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Visceral fat percentage for prediction of outcome in uterine cervical cancer

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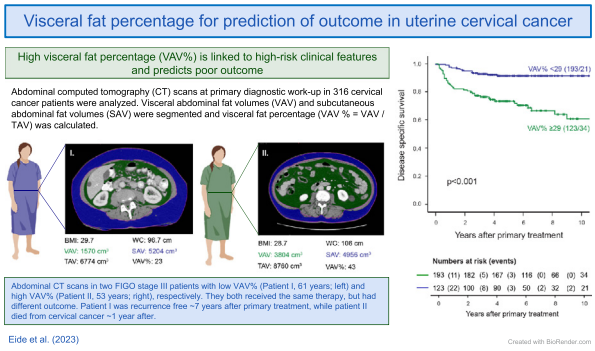
HIGHLIGHTS

- Visceral fat predominance is associated with poor survival in cervical cancer.
- Visceral fat percentage ≥ 29 is linked to large tumor size and high-grade histology.
- Tumors arising in visceral adiposity exhibit increased inflammatory signaling.
- Assessing abdominal fat compartments by CT is both feasible and reliable.

GRAPHICAL ABSTRACT



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ABSTRACT

Objective. The prognostic role of adiposity in uterine cervical cancer (CC) is largely unknown. Abdominal fat distribution may better reflect obesity than body mass index. This study aims to describe computed tomography (CT)-assessed abdominal fat distribution in relation to clinicopathologic characteristics, survival, and tumor gene expression in CC.

Methods. The study included 316 CC patients diagnosed during 2004–2017 who had pre-treatment abdominal CT. CT-based 3D segmentation of total-, subcutaneous- and visceral abdominal fat volumes (TAV, SAV and VAV) allowed for calculation of visceral fat percentage (VAV% = VAV/TAV). Liver density (LD) and waist circumference (at L3/L4-level) were also measured. Associations between CT-derived adiposity markers, clinicopathologic characteristics and disease-specific survival (DSS) were explored. Gene set enrichment of primary tumors were examined in relation to fat distribution in a subset of 108 CC patients.

Results. High TAV, VAV and VAV% and low LD were associated with higher age (≥44 yrs.; $p \leq 0.017$) and high International Federation of Gynecology and Obstetrics (FIGO) (2018) stage ($p \leq 0.01$). High VAV% was the only CT-marker predicting high-grade histology ($p = 0.028$), large tumor size ($p = 0.016$) and poor DSS (HR 1.07, $p < 0.001$). Patients with high VAV% had CC tumors that exhibited increased inflammatory signaling (false discovery rate [FDR] < 5%).

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Conclusions. High VAV% is associated with high-risk clinical features and predicts reduced DSS in CC patients. Furthermore, patients with high VAV% had upregulated inflammatory tumor signaling, suggesting that the metabolic environment induced by visceral adiposity contributes to tumor progression in CC.

1. Introduction

Uterine cervical cancer is the most common gynecologic malignancy and the fourth leading cause of cancer-related death in women worldwide [1]. While patients with early-stage disease generally have excellent prognosis, patients with locally advanced, metastatic or recurrent disease have poor long-time survival [2]. Prognostic factors for locally advanced cervical cancers include histological subtype, grade, age and lymph node involvement [2]. Obesity has been reported as a prognostic factor in several cancers [2,3], but for cervical cancer, reports on the prognostic role of obesity are inconsistent. Abdominal fat distribution may better reflect obesity than the more commonly used body mass index (BMI), as visceral and subcutaneous adipose tissue have different structural and physiological properties [4,5]. Compared to subcutaneous adipose tissue, visceral adipose tissue is more cellular and vascular, contains more inflammatory cells, and has increased endocrine- and metabolic activity; all factors known to contribute to chronic low-grade systemic inflammation [6–8].

