
Abdominal complication	24 (41%)
Systemic complication	17 (29%)
Abdominal and systemic complications	5 (9.0%)
Clavien-Dindo > IIIa	
Yes	17 (29%)
No	41 (71%)
Comprehensive Complication Index	20.92 (0.0–32.55)
Histologic type	
Liposarcoma	35 (60%)
Leiomyosarcoma	9 (16%)
Pleomorphic sarcoma	1 (1.7%)
Other	13 (22%)
Tumour size, cm	20 (11–30)
FNCLCC grade	
1	15 (26%)
2	11 (19%)
3	23 (40%)
Unknown	9 (16%)
Stage AJCC (8th edition)	
1A	1 (1.7%)
1B	23 (40%)
3A	6 (10%)
3B	28 (48%)
Completeness of surgical resection	
R0	47 (81%)
R1/R2	11 (19%)

AJCC = The American Joint Committee on Cancer; ASA = American Society of Anesthesiologists classification; EWGSOP2 = The European Working Group on Sarcopenia in Older People; FNCLCC = Fédération Nationale des Centres de Lutte Contre Le Cancer

Summary for continuous variables is presented as median (interquartile range) and the statistical test is Kruskal-Wallis/Mann-Whitney; [a] cut-off values displayed in Table 3

Survival and statistical analysis

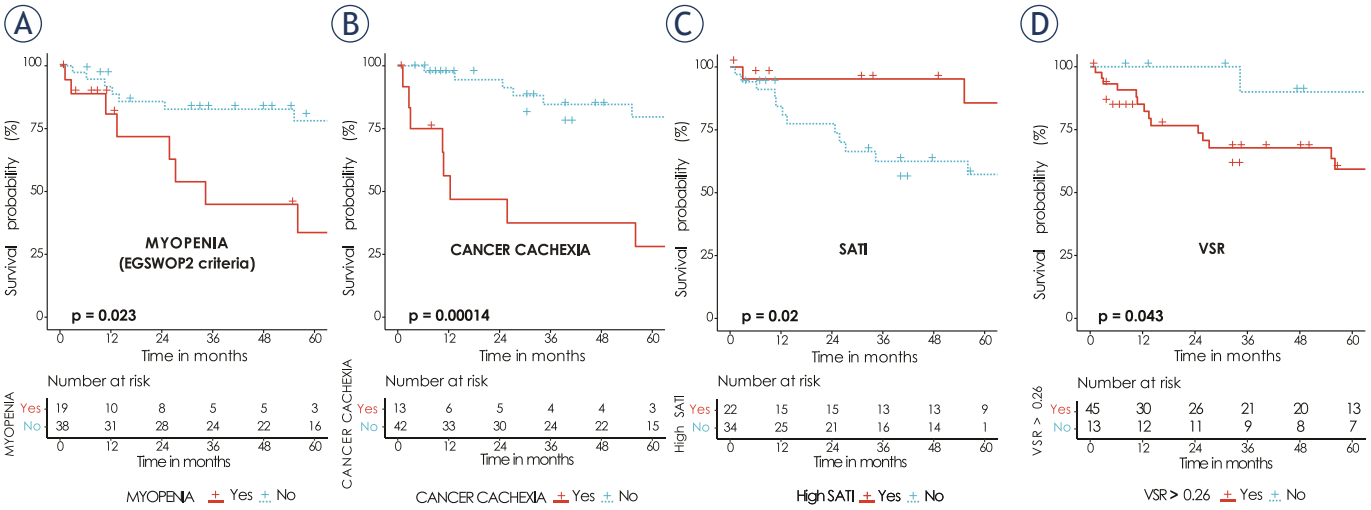
Final survival follow-up time was set as last follow-up date in the study period or the event of death. OS was defined as time between the date of the operation and date of death from any cause or last follow-up. LRFS was defined as the time interval between operation date and date of first documented local progression, and instances involving deaths without evidence of disease and the occurrence of distant metastases considered as competing events. Survival curves were estimated using Kaplan-Meier method. Log-rank test, linear regression and Cox proportional hazard regression models were used to analyse the relationship between clinicopathological parameters

TABLE 2. Comparison of clinical and body composition parameters between myopenic and non-myopenic patients (EGSWOP2 criteria)

Clinicopathological factor	Level[a]	Myopenic[b]	Non Myopenic[b]	p
Age, years	Median (IQR)	66.0 (50.5–71.5)	61.0 (46.0–64.8)	0.236
Gender	Male	11(57.9)	23 (60.5)	1
	Female	8(42.1)	15 (39.5)	
ASA Grade, 2–3 vs. 1	1	3 (15.8)	6 (15.8)	1
	2–3	16 (84.2)	32 84.2)	
FNCLCC Grade	1	5 (29.4)	10 (32.3)	0.547
	2	5 (29.4)	5 (16.1)	
	3	7 (41.2)	16 (51.6)	
	(Missing)	7 (18.4)	2 (10.5)	
Tumour size, cm	Median (IQR)	26.0 (20.5–34.0)	17.5 (10.0–24.8)	0.005
Clavien-Dindo > IIIa	Yes	3 (15.8)	14 (36.8)	0.183
	No	16 (84.2)	24 (63.2)	
Neutrophil-lymphocyte ratio	Median (IQR)	3.9 (2.4–4.7)	3.0 (2.1–4.7)	0.504
Baseline albumin, g/L	Median (IQR)	40.0 (32.0–42.5)	43.0 (35.0–45.8)	0.232
Baseline C-reactive protein, mg/L	Median (IQR)	44.0 (7.5–99.5)	6.0 (2.0–45.0)	0.088
Haemoglobin level, g/L	Median (IQR)	128.0 (101.5–136.5)	132.5 (115.2-145.8)	0.141
Preoperative radiotherapy	No	19 (100.0)	37 (97.4)	1
	Yes	0 (0.0)	1 (2.6)	
Resection status	R0	17 (89.5)	29 (76.3)	0.406
	R1	2 (10.5)	9 (23.7)	
Intraoperative blood loss, ml	Median (IQR)	1300.0 (425.0–4100.0)	1350.0 (500.0–2075.0)	0.78
Stage AJCC, 8th edition	1A–1B	7 (36.8)	17 (44.7)	0.776
	3A–3B	12 (63.2)	21 (55.3)	
Histology subtype	Pleomorphic	1 (5.3)	0 (0.0)	0.184
	Liposarcoma	14 (73.7)	21 (55.3)	
	Leiomyosarcoma	2 (10.5)	6 (15.8)	
	Other	2 (10.5)	11 (28.9)	
Nutrition team before surgery	Yes	12 (63.2)	16 (42.1)	0.223
	No	7 (36.8)	22 (57.9)	
Length of hospital stay, days	Median (IQR)	20.0 (11.0–28.8)	15.0 (11.5–27.0)	0.593
Visceral obesity	Yes	4 (21.1)	16 (42.1)	0.202
	No	15 (78.9)	22 (57.9)	
Myosteatosis	Yes	16 (84.2)	21 (56.8)	0.079
	No	3 (15.8)	16 (43.2)	
Cancer cachexia	No	12 (63.2)	31 (83.8)	0.163
	Yes	7 (36.8)	6 (16.2)	
Body Mass Index, kg/m^2	Median (IQR)	25.7 (23.3–27.2)	26.9 (24.8–30.9)	0.071
Skeletal Muscle Area, HU	Median (IQR)	115.8 (106.5–153.3)	149.9 (130.6-177.1)	0.019
Skeletal Muscle Index, cm^2/m^2	Median (IQR)	41.0 (38.3–46.8)	53.5 (46.2–58.8)	< 0.001
Muscle Radiation Attenuation, HU	Median (IQR)	35.6 (31.8–43.2)	38.1 (29.9–42.2)	0.959
Subcutaneous Adipose Tissue Area, cm^2	Median (IQR)	156.4 (103.2–194.4)	185.4 (131.4-254.1)	0.078
Visceral Adipose Tissue Area, cm^2	Median (IQR)	64.6 (38.1–131.6)	125.5 (66.1–201.7)	0.07
Visceral-to-subcutaneous adipose tissue area ratio	Median (IQR)	0.5 (0.2–0.9)	0.8 (0.3–1.1)	0.393
Body fat, %	Median (IQR)	28.3 (21.3–31.6)	31.1 (28.1–33.3)	0.024
Lean Body Mass, kg	Median (IQR)	52.5 (50.4–57.7)	52.8 (49.8–56.4)	0.684
Subcutaneous Adipose Tissue Index, cm^2/m^2	Median (IQR)	46.8 (30.6–67.2)	64.6(43.9–95.0)	0.048
Visceral Adipose Tissue Index, cm^2/m^2	Median (IQR)	20.6 (13.2–43.8)	42.3 (24.2–63.6)	0.025