Image processing software enables quantification of the different abdominal fat compartments from abdominal computed tomography (CT) scans, yielding morphometric adiposity markers [9]. Since 2018, imaging findings have been incorporated in the International Federation of Gynecology and Obstetrics (FIGO) CC staging system [10]. Pelvic-, abdominal- and thoracic CT is often performed at primary diagnostic work-up to detect lymph node metastases or distant spread prior to treatment planning [11]. Assessing the abdominal fat compartments by CT is both feasible and reliable [9,12]. Furthermore, liver attenuation can be measured by CT, allowing the assessment of hepatic steatosis, which is known to be linked to obesity [3]. Different fat distribution patterns may reflect unique metabolic environments relevant for disease development. Visceral adiposity has been associated with metabolic syndrome and cardiovascular disease [4,7] and with reduced cancer survival in malignant melanomas [13], endometrial- [12,14], colorectal- [15] and postmenopausal breast cancers [16]. For cervical cancer, the prognostic role of abdominal fat distribution is largely unknown.

In this study, we report on CT-assessed abdominal fat distribution in a large patient series and explore associations between fat distribution markers and clinicopathologic patient characteristics and survival in cervical cancer. We further investigate whether abdominal fat distribution patterns are linked to specific alterations in signaling pathways of the primary tumors.

2. Materials and methods

2.1. Patient series

From a prospective series of all consenting patients (606 women) diagnosed with uterine cervical cancer during 2004–2017 at Haukeland University Hospital, Bergen, Norway, all patients that had an abdominal CT at primary diagnostic work-up available in our picture archiving and communication system (PACS), were included in this study ($n = 316$). All patients signed a written informed consent, and the study was approved by the regional ethical committee (REK 2015/2333, REK2018/591 and REK 2014/1907).

All patients were clinically staged according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 guidelines and later restaged according to the FIGO 2018 staging criteria [10]. Clinicopathologic- and follow-up data were collected based on review of medical records (last accessed in March 2021). Median (range) follow-up time was 7.1 (3.7–17.6) years after primary treatment. Histologic type and tumor grade were assessed by an expert pathologist, following standard procedures [17]. For fresh frozen tumor biopsies, an expert pathologist evaluated tumor cellularity on hematoxylin and eosin-stained sections. Biopsies were included if tumor content was >50% and preferably above 80%. RNA was extracted from the fresh frozen tissue using AllPrep DNA/RNA Mini Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. Quality and yield was assessed as previously described [18].

2.2. Image analysis

All included patients had undergone pre-treatment abdominal contrast-enhanced CT ($n = 315$) or non-contrast enhanced CT ($n = 1$), as part of the routine primary diagnostic work-up. A semi-automated algorithm for 3D segmentation and quantification of fat volumes (Aquarius iNtuition, TeraRecon Inc., San Mateo, CA, USA) was used to quantify the abdominal fat compartments based on CT density thresholds. Cross-sectional images were segmented for adipose tissue from the level of upper right diaphragm to the level of vertebra L5/S1. Calculation of fat compartments was based on an automated segmentation of pixels with densities within the range of −195 to −45 Hounsfield units (HU), representing adipose tissue [9]. Segmentations were manually verified, and if needed, manually adjusted to ensure correct segmentation. The observer was blinded to patient outcome and clinicopathologic characteristics when verifying the segmentations. A second reader performed independent segmentations on 20 representative cases, demonstrating excellent inter-reader reproducibility for the abdominal fat volume measurements with Intraclass Correlation Coefficients (ICC) of 0.996–0.999 ($p < 0.001$ for all) (Supplementary Table 1). The time consume for performing the segmentations was ~5 min per case. Total abdominal fat volume (TAV, cm^3), subcutaneous abdominal fat volume (SAV, cm^3) and visceral abdominal fat volume (VAV, cm^3) were quantified, and visceral fat percentage of the total fat volume (VAV% = VAV/TAV) was calculated (Fig. 1A). Waist circumference (cm) was measured at the level of L3/L4. Liver parenchymal density (HU) was measured in three manually drawn circular regions of interest (ROI) (diameters of 15 mm), and the mean value was used for further analyses. When drawing the ROI, care was taken to avoid inclusion of visually distinct vessels, biliary ducts, or focal liver lesions.

2.3. Gene expression analyses

mRNA expression profiles were generated using L1000 data [19] for a subset of 108 CC patients. L1000 expression values were calculated using an algorithm that extrapolates the expression of 978 landmark genes (directly measured by ligation-mediated amplification and fluorescent labelling) to obtain transcriptional profiles of 12,328 genes [19]. Replicate-collapsed z-scores (level-5 data) were utilized for subsequent L1000 analyses. Gene set enrichment analysis (GSEA) was performed in the JExpress software (www.molmine.com) [20] with Golub scoring method (signal-to-noise) and 1000 permutations on genes. Gene set collections C2, C5 and Hallmarks of the Molecular Signature database v4.0 (MSigDB, Broad Institute, USA) were queried for

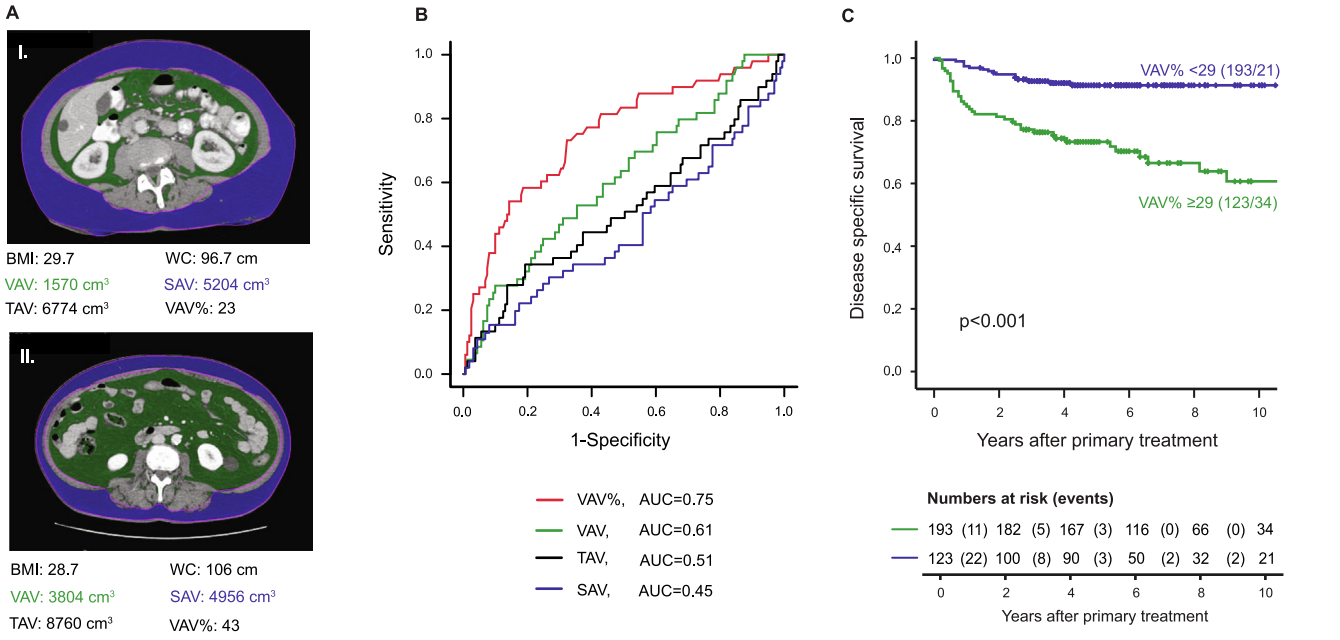

Fig. 1. The effect of abdominal fat distribution patterns on disease-specific survival in $n = 316$ cervical cancer patients.
(A) Abdominal computed tomography (CT) scans with segmentation of visceral and subcutaneous fat compartments in two different patients both diagnosed with squamous cell carcinoma, International Federation of Gynecology and Obstetrics (FIGO) (2018) stage IIIC1. Patient I, aged 61 yrs. who had low VAV% (23%) received primary radiation therapy and subsequent chemotherapy with cisplatin. She had no signs of recurrence 6.6 years after primary treatment. Patient II, aged 53 yrs. who had high VAV% (43%) received primary radiation therapy and subsequent chemotherapy with cisplatin. She developed pelvic metastases and died from cervical cancer 14 months after primary treatment.
(B) Time-dependent receiver operating characteristic (tdROC) curves for predicting disease-specific survival (DSS) at 5 years after diagnosis based on visceral abdominal fat percentage (VAV%), visceral abdominal fat volume (VAV), total abdominal fat volume (TAV) and subcutaneous abdominal fat volume (SAV). VAV% yielded significantly higher AUC (0.75) than the other morphometric markers ($p < 0.001$ for all).
(C) Kaplan-Meier plot depicting significantly reduced DSS in patients with VAV% ≥ 29 compared with patients with VAV % < 29 ($p < 0.001$).