[a] Summary for continuous variables is median (interquartile range) and the statistical test is Kruskal-Wallis/Mann-Whitney; [b] Median (IQR); n (%);

AJCC =The American Joint Committee on Cancer; ASA = American Society of Anesthesiologists; EGSWOP2 = The European Working Group on Sarcopenia in Older People; FNCLCC = Fédération Nationale des Centres de Lutte Contre Le Cancer; HU = Hounsfield units



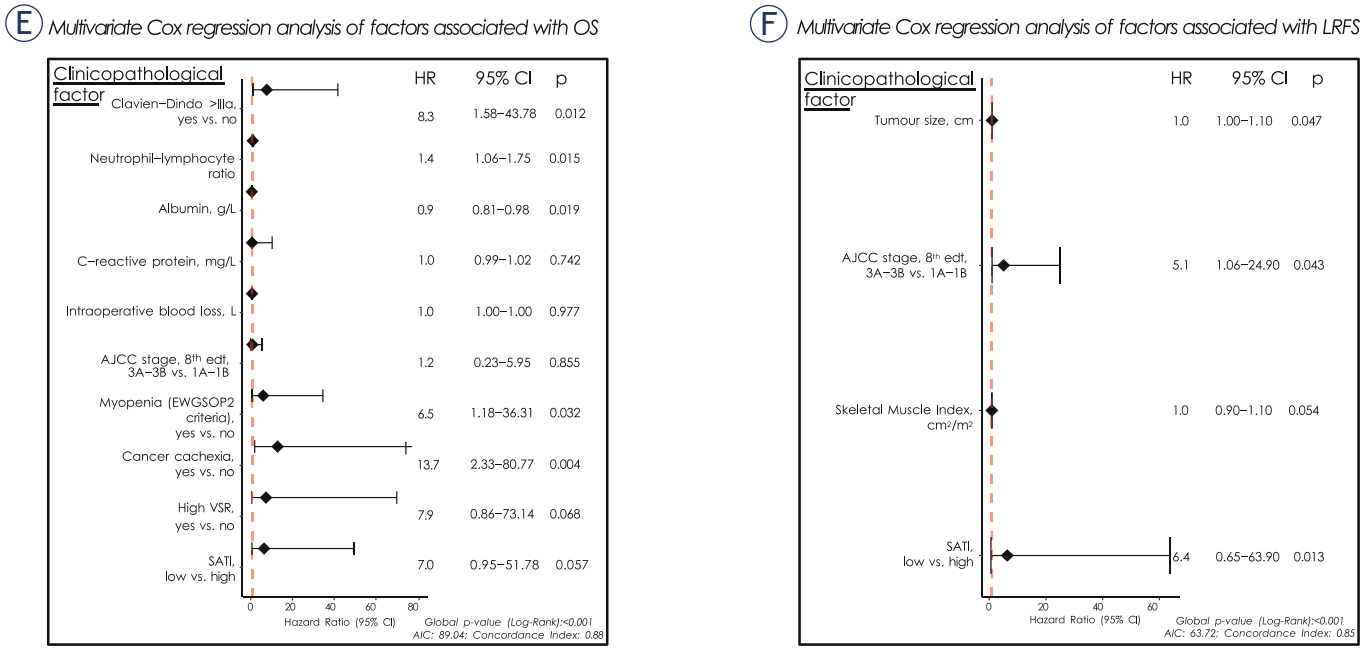


FIGURE 2. Kaplan-Meier curves for OS **(A–D)** and forest plots of multivariate Cox regression analysis of factors associated with OS **(E)** and LRFS **(F).** Kaplan-Meier curves for OS according to presence of: **(A)** myopenia based on EWGSOP2 criteria (red = myopenic, blue = non-myopenic), **(B)** cancer cachexia (red = cachectic, blue = non-cachectic), **(C)** high SATI (red = SATI above estimated cohort cut-off, blue = SATI below estimated cohort cut-off) and **(D)** high VSR (red = VSR > 0.26, blue = VSR < 0.26);

EWGSOP2 = The European Working Group on Sarcopenia in Older People revised criteria from 2018; SATI = Subcutaneous Adipose Tissue Index, cm²/m²; SMI = Skeletal Muscle Index; VSR = Visceral-to-subcutaneous adipose tissue area ratio; OS = Overall survival; LRFS = Local recurrence-free survival; HR = Hazard ratio; AIC = Akaike Information Criterion

and survival. Hosmer-Lemeshow test assessed the prediction accuracy (goodness of fit) of regression models. Hazard ratios (HRs) and 95% confidence intervals (CIs) were obtained.

In addition to body composition parameters, following known prognostic factors or other clinical features were considered: age, gender, American Society of Anesthesiologists (ASA) classification, Albumin level (g/dL), C-reactive protein (mg/L), neutrophil-to-lymphocyte ratio (NLR), preoperative radiotherapy, tumour size (cm), and intraoperative blood loss (ml). Results were statistically significant if two-sided p value < 0.05 was achieved. R statistical software (version 4.2.1, R core Team) was used.

TABLE 3. Results of optimal stratification analysis for body composition parameters

BMI, kg/m²	Skeletal Muscle Index[a], cm²/m²		Visceral Adipose Tissue Index[b], cm²/m²		Subcutaneous Adipose Tissue Index[b], cm²/m²		Visceral to subcutaneous ratio[c]		Muscle Radiation Attenuation[d], HU	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
< 25	49.21	49.21	61.38	25.55	49.23	86.89	0.26		47.41	
≥ 25	49.90	50.64							35.88	

BMI = body mass index; HU = Hounsfield Unit; [a] adjusted for gender and BMI; [b] adjusted for gender only; [c] cut-off determined on the level of whole cohort, not stratified for BMI nor gender; [d] adjusted for BMI only.

Results

Demographic and clinical characteristics

Out of 89 primary localized RPS cases, clinical and pathological characteristics and preoperative abdominal CT scans technically adequate for analysis were available for 58 patients, representing the final study cohort (Figure 1). The demographic and clinical characteristics of the patients are provided in Table 1. In the cohort, 34 (58.6%) were males and 24 (41.4%) were females. Median age at diagnosis was 61.0 (46.0–67.0). Loss of muscle mass according to EWGSOP2 criteria, was present in 19 patients (32.8%). Applying our cut-off values for low SMI, comparable number of myopenic patients was detected, 12 males (66.7%) and 6 females (33.33%). Significant difference between myopenic and non-myopenic group was detected in tumour size (median 26 *vs.* 17.5 cm, p = 0.005), SMA (median 115.8 *vs.* 149.9 cm², p = 0.019), SMI (median 41 *vs.* 53.5 cm²/m², p < 0.001), SATI (46.8 *vs.* 64.6 cm²/m², p = 0.048) and VATI (20.6 *vs.* 42.3 cm²/m², p = 0.025) (Table 2). There was no significant difference in clinical management among myopenic and non-myopenic group.