enriched gene sets [21]. A false discovery rate (FDR) <5% was considered significant when defining differentially expressed gene sets between patient groups.

2.4. Statistical analyses

For statistical analyses of imaging markers and clinical data, SPSS version 26 (SPSS Inc., Chicago, IL, USA) and R software (version 4.0.3, R Foundation for Statistical Computing, Vienna, Austria) were used. Correlations and associations were assessed using Spearman's rank correlation (ρ = rho), Mann-Whitney *U* test, Kruskal-Wallis test and Jonckheere-Terpstra trend test. To compare the diagnostic performance of the CT-markers for predicting disease-specific survival (DSS) at 5 years after primary diagnosis, time-dependent receiver operating characteristic (tdROC) analyses were used. *P*-values involving multiple comparisons of area under the tdROC curves (AUCs) were adjusted using Holm-Bonferroni corrections. Optimal cut-off for VAV% (<29% and ≥ 29%) was identified from the tdROC curve using the Youden index. Kaplan-Meier plot and Mantel-Cox log-rank test were used to compare DSS for different patient subgroups. Cox Proportional Hazards Regression analysis stratified for FIGO stages I-IV was used to assess DSS in relation to obesity markers and patient age. To account for a possible interaction between VAV% and age, an interaction term was incorporated in the multivariable Cox model, but no statistical interaction was found ($p = 0.88$). All *p*-values were two-sided and considered statistically significant if $p < 0.05$.

3. Results

3.1. Clinicopathologic patient characteristics

Clinicopathologic patient characteristics of the study cohort ($n = 316$) were similar to that of the entire CC cohort ($n = 606$) treated at the same university hospital during 2004–2017 (Supplementary Table 2). Median (IQR) patient age in the study cohort was 44 (35–54) years, 69% (217/316) of the women were pre- or perimenopausal, and 10% (31/316) had BMI < 20 at primary diagnosis (Table 1). In total, 63% (200/316) of patients were FIGO (2018) stage I, 11% (35/316) FIGO II, 20% (62/316) FIGO III and 6% (19/316) FIGO IV. Primary treatment consisted of surgery alone in 51% (162/316), surgery with adjuvant treatment in 12% (37/316), primary radiotherapy with or without chemotherapy in 35% (112/316) and palliative treatment/only chemotherapy in 2% (5/316).

3.2. CT derived fat volumes are positively correlated with BMI and VAV% increases with age

Visceral abdominal fat volume (VAV), subcutaneous abdominal fat volume (SAV), total abdominal fat volume (TAV) and waist circumference were strongly positively correlated with BMI ($\rho = 0.77$–0.91, $p < 0.001$), and with each other ($\rho = 0.79$–0.97, $p < 0.001$, Table 2). BMI was moderately positively correlated with VAV% ($\rho = 0.17$, $p < 0.001$). VAV% was strongly positively correlated with age ($\rho = 0.68$, $p < 0.001$), while BMI only moderately correlated with age ($\rho = 0.16$, $p < 0.001$). Liver density was moderately negatively correlated with BMI, age, and all the CT morphometric obesity markers ($\rho = -0.17$ to -0.43, $p < 0.001$ for all).

3.3. High VAV% is associated with high-risk clinicopathologic features and poor outcome

When comparing CT-assessed fat distribution markers in relation to clinical features, patients ≥44 years had significantly higher intraabdominal fat volumes ($p \leq 0.02$), VAV% ($p < 0.001$), BMI ($p = 0.01$), and lower liver density ($p = 0.017$) than patients <44 years (Table 3). Patients with advanced FIGO stage had significantly higher VAV

Table 1
Clinicopathologic patient characteristics of the cervical cancer study cohort ($n = 316$).

	n (%)
Age at primary treatment (yrs.)	
Median (IQR) [range]	44 (35–54) [23–95]
BMI (kg/m^2) ($n = 315$)	
Median (IQR) [range]	25 (22–27) [15–52]
Menopausal status ($n = 310$)	
Pre/perimenopausal	217 (69)
Postmenopausal	98 (31)
FIGO stage (2018)	
Stage I	200 (63)
Stage II	35 (11)
Stage III	62 (20)
Stage IV	19 (6)
Primary treatment	
Surgery only[1]	162 (51)
Surgery with adjuvant treatment[2]	37 (12)
Radiotherapy with or without chemotherapy	112 (35)
Palliation or chemotherapy only	5 (2)
Histological subtype	
Squamous cell carcinoma	228 (72)
Adenocarcinoma	68 (22)
Other[3]	20 (6)
Histologic grade ($n = 264$)	
Low/medium	188 (71)
High	76 (29)
Clinical tumor size ($n = 165$)	
<2 cm	30 (18)
2–4 cm	82 (50)
>4 cm	53 (32)

Abbreviations: BMI: Body mass index; FIGO: International Federation of Gynecology and Obstetrics; IQR: Interquartile range; n: number of patients in each category; SD: Standard deviation.
[1] Surgery; conization = 29 patients; hysterectomy without BSO = 101 patients; hysterectomy with BSO = 32 patients.
[2] Adjuvant treatment: chemoradiation combined, chemotherapy only or radiotherapy only.
[3] Other: Neuroendocrine tumor = 7 patients; Undifferentiated carcinoma = 7 patients; Adenosquamous carcinoma = 2 patients.

($p < 0.001$), TAV ($p = 0.02$), VAV% ($p < 0.001$) and lower liver density ($p < 0.001$). High VAV% was the only fat distribution marker associated with high-grade histology ($p = 0.028$) and large clinical tumor size ($p = 0.016$).

Among the fat distribution markers, VAV% yielded highest area under the ROC curve (AUC = 0.75) for predicting 5-year DSS (Fig. 1B). The AUC for VAV% (AUC = 0.75) was significantly higher than that of VAV (AUC = 0.61), TAV (AUC = 0.51), SAV (AUC = 0.45), waist circumference (AUC = 0.51) and liver density (AUC = 0.46) ($p < 0.001$ for all). Optimal cut-off (based on Youden index) for VAV% for prognostication was </≥29. Patients with VAV% ≥29 ($n = 123$) had significantly reduced DSS compared to patients with VAV% < 29 ($n = 193$) (Fig. 1C; $p < 0.001$). Patients with BMI < 20 ($n = 31$) and patients with BMI > 20 ($n = 284$) had similar DSS ($p = 0.13$). The prognostic role of VAV% was further confirmed in a univariable Cox-regression model stratified for FIGO 2018 stages I-IV, where only VAV% (hazard ratio (HR): 1.07, $p < 0.001$) and age (HR: 1.04, $p < 0.001$) predicted DSS (Table 4). In the multivariable Cox-regression model stratified for FIGO stage including age and VAV%, only high VAV% remained a significant independent predictor of poor survival (HR: 1.04, $p = 0.03$).

3.4. Gene sets related to chronic systemic inflammation are enriched in tumors from patients with high VAV%

To evaluate if transcriptional signatures differed between tumors from patients with high and low VAV%, gene set enrichment analysis (GSEA) was performed using gene expression data generated from patient tumors. For tumors from patients with VAV% ≥29% ($n = 52$), 60% (12/20) of the top ranked ontology (C5) gene sets were related to inflammatory signaling, e.g., interferon (IFN) α- and γ-signaling. For tumors from patients with VAV% <29% ($n = 56$), 60% (12/20) of the top ranked ontology gene sets were related to protein synthesis, and 35% (7/20) of the gene sets to proliferation (Fig. 2).