Males had significantly higher mean values of SMA (163.7 *vs.* 120 cm², p < 0.001), SMI (52.8 *vs.* 45.3 cm²/m², p = 0.006), VAT (153.9 *vs.* 96 cm², p = 0.045) and VSR (1.0 *vs.* 0.5, p = 0.001), while in females SAT (227.2 *vs.* 155.1 cm², p = 0.003) and SATI (85.0 *vs.* 49.8 cm²/m², p = 0.001) were significantly higher (Supplementaly Table 1).

The results of optimal stratification analysis for finding cut-off values for SMI, VATI, SATI, VSR and MRA are presented in Table 3 and Supplementaly Figures 1–4.

Survival analysis

Overall survival

In the cohort, median follow up time was 116 months, with 5-year OS of 66.8% (95% CI 53.9–82.7). The result of univariate analysis of OS is presented in Supplementaly Table 2. Of the nutritional and body composition features, myopenia (HR 3.18, 95% CI 1.11–8.56, p = 0.020), cancer cachexia (HR 6.07, 95% CI 2.24–16.46, p < 0.001), high VSR (HR 4.32, p = 0.043) and low SATI (HR 4.91, 95% CI 1.11–21.65, p = 0.02) were associated with elevated risk for overall mortality. SMI and BMI had small protective impact on OS in univariate analysis (HR 0.95, p = 0.040 and HR 0.83, p = 0.036, respectively). Of the known prognostic factors, preoperative levels of albumin, CRP, NLR, and AJCC stage were associated with OS. Major postoperative morbidity (CD > IIIa) was significantly correlated with shorter OS (HR 3.16, 95% CI, 1.24–8.04, p = 0.016). Multivariate analysis of OS confirmed the significance of myopenia (myopenic vs. non-myopenic: adjusted HR 6.5, p = 0.032), cancer cachexia (cachectic vs. non-cachectic: adjusted HR 13.7, p = 0.004) and high SATI (adjusted HR 7.00, p = 0.057). Major postoperative morbidity, NLR and albumin level also remained significant in multivariate OS analysis (Figure 2 A–E).

Local-recurrence free survival

The 5-year LRFS for whole study cohort was 77.6% (95% CI, 65.2–92). In univariate analysis among all body composition parameters, only SMI and SATI (low *vs.* high) showed association with LRFS (HR 0.94, 95% CI 0.88–1.00, p = 0.052 and HR 8.77, 95% CI 1.12–68.69, p = 0.039, respectively). Tumour size (HR 1.05, 95% CI 1.01–1.09, p = 0.016) and AJCC stage (3A–3B *vs.* 1A–1B, HR 4.46, 95% CI, 0.95–20.95, p = 0.058) were also associated with LRFS. However, SMI and SATI lost statistical significance in multivariate model, while tumour size and AJCC stage remained significant (Figure 2 F and Supplementaly Table 2).

Postoperative outcome and morbidity

We performed univariate and multivariate risk factor analysis to evaluate factors associated with

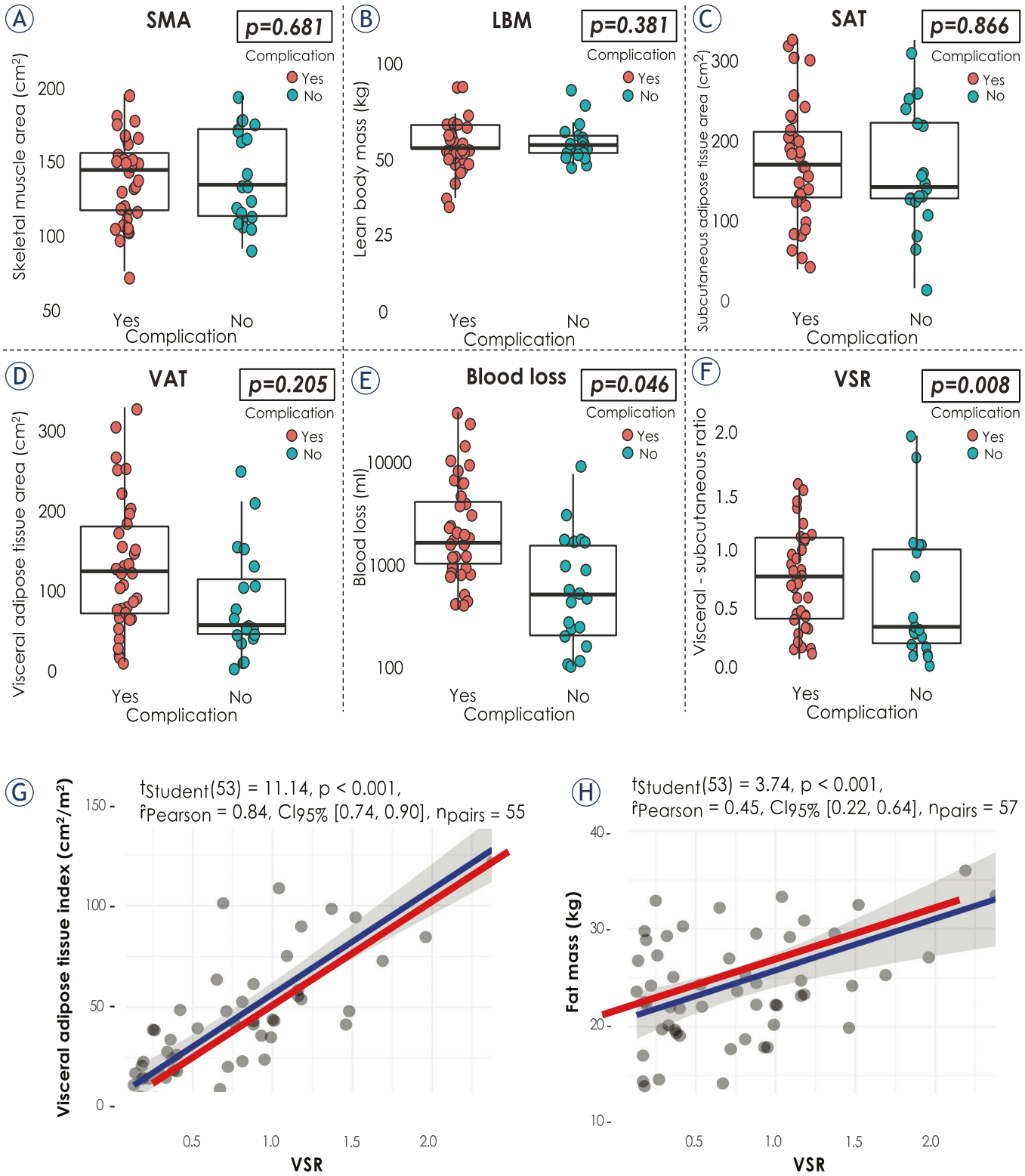


FIGURE 3. Association between overall morbidity following surgery for primary RPS and body composition **(A–F)** and linear correlation analysis between VSR and VATI **(G)** and VSR and fat mass **(H)**. VSR **(F)** and intraoperative blood loss **(E)** independently predicted worse postoperative outcome. In multivariate analysis skeletal muscle index (SMA), lean body mass (LBM), subcutaneous adipose tissue area (SAT) and visceral adipose tissue area (VAT) were not associated with statistically higher overall postoperative morbidity **(A–D)**.