4. Discussion

This large CT study links CT-derived visceral adiposity markers, i.e., high visceral fat percentage (VAV%) to high-risk clinical features and poor survival in uterine cervical cancer. High VAV% was found to associate with increased immunogenic- and inflammatory response signaling in the primary tumors. These findings suggest a possible relation between the metabolic environment induced by visceral adiposity and tumor progression in cervical cancer.

Several large epidemiological studies have linked obesity, defined as BMI > 30, to increased mortality in several cancers, including postmenopausal breast-, endometrial- and colorectal cancer [3]. In this study, BMI did not predict cervical cancer survival, and high BMI did not associate with high-risk clinical features, except for high age. Previous studies reporting prognostic impact of BMI in cervical cancer survival are conflicting [22–25]. A large retrospective cohort study ($n = 3086$) found that morbid obesity (BMI ≥ 35) was an independent risk factor for mortality in cervical cancer [25]. Another study found that both underweight (BMI < 18.5) and overweight/obese (BMI >25) cervical cancer patients had reduced overall survival [22]. Conversely, two cohort studies (($n = 738$) [24]; ($n = 404$) [23]) reported BMI > 25 to be a favorable prognostic factor in cervical cancer. These contradictory findings are in line with the "obesity paradox", a phenomenon characterized by the ambiguity in the role of obesity in cancer survival [2,26]. Importantly, BMI has clear limitations as a surrogate marker for obesity, as it does not distinguish between fat and muscle mass, nor between subcutaneous and visceral abdominal fat compartments [7,12,14]. More refined obesity markers, reflecting e.g., abdominal fat distribution, may prove to be more biologically relevant for carcinogenesis or tumor progression in specific cancers.

Table 2
Correlations between CT-assessed fat distribution markers, BMI, and age in $n = 316$ cervical cancer patients.

	Mean ± SD (range), unit	VAV	SAV	TAV	VAV%	WC	LD	BMI
Visceral abdominal fat volume (VAV)	1696 ± 1261 (115–7056) cm^3							
Subcutaneous abdominal fat volume (SAV)	4300 ± 2495 (135–19,584), cm^3	0.79						
Total abdominal fat volume (TAV)	5995 ± 3512 (250–24.837) cm^3	0.91	0.97					
Visceral fat percentage (VAV%)	27 ± 9 (7–58), %	0.65	N/S	0.31				
Waist circumference (WC, L3-L4 level)	91 ± 12 (65–138), cm	0.86	0.91	0.94	0.32			
Liver density (LD)	118 ± 24 (49–191), HU	−0.43	−0.34	−0.39	−0.27	−0.42		
Body mass index (BMI)*	25 ± 5 (15–52) kg/m^2	0.77	0.91	0.91	0.17	0.90	−0.40	
Age at primary treatment	46 ± 14 (23–95), years	0.50	N/S	0.27	0.68	0.33	−0.17	0.16

Correlations are significant at $p < 0.01$ level (2-tailed).
N/S: not significant at $p < 0.01$ level.
Abbreviations: BMI: Body mass index; CT: Computed tomography; HU: Hounsfield units; LD: Liver density; SD: Standard deviation; SAV: Subcutaneous abdominal fat volume; TAV: Total abdominal fat volume; VAV: Visceral abdominal fat volume; VAV%: Visceral abdominal fat percentage; WC: Waist circumference.
* BMI data missing for one patient.

Table 3
CT-assessed fat distribution markers and BMI in relation to clinicopathologic factors in n = 316 cervical cancer patients.