VATI = Visceral Adipose Tissue Index; VSR = Visceral-to-subcutaneous adipose tissue area ratio. $r_{Pearson}$ = Pearson Correlation Coefficient; $t_{Student}$ = result of t-test for correlation

TABLE 4. Summary of univariate and multivariate analysis of association between body composition and outcome following surgery for primary RPS

Clinico-pathological factor	Length of hospital stay (> 10 days)				Clavien-Dindo > IIIa				Any complication (overall morbidity)			
	Uni-variable		Multi-variable		Uni-variable		Multi-variable		Uni-variable		Multi-variable	
	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p	OR (95% CI)	p
Myopenia, yes vs. no[a]	1.34 (0.38-5.54)	0.664	-	-	0.32 (0.07-1.18)	0.112	-	-	3.11 (0.85-15.08)	0.112	-	-
Visceral obesity, yes vs. no	2.54 (0.68-12.40)	0.196	-	-	0.65 (0.18-2.13)	0.49	-	-	3.61 (1.09-14.44)	0.047	-	-
Myopenic obesity, yes vs. no	0.01 (0.00-0.001)	0.993	-	-	20090605.83 (0.00-NA)	0.993	-	-	279.10 (0.00-NA)	0.993	-	-
Myosteatosis, yes vs. no	1.39 (0.39-5.76)	0.626	-	-	2.17 (0.58-10.58)	0.282	-	-	5.05 (1.39-24.41)	0.023	4.63 (1.03-28.42)	0.063
Cancer cachexia, yes vs. no	0.68 (0.18-2.94)	0.585	-	-	2.83 (0.76-10.59)	0.117	-	-	0.95 (0.27- 3.60)	0.935	-	-
Body mass index, kg/m^2	1.00 (0.89-1.14)	0.992	-	-	0.94 (0.81-1.06)	0.351	-	-	0.95 (0.27- 3.60)	0.935	-	-
Skeletal Muscle Area, HU	1.00 (0.99-1.02)	0.869	-	-	1.00 (0.98-1.01)	0.679	-	-	1.00 (0.99- 1.02)	0.681	-	-
Skeletal Muscle Index, cm^2/m^2	1.00 (0.95-1.07)	0.88	-	-	1.00 (0.95-1.06)	0.909	-	-	1.04 (0.98- 1.10)	0.230	-	-
Muscle Radiation Attenuation, HU	0.98 (0.92-1.04)	0.526	-	-	0.99 (0.93-1.05)	0.775	-	-	0.94 (0.88- 1.00)	0.076	-	-
SAT, cm^2	1.00 (0.99-1.00)	0.336	-	-	1.00 (0.99-1.00)	0.48	-	-	1.00 (0.99- 1.01)	0.866	-	-
VAT, cm^2	1.00 (1.00-1.01)	0.769	-	-	1.00 (0.99-1.00)	0.622	-	-	1.00 (1.00- 1.01)	0.205	-	-
VSR	1.55 (0.53-5.51)	0.456	-	-	1.09 (0.39-2.861)	0.861	-	-	1.72 (0.66- 5.19)	0.292	-	-
High VSR[b], yes vs. no	2.50 (0.63-9.52)	0.179	-	-	2.75 (0.63-19.26)	0.224	-	-	6.19 (1.69-26.52)	0.008	5.05 (1.08-29.74)	0.05
Body fat, %	0.96 (0.87-1.05)	0.380	-	-	1.00 (0.92-1.09)	0.962	-	-	1.00 (0.93- 1.09)	0.912	-	-
Lean Body Mass, kg	1.01 (0.96-1.07)	0.765	-	-	1.02 (0.97-1.08)	0.381	-	-	1.02 (0.97- 1.08)	0.381	-	-
SATI, cm^2/m^2	0.99 (0.97-1.01)	0.279	-	-	0.99 (0.97-1.01)	0.344	-	-	1.00 (0.99- 1.02)	0.794	-	-
VATI, cm^2/m^2	1.00 (0.99-1.02)	0.625	-	-	1.00 (0.98-1.01)	0.706	-	-	1.01 (1.00- 1.04)	0.122	-	-
High SATI[c], yes vs. no	1.80 (0.52-6.25)	0.346	-	-	0.90 (0.26-2.93)	0.863	-	-	1.50 (0.49- 4.81)	0.481	-	-
High VATI[d], yes vs. no	0.49 (0.10-1.87)	0.327	-	-	0.38 (0.08-1.44)	0.184	-	-	2.83 (0.84-11.45)	0.111	-	-

OR = Odds Ratio; SAT = Subcutaneous Adipose Tissue Area; SATI = Subcutaneous Adipose Tissue Index; VAT = Visceral Adipose Tissue Area; VATI = Visceral Adipose Tissue Index; VSR = Visceral-to-subcutaneous adipose tissue area ratio;

[a] assessed by the European Working Group on Sarcopenia in Older People revised criteria from 2018;[b] defined as VSR > 0.26; [c] defined as SATI > 49.23 for males and SATI > 86.89 for females;[d] defined as VATI > 61.38 for males and VATI > 25.55 for females

Only significant variables (p < 0.05) were included in multivariate analysis.

postoperative morbidity, intrahospital length of stay (LOS) and major postoperative complications.

The median postoperative LOS was 18 days (IQR: 11.25–28.75). In univariate analysis, higher ASA grade (2–3 *vs.* 1, OR 5.56, p = 0.025) and tumour size (OR 1.12, p = 0.007) showed correlation with prolonged LOS. Preoperative CRP (OR 1.02, p = 0.007), resection status (R1–R2 *vs.* R0 OR 4.87, p = 0.046) and intraoperative blood loss (OR 1.10, p = 0.065) were associated with major postoperative morbidity (Table 4 and Supplementaly Table 3).

In univariate analysis of overall postoperative morbidity, the presence of myosteatosis (OR 5.05, p = 0.023), VO (OR 3.61, p = 0.047) and high VSR (OR 6.19, p = 0.008) were associated with significantly higher overall complication rate. Adjusted for other covariates in multivariate analysis, high VSR maintained significant impact (adjusted OR 5.05, p = 0.05). We omitted VO from multivariate analysis to avoid multicollinearity. Figure 3 (panels A–F) summarises our analysis of morbidity following surgery for primary RPS.

Discussion

Our study provided new insight into the association between preoperative body composition and postoperative and oncologic outcome in primary RPS patients. We focused on evaluation of the sig-

nificance of preoperative nutrition status-related syndromes. Furthermore, we examined the predictive value of SMI and MRA, measures of muscular quantity and quality, as well as, VATI, SATI and VSR, measures of adiposity, for possible clinical use in preoperative clinical assessment of patients diagnosed with this rare malignancy. To address the lack of literature and inconsistency in used body composition cut points, we used maximally selected rank statistics to defined cohort – specific cut point. This method incorporated follow-up time and time-to-event outcomes, dividing the patients into two groups with the most significant statistics between each other in term of survival.[56]

In our cohort, both myopenia and VO were associated with poorer OS. Patients with myopenia had 5-year OS of 33.7%, compared to significantly higher 78.3% 5-year OS for non-myopenic patients (p = 0.009). SMI predicted LRFS on univariate analysis and lost prognostic value in multivariate analysis.

These findings are in line with knowledge that sarcopenic surgical oncology patients are at greater risk for poor operative outcome because of underlying muscle mass loss which is an integral component of sarcopenia and also facilitates the impairment of muscle function and physical performance.[57] Therefore we used the cut-off values for diagnosis of myopenia which are the component of diagnostic criteria and tools that define and characterize sarcopenia in EWGSOP2 Revised European Consensus.[48] Our optimal fitting method analysis for establishing the cut-off value for defining low SMI (used for comparative and descriptive purposes) resulted in slightly different cut-off values: SMI < 49.21 cm^2/m^2 for males and females with BMI < 25, and SMI < 49.9 cm^2/m^2 for males with BMI ≥ 25 and SMI < 50.64 cm^2/m^2 for females with BMI ≥ 25. Both EWGSOP2 criteria for low SMI and our cut-off values were able to predict poor prognosis. It seems, that difference is generated because our cohort consisted of only patients with primary RPS with resectable disease rather than a heterogeneous cohort. We also found that SMI analysed as continuous variable was not able to predict poor outcome. This is another proof that in clinical practice SMI should be evaluated as body composition (myopenia) parameter defined with cut-off values below which the risk of poor prognosis is increased significantly, rather than discretional decrease.[58]

Several studies demonstrated the superior predictive value of myosteatosis to sarcopenia or myopenia for poor survival.[59-61] Most of this data is founded on reports about patients operated on for gastrointestinal cancers. In our study cohort myosteatosis was also associated with greater overall complication rate (OR 5.05, 95% CI 1.39-24.41, p = 0.023) in univariate analysis, but it was not confirmed in multivariate analysis. Myosteatosis was not associated with OS, LRFS or postoperative outcome. However, recently a group of authors reported significant association between myosteatosis and major complication rate and OS in retroperitoneal and trunk soft tissue sarcoma.[29] They used preoperative MRA as continuous variable to define myosteatosis, not providing any cut-off point for reference. We defined myosteatosis based on optimal cut point analysis for MRA, and determined cut-offs are comparable to most commonly used range of MRA cut-offs for myosteatosis.[62]

In order to evaluate obesity and the distribution of fat tissue, we calculated VAT, SAT and corresponding height-adjusted indexes VATI and SATI. We also considered BMI. Higher value of BMI (≥ 25) was not associated with oncologic or postoperative outcome. This is in line with number of studies suggesting that BMI is not reliable prognostic parameter for predicting perioperative outcome in cancer patients.[63-65] Stratified for myopenia, comparison of the subgroups revealed that body fat and VATI were significantly higher in non-myopenic patients (median 31.1 *vs.* 28.1%, p = 0.024 and 42.3 *vs.* 20.6 cm^2/m^2, p = 0.025, respectively) (Table 2). Further on, we used VAT to assess VO applying the ESPEN/EASO criteria.[39] VO predicted poorer OS and higher postoperative complication rate. VAT alone had no impact on OS or postoperative outcome. Recent study on soft tissue sarcoma patients reported identical findings.[29] We considered VSR into adiposity analysis defining subgroup of patients with normal and high VSR (> 0.26) based on optimal cut-off analysis. In multivariate analysis VSR was an independent predictor for overall complication rate following surgery. High VSR group experienced significantly more complications compared to normal VSR group (33 (89.2%) *vs.* 4 (10.8%), p = 0.008). These results are comparable with previous reports in which VSR was superior to VAT as independent risk factor for death and local recurrence. [34,35,58,66,67] Linear regression analysis showed significant corelation between VSR and both VATI and fat mass (Figure 3 – panels G–H and Supplementaly Figure 5), confirming the importance of balance between visceral and subcutaneous adipose tissue. Recent studies demonstrated that predictive values of VSR for cardiovascular and metabolic disease incidence is superior to

VAT.[34,36,37,68] However, to our knowledge, only a few studies investigated the impact of VSR and VAT on survival and postoperative outcome in patients operated on for primary RPS.[29] Our study underlined that high VSR is not only superior to VAT but also to BMI in predicting poor oncologic and perioperative outcome. These findings suggest that VSR better estimates adipose tissue distribution and poses an additional difficulty for performing the surgery itself. High VSR is strong independent predictor for overall postoperative morbidity (multivariable-adjusted OR 5.05, p = 0.05). On the other hand, in the context of survival analysis, the multivariate regression model was not able to confirm the statistical significance of VSR (p = 0.068). This suggests that the impact of VSR on survival of RPS patients may be attenuated when considered alongside the broader set of predictors. One of the reasons may be the fact that, the presence of high VSR, as determined by specific gender-independent cut-off criteria, exhibited a statistically significant gender difference, with females having higher odds (OR = 4.5, p = 0.027) compared to males. Furthermore, we found a statistically significant difference in the distribution of SMI, between the two groups defined by VSR (high VSR *vs*. low VSR OR = 0.926, p = 0.047). Logistic regression model revealed significant association of SMI with a reduced odds of the specified outcome within the "high VSR" group. Based on our initial hypothesis that "high VSR" has a negative impact on survival, supported by univariate analysis, this implies that SMI (approximation of myopenia) may be a factor that mitigates the negative impact of "high VSR" on patient survival or serves as a positive influence, hence confounding the effect of VSR in multivariate settings. Further prospective studies need to be developed to confirm the importance of preoperative VSR for poor postoperative survival. In contrast to high VAT, low SATI, independently predicted poorer OS (adjusted HR 7.00, p = 0.057). Recent study reported similar protective effect of higher subcutaneous fat in RPS patients[29], which confirms the known benefits of SATI in processes of carcinogenesis and metabolism.[30,69-71]

The multivariate analysis demonstrated that, when assessed as a continuous variable, albumin levels (HR 0.9, 95% CI 0.81–0.98, p = 0.019) and NLR (HR 1.4, 95% CI 1.06–1.75, p = 0.015) were independently associated with overall survival. This finding underscores the pivotal role of these inflammatory biomarkers in clinical practice and management of surgical oncology patients. Our results align with previous findings.[17,18,72-77] Furthermore, our observation suggests that hypoalbuminemia identifies a high-risk cohort that may derive greater benefits from enhanced nutritional support preoperatively. The omission of descriptive statistical analysis for serum albumin and NLR, in term of patients' outcome, limits the depth of our data exploration.

Our study had some limitations. It was a single center report including relatively small number of patients which might influence the power of drown conclusions. Another weakness was the fact that we didn't assess all comorbidities in our analyses, as they were considered negligible in patients with soft tissue sarcoma. However, since our Institution is the only referral sarcoma center in Slovenia, having population of 2.1 million, our study cohort consisted of unique set of primary RPS patients eligible for curative surgery. We reported the most distinguishable, cohort – specific, cut points for CT measured body composition (muscle and adipose tissue) parameters in regard to long term prognosis. And finally, providing a unique and new insight into the association between preoperative body composition and postoperative and oncologic outcome in primary RPS patients was the main strength of the study.

Conclusions

Patients with primary RPS are in a great risk for nutritional disorders for number of reasons such as: requirement for demanding abdominal surgery in their management, long preclinical history and tumour size.[4,10,18,78,79] In our study cohort there was a high prevalence of myopenia (32.8%) and visceral obesity (36.2%). Myopenia, cancer cachexia and low SATI were strongly associated with poor OS. High VSR was strong independent predictor for overall postoperative morbidity. Additional prospective studies are required to substantiate the role of preoperative VSR as independent prognostic factor for postoperative survival. Our findings suggest that clinical nutrition interventions towards improving visceral adiposity and myopenia may benefit surgical and oncologic outcome in primary RPS patients.

References

1. Van Tine BA. 90 - Sarcomas of soft tissue. In: Niederhuber JE, Armitage JO, Kastan MB, Doroshow JH, Tepper JE, editors. *Abeloff's clinical oncology* (Sixth Edition). Philadelphia: Elsevier; 2019. p. 1655-93.e11.

2. Stiller CA, Trama A, Serraino D, Rossi S, Navarro C, Chirlaque MD, et al. Descriptive epidemiology of sarcomas in Europe: report from the RARECARE project. *Eur J Cancer* 2013; **49:** 684-95. doi: 10.1016/j.ejca.2012.09.011

3. Gholami S, Jacobs CD, Kapp DS, Parast LM, Norton JA. The value of surgery for retroperitoneal sarcoma. *Sarcoma* 2009; **2009:** 605840. doi: 10.1155/2009/605840

4. Trans-Atlantic RPSWG. Management of primary retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. *Ann Surg Oncol* 2015; **22:** 256-63. doi: 10.1245/s10434-014-3965-2

5. Trans-Atlantic RPSWG. Erratum to: Management of recurrent retroperitoneal sarcoma (RPS) in the adult: a consensus approach from the Trans-Atlantic RPS Working Group. *Ann Surg Oncol* 2017; **24:** 688-9. doi: 10.1245/s10434-017-5889-0

6. Bonvalot S, Gronchi A, Le Péchoux C, Swallow CJ, Strauss D, Meeus P, et al. Preoperative radiotherapy plus surgery versus surgery alone for patients with primary retroperitoneal sarcoma (EORTC-62092: STRASS): a multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol* 2020; **21:** 1366-77. doi: 10.1016/s1470-2045(20)30446-0

7. Bonvalot S, Gronchi A, Le Pechoux C, Swallow CJ, Strauss DC, Meeus P, et al. STRASS (EORTC 62092): a phase III randomized study of preoperative radiotherapy plus surgery versus surgery alone for patients with retroperitoneal sarcoma. [abstract]. *J Clin Oncol* 2019; **37(15 Sppl):** 11001. doi: 10.1200/JCO.2019.37.15_suppl.11001

8. Callegaro D, Raut CP, Ajayi T, Strauss D, Bonvalot S, Ng D, et al. Preoperative radiotherapy in patients with primary retroperitoneal sarcoma: EORTC-62092 Trial (STRASS) versus off-trial (STREXIT) results. *Ann Surg* 2023; **278:** 127-34. doi: 10.1097/sla.0000000000005492

9. Bonvalot S, Raut CP, Pollock RE, Rutkowski P, Strauss DC, Hayes AJ, et al. Technical considerations in surgery for retroperitoneal sarcomas: position paper from E-Surge, a master class in sarcoma surgery, and EORTC-STBSG. *Ann Surg Oncol* 2012; **19:** 2981-91. doi: 10.1245/s10434-012-2342-2

10. Bonvalot S, Rivoire M, Castaing M, Stoeckle E, Le Cesne A, Blay JY, et al. Primary retroperitoneal sarcomas: a multivariate analysis of surgical factors associated with local control. *J Clin Oncol* 2009; **27:** 31-7. doi: 10.1200/jco.2008.18.0802

11. Gutierrez JC, Perez EA, Moffat FL, Livingstone AS, Franceschi D, Koniaris LG. Should soft tissue sarcomas be treated at high-volume centers? An analysis of 4205 patients. *Ann Surg* 2007; **245:** 952-8. doi: 10.1097/01.sla.0000250438.04393.a8

12. van Dalen T, Hennipman A, Van Coevorden F, Hoekstra HJ, van Geel BN, Slootweg P, et al. Evaluation of a clinically applicable post-surgical classification system for primary retroperitoneal soft-tissue sarcoma. *Ann Surg Oncol* 2004; **11:** 483-90. doi: 10.1245/aso.2004.09.005

13. Andritsch E, Beishon M, Bielack S, Bonvalot S, Casali P, Crul M, et al. ECCO Essential Requirements for Quality Cancer Care: soft tissue sarcoma in adults and bone sarcoma. A critical review. *Crit Rev Oncol Hematol* 2017; **110:** 94-105. doi: 10.1016/j.critrevonc.2016.12.002

14. Novak M, Perhavec A, Povšič M, Arnuš M, Eržen D. Primary localized retroperitoneal sarcomas: report from Slovenian sarcoma referral center. *World J Surg Oncol* 2020; **18:** 277. doi: 10.1186/s12957-020-02038-9

15. Balderas-Pena LM, Gonzalez-Barba F, Martinez-Herrera BE, Palomares-Chacon UR, Duran-Anguiano O, Salazar-Paramo M, et al. Body composition and biochemical parameters of nutritional status: correlation with health-related quality of life in patients with colorectal cancer. *Nutrients* 2020; **12:** 2110. doi: 10.3390/nu12072110

16. Arends J, Baracos V, Bertz H, Bozzetti F, Calder PC, Deutz NEP, et al. ESPEN expert group recommendations for action against cancer-related malnutrition. *Clin Nutri* 2017; 36: 1187-96. doi: 10.1016/j.clnu.2017.06.017

17. Kirov KM, Xu HP, Crenn P, Goater P, Tzanis D, Bouhadiba MT, et al. Role of nutritional status in the early postoperative prognosis of patients operated for retroperitoneal liposarcoma (RLS): a single center experience. *Eur J Surg Oncol* 2019; **45:** 261-7. doi: 10.1016/j.ejso.2018.07.001

18. Previtali P, Fiore M, Colombo J, Arendar I, Fumagalli L, Pizzocri M, et al. Malnutrition and perioperative nutritional support in retroperitoneal sarcoma patients: results from a prospective study. *Ann Surg Oncol* 2020; **27:** 2025-32. doi: 10.1245/s10434-019-08121-0

19. Nipp RD, Fuchs G, El-Jawahri A, Mario J, Troschel FM, Greer JA, et al. Sarcopenia is associated with quality of life and depression in patients with advanced cancer. *Oncologist* 2018; **23:** 97-104. doi: 10.1634/theoncologist.2017-0255

20. Chen LK, Lee WJ, Peng LN, Liu LK, Arai H, Akishita M. Recent advances in sarcopenia research in Asia: 2016 update from the Asian Working Group for Sarcopenia. *J Am Med Dir Assoc* 2016; **17:** 767.e1-7. doi: 10.1016/j.jamda.2016.05.016

21. Czigany Z, Kramp W, Bednarsch J, van der Kroft G, Boecker J, Strnad P, et al. Myosteatosis to predict inferior perioperative outcome in patients undergoing orthotopic liver transplantation. *Am J Transplant* 2020; **20:** 493-503. doi: 10.1111/ajt.15577

22. Aro R, Mäkäräinen-Uhlbäck E, Ämmälä N, Rautio T, Ohtonen P, Saarnio J, et al. The impact of sarcopenia and myosteatosis on postoperative outcomes and 5-year survival in curatively operated colorectal cancer patients – a retrospective register study. *Eur J Surg Oncol* 2020; **46:** 1656-62. doi: 10.1016/j.ejso.2020.03.206

23. Rier HN, Jager A, Sleijfer S, Maier AB, Levin MD. The prevalence and prognostic value of low muscle mass in cancer patients: a review of the literature. *Oncologist* 2016; **21:** 1396-409. doi: 10.1634/theoncologist.2016-0066

24. Deng CY, Lin YC, Wu JS, Cheung YC, Fan CW, Yeh KY, et al. Progressive sarcopenia in patients with colorectal cancer predicts survival. *AJR Am J Roentgenol* 2018; **210**: 526-32. doi: 10.2214/ajr.17.18020

25. Jung AR, Roh JL, Kim JS, Kim SB, Choi SH, Nam SY, et al. Prognostic value of body composition on recurrence and survival of advanced-stage head and neck cancer. *Eur J Cancer* 2019; **116:** 98-106. doi: 10.1016/j.ejca.2019.05.006

26. Prado CM, Lieffers JR, McCargar LJ, Reiman T, Sawyer MB, Martin L, 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:** 629-35. doi: 10.1016/S1470-2045(08)70153-0

27. Strassmann D, Hensen B, Grünwald V, Stange K, Eggers H, Länger F, et al. Impact of sarcopenia in advanced and metastatic soft tissue sarcoma. *Int J Clin Oncol* 2021; **26:** 2151-60. doi: 10.1007/s10147-021-01997-7

28. Bays H. Central obesity as a clinical marker of adiposopathy; increased visceral adiposity as a surrogate marker for global fat dysfunction. *Curr Opin Endocrinol Diabetes Obes* 2014; **21:** 345-51. doi: 10.1097/med.0000000000000093

29. Boyle EA, Elliott JA, McIntyre TV, Barnes ME, Donlon NE, Umair M, et al. Body composition is associated with operative and oncologic outcomes in the management of retroperitoneal and trunk soft tissue sarcoma. *Am J Surg* 2022; **223:** 729-37. doi: 10.1016/j.amjsurg.2021.08.005

30. O'Sullivan J, Lysaght J, Donohoe CL, Reynolds JV. Obesity and gastrointestinal cancer: the interrelationship of adipose and tumour microenvironments. *Nat Rev Gastroenterol Hepatol* 2018; **15:** 699-714. doi: 10.1038/s41575-018-0069-7

31. Shirazipour CH, Freedland SJ. Obesity, visceral adiposity, and prostate cancer: what is the role of lifestyle interventions? *Cancer* 2019; **125:** 2730-1. doi: 10.1002/cncr.32165

32. Baastrup NN, Christensen JK, Jensen KK, Jørgensen LN. Visceral obesity and short-term outcomes after laparoscopic rectal cancer resection. *Surg Endosc* 2020; **34:** 177-85. doi: 10.1007/s00464-019-06748-4

33. Silveira EA, Kliemann N, Noll M, Sarrafzadegan N, de Oliveira C. Visceral obesity and incident cancer and cardiovascular disease: an integrative review of the epidemiological evidence. *Obes Rev* 2021; **22:** e13088. doi: 10.1111/obr.13088

34. Hamaguchi Y, Kaido T, Okumura S, Kobayashi A, Shirai H, Yagi S, et al. Impact of skeletal muscle mass index, intramuscular adipose zissue content, and visceral to subcutaneous adipose tissue area ratio on early mortality of living donor liver transplantation. *Transplantation* 2017; **101:** 565-74. doi: 10.1097/tp.0000000000001587

35. Okamura A, Watanabe M, Mine S, Nishida K, Imamura Y, Kurogochi T, et al. Clinical impact of abdominal fat distribution on prognosis after esophagectomy for esophageal squamous cell carcinoma. *Ann Surg Oncol* 2016; **23:** 1387-94. doi: 10.1245/s10434-015-5018-x

36. Hamaguchi Y, Kaido T, Okumura S, Kobayashi A, Shirai H, Yao S, et al. Preoperative visceral adiposity and muscularity predict poor outcomes after hepatectomy for hepatocellular carcinoma. *Liver Cancer* 2019; **8:** 92-109. doi: 10.1159/000488779

37. Grignol VP, Smith AD, Shlapak D, Zhang X, Del Campo SM, Carson WE. Increased visceral to subcutaneous fat ratio is associated with decreased overall survival in patients with metastatic melanoma receiving anti-angiogenic therapy. *Surg Oncol* 2015; **24:** 353-8. doi: 10.1016/j.suronc.2015.09.002

38. Baracos VE, Arribas L. Sarcopenic obesity: hidden muscle wasting and its impact for survival and complications of cancer therapy. *Ann Oncol* 2018; **29:** ii1-9. doi: 10.1093/annonc/mdx810

39. Donini LM, Busetto L, Bischoff SC, Cederholm T, Ballesteros-Pomar MD, Batsis JA, et al. Definition and diagnostic criteria for sarcopenic obesity: ESPEN and EASO consensus statement. *Clin Nutr* 2022; **41:** 990-1000. doi: 10.1016/j.clnu.2021.11.014

40. Vehmas T, Kairemo KJ, Taavitsainen MJ. Measuring visceral adipose tissue content from contrast enhanced computed tomography. *Int J Obes Relat Metab Disord* 1996; **20:** 570-3. PMID: 8782734

41. Mitsiopoulos N, Baumgartner RN, Heymsfield SB, Lyons W, Gallagher D, Ross R. Cadaver validation of skeletal muscle measurement by magnetic resonance imaging and computerized tomography. *J Appl Physiol* 1998; **85:** 115-22. doi: 10.1152/jappl.1998.85.1.115

42. Maurovich-Horvat P, Massaro J, Fox CS, Moselewski F, O'Donnell CJ, Hoffmann U. Comparison of anthropometric, area- and volume-based assessment of abdominal subcutaneous and visceral adipose tissue volumes using multi-detector computed tomography. *Int J Obes* 2007; **31:** 500-6. doi: 10.1038/sj.ijo.0803454

43. Mourtzakis M, Prado CM, Lieffers JR, Reiman T, McCargar LJ, Baracos VE. 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. doi: 10.1139/H08-075

44. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg* 2004**; 240:** 205-13. doi: 10.1097/01.sla.0000133083.54934.ae

45. Trojani M, Contesso G, Coindre JM, Rouesse J, Bui NB, de Mascarel A, et al. Soft-tissue sarcomas of adults; study of pathological prognostic variables and definition of a histopathological grading system. *Int J Cancer* 1984; **33:** 37-42. doi: 10.1002/ijc.2910330108

46. Popuri K, Cobzas D, Esfandiari N, Baracos V, Jägersand M. Body composition assessment in axial CT images using FEM-based automatic segmentation of skeletal muscle. *IEEE Trans Med Imaging* 2016; **35:** 512-20. doi: 10.1109/tmi.2015.2479252

47. Doyle SL, Bennett AM, Donohoe CL, Mongan AM, Howard JM, Lithander FE, et al. Establishing computed tomography – defined visceral fat area thresholds for use in obesity – related cancer research. *Nutr Res* 2013; **33:** 171-9. doi: 10.1016/j.nutres.2012.12.007

48. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. *Age Ageing* 2019; **48:** 601. doi: 10.1093/ageing/afz046

49. Fearon K, Strasser F, Anker SD, Bosaeus I, Bruera E, Fainsinger RL, et al. Definition and classification of cancer cachexia: an international consensus. *Lancet Oncol* 2011; **12:** 489-95. doi: 10.1016/s1470-2045(10)70218-7

50. Contal C, O'Quigley J. An application of changepoint methods in studying the effect of age on survival in breast cancer. *Comput Stat Data Anal* 1999; **30:** 253-70. doi: 10.1016/S0167-9473(98)00096-6

51. Caan BJ, Meyerhardt JA, Kroenke CH, Alexeeff S, Xiao J, Weltzien E, et al. Explaining the obesity paradox: the association between body composition and colorectal cancer survival (C-SCANS Study). *Cancer Epidemiol Biomarkers Prev* 2017; **26:** 1008-15. doi: 10.1158/1055-9965.Epi-17-0200

52. Hassen W, Kassambara A, Reme T, Sahota S, Seckinger A, Vincent L, et al. Drug metabolism and clearance system in tumor cells of patients with multiple myeloma. *Oncotarget* 2015; **6:** 6431-47. doi: 10.18632/oncotarget.3237

53. Kassambara A, Gourzones-Dmitriev C, Sahota S, Reme T, Moreaux J, Goldschmidt H, et al. A DNA repair pathway score predicts survival in human multiple myeloma: the potential for therapeutic strategy. *Oncotarget* 2014; **5:** 2487-98. doi: 10.18632/oncotarget.1740

54. He WZ, Jiang C, Liu LL, Yin CX, Rong YM, Hu WM, et al. Association of body composition with survival and inflammatory responses in patients with non-metastatic nasopharyngeal cancer. *Oral Oncology* 2020; **108:** 104771. doi: 10.1016/j.oraloncology.2020.104771

55. Caan BJ, Feliciano EMC, Prado CM, Alexeeff S, Kroenke CH, Bradshaw P, et al. Association of muscle and adiposity measured by computed tomography with survival in patients with nonmetastatic breast cancer. *JAMA Oncol* 2018; **4:** 798-804. doi: 10.1001/jamaoncol.2018.0137

56. Lausen B, Schumacher M. Maximally selected rank statistics. *Biometrics* 1992; 48: 73-85. doi: 10.2307/2532740

57. Cederholm T, Barazzoni R, Austin P, Ballmer P, Biolo G, Bischoff SC, et al. ESPEN guidelines on definitions and terminology of clinical nutrition. *Clin Nutr* 2017; **36:** 49-64. doi: 10.1016/j.clnu.2016.09.004

58. Fujiwara N, Nakagawa H, Kudo Y, Tateishi R, Taguri M, Watadani T, et al. Sarcopenia, intramuscular fat deposition, and visceral adiposity independently predict the outcomes of hepatocellular carcinoma. *J Hepatol* 2015; **63:** 131-40. doi: 10.1016/j.jhep.2015.02.031

59. McSorley ST, Black DH, Horgan PG, McMillan DC. The relationship between tumour stage, systemic inflammation, body composition and survival in patients with colorectal cancer. *Clin Nutr* 2018; **37:** 1279-85. doi: 10.1016/j.clnu.2017.05.017

60. Martin L, Birdsell L, MacDonald N, Reiman T, Clandinin MT, McCargar LJ, 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:** 1539-47. doi: 10.1200/jco.2012.45.2722

61. Srpcic M, Jordan T, Popuri K, Sok M. Sarcopenia and myosteatosis at presentation adversely affect survival after esophagectomy for esophageal cancer. *Radiol Oncol* 2020; **54:** 237-46. doi: 10.2478/raon-2020-0016

62. Aleixo GFP, Shachar SS, Nyrop KA, Muss HB, Malpica L, Williams GR. Myosteatosis and prognosis in cancer: systematic review and meta-analysis. *Crit Rev Oncol Hematol* 2020; **145:** 102839. doi: 10.1016/j.critrevonc.2019.102839

63. Prentice AM, Jebb SA. Beyond body mass index. *Obes Rev* 2001; **2:** 141-7. doi: 10.1046/j.1467-789x.2001.00031.x

64. Kobayashi A, Kaido T, Hamaguchi Y, Okumura S, Shirai H, Kamo N, et al. Impact of visceral adiposity as well as sarcopenic factors on outcomes in patients undergoing liver resection for colorectal liver metastases. *World J Surg* 2018; **42:** 1180-91. doi: 10.1007/s00268-017-4255-5

65. Rickles AS, Iannuzzi JC, Mironov O, Deeb AP, Sharma A, Fleming FJ, et al. Visceral obesity and colorectal cancer: are we missing the boat with BMI? *J Gastrointest Surg* 2013; **17:** 133-43; discussion p.43. doi: 10.1007/s11605-012-2045-9

66. Smith AD, Gray MR, del Campo SM, Shlapak D, Ganeshan B, Zhang X, et al. Predicting overall survival in patients with metastatic melanoma on antiangiogenic therapy and RECIST stable disease on initial posttherapy images using CT texture analysis. *AJR Am J Roentgenol* 2015; **205:** W283-93. doi: 10.2214/ajr.15.14315

67. Okumura S, Kaido T, Hamaguchi Y, Fujimoto Y, Masui T, Mizumoto M, et al. Impact of preoperative quality as well as quantity of skeletal muscle on survival after resection of pancreatic cancer. *Surgery* 2015; **157:** 1088-98. doi: 10.1016/j.surg.2015.02.002

68. He AQ, Li CQ, Zhang Q, Liu T, Liu J, Liu G. Visceral-to-subcutaneous fat ratio is a potential predictor of postoperative complications in colorectal cancer. *Med Sci Monit* 2021; **27:** e930329. doi: 10.12659/msm.930329

69. Tran TT, Yamamoto Y, Gesta S, Kahn CR. Beneficial effects of subcutaneous fat transplantation on metabolism. *Cell Metab* 2008; **7:** 410-20. doi: 10.1016/j.cmet.2008.04.004

70. Ebadi M, Martin L, Ghosh S, Field CJ, Lehner R, Baracos VE, et al. Subcutaneous adiposity is an independent predictor of mortality in cancer patients. *Br J Cancer* 2017; **117:** 148-55. doi: 10.1038/bjc.2017.149

71. Ebadi M, Baracos VE, Bathe OF, Robinson LE, Mazurak VC. Loss of visceral adipose tissue precedes subcutaneous adipose tissue and associates with n-6 fatty acid content. *Clin Nutr* 2016; **35:** 1347-53. doi: 10.1016/j.clnu.2016.02.014

72. Di Prata C, Renouf B, Tzanis D, Bouhadiba T, Watson S, Zein SE, et al. Significant predictors of postoperative morbidity after radical resection of retroperitoneal sarcoma in a tertiary center. *Ann Surg Oncol* 2023; **30:** 4515-26. doi: 10.1245/s10434-023-13459-7

73. Nasirishargh A, Grova M, Bateni CP, Judge SJ, Nuno MA, Basmaci UN, et al. Sarcopenia and frailty as predictors of surgical morbidity and oncologic outcomes in retroperitoneal sarcoma. *J Surg Oncol* 2023; **127:** 855-61. doi: 10.1002/jso.27199

74. Choi ES, Kim HS, Han I. Elevated preoperative systemic inflammatory markers predict poor outcome in localized soft tissue sarcoma. *Ann Surg Oncol* 2014; **21:** 778-85. doi: 10.1245/s10434-013-3418-3

75. Fiore M, Ljevar S, Pasquali S, Morelli D, Callegaro D, Sanfilippo R, et al. Preoperative neutrophil-to-lymphocyte ratio and a new inflammatory biomarkers prognostic index for primary retroperitoneal sarcomas: retrospective monocentric study. *Clin Cancer Res* 2023; **29:** 614-20. doi: 10.1158/1078-0432.CCR-22-2897

76. Schwartz PB, Poultsides G, Roggin K, Howard JH, Fields RC, Clarke CN, et al. PLR and NLR are poor predictors of survival outcomes in sarcomas: a new perspective from the USSC. *J Surg Res* 2020; **251:** 228-38. doi: 10.1016/j.jss.2020.01.008

77. Netanyahu Y, Gerstenhaber F, Shamai S, Sher O, Merimsky O, Klausner JM, et al. Innate inflammatory markers for predicting survival in retroperitoneal sarcoma. *J Surg Oncol* 2020; **122:** 1655-61. doi: 10.1002/jso.26178

78. Swallow CJ, Strauss DC, Bonvalot S, Rutkowski P, Desai A, Gladdy RA, et al. Management of primary retroperitoneal sarcoma (RPS) in the adult: an updated consensus approach from the transatlantic australasian RPS Working Group. *Ann Surg Oncol* 2021; **28:** 7873-88. doi: 10.1245/s10434-021-09654-z

79. Fearon KC, Luff R. The nutritional management of surgical patients: enhanced recovery after surgery. *Proc Nutr Soc* 2003; **62:** 807-11. doi: 10.1079/PNS2003299