		VAV (cm^3)		SAV (cm^3)		TAV (cm^3)		VAV%		WC (cm)		LD (HU)		BMI (kg/m^2)*	
	n (%)	median	p	median	p	median	p	median	p	median	p	median	p	median	p
Age at primary treatment			**<0.001**		**0.02**		**<0.001**		**<0.001**		**<0.001**		**0.017**		**0.01**
<44 years	157 (50)	911		3536		4652		20.9		86.6		122		24.1	
≥44 years	157 (50)	1922		4223		6335		31.2		93.2		113		25.5	
Menopausal status (*n* = 309)			**<0.001**		**<0.001**		**0.001**		**<0.001**		**<0.001**		**0.046**		0.34
Pre−/perimenopausal	211 (68)	1089		3825		5009		22.6		88.6		120		24.6	
Postmenopausal	98 (32)	2213		2987		6802		34.3		94.5		114		25.1	
FIGO stage (2018)			**<0.001**		0.35		**0.02**		**<0.001**		0.06		**<0.001**		0.22
I	200 (63)	1146		3875		5130		23.5		89.9		122		24.6	
II	35 (11)	1824		4037		6622		30.0		92.2		112		25.8	
III	62 (20)	1537		3753		5378		27.6		89.7		115		23.8	
IV	19 (6)	2978		4316		7367		37.3		95.6		107		26.4	
Histological subtype			0.80		0.22		0.40		0.31		0.64		0.09		0.40
Squamous cell carcinoma	228 (72)	1380		3855		5436		26.5		90.2		120		24.8	
Adenocarcinoma	70 (22)	1172		3958		5332		24.6		89.9		115		24.6	
Other	18 (6)	1756		4539		6456		29.2		91.6		103		25.9	
Histologic grade (*n* = 261)			0.31		0.68		0.92		**0.028**		0.99		0.15		0.79
Grade 1 & 2	187 (72)	1328		3912		5438		25.9		90.0		119		24.7	
Grade 3	74 (28)	1540		3677		5460		28.8		89.6		114		24.6	
Clinical tumor size (n = 165)			0.82		0.29		0.49		**0.016**		0.54		0.96		0.27
<2 cm	30 (18)	1747		4381		6278		26.4		91.6		114		25.2	
2–4 cm	82 (50)	1339		3971		5697		24.8		88.8		113		25.0	
>4 cm	53 (32)	1466		3628		5490		31.8		93.9		112		23.9	

Statistical tests: Mann-Whitney U test (for age, menopausal status, and histologic grade), Independent samples Jonckheere-Terpstra test (for FIGO stage and clinical tumor size) and Kruskal-Wallis test (for histological subtype).
Abbreviations: BMI: Body mass index; CT: Computed tomography; FIGO: International Federation of Gynecology and Obstetrics; HU: Hounsfield units; LD: Liver density; p: p-values; SAV: Subcutaneous abdominal fat volume; TAV: Total abdominal fat volume; VAV: Visceral abdominal fat volume; VAV%: Visceral fat percentage; WC: Waist circumference.
* Data missing for one patient.

Quantification of abdominal adipose tissue volumes from CT images provides more accurate measures of adiposity compared to BMI [7,27]. Visceral adipose tissue has been explored in relation to several cancers, but for cervical cancer, the prognostic impact of visceral adiposity is largely unknown. A study including 189 patients with gynecologic malignancies (endometrial- ($n = 54$), ovarian- ($n = 31$) and cervical ($n = 104$) cancer) found no prognostic impact of abdominal adiposity, measured from one single CT image slice at L2/L4 level [28]. However, they reported that cervical cancer patients with high skeletal muscle index had better survival. In our study, we found that visceral adiposity defined by VAV% ≥29 independently predicted poor survival in cervical cancer patients. Furthermore, we found that cervical cancer patients with high VAV%, more often presented with high-risk clinicopathologic features suggesting a likely more aggressive cervical cancer phenotype. Overall, our findings suggest that a body composition with visceral fat predominance, rather than obesity or high BMI in itself, may play a role in cervical cancer tumor progression.

High patient age has been described as a poor prognostic factor in patients with locally advanced cervical cancer [29]. In our study, we found strong positive correlations between VAV, VAV% and age. This is in line with previous studies reporting a physiological redistribution of abdominal fat to the visceral compartment with increasing age [30–32]. High patient age has been described as a poor prognostic factor in patients with locally advanced cervical cancer [29]. In our study, both age above median (≥44 years) and high VAV% predicted reduced disease-specific survival (DSS) in univariable analyses. However, in multivariable analyses (including both age and VAV%), only VAV% had an independent impact on survival. This finding could indicate that the poor prognostic role of high age may be partly due to co-existing visceral adiposity being more common with higher age.

Table 4
Cox's proportional hazard regression model stratified for FIGO (2018) stage, analysis of the effect on disease-specific survival of the CT-assessed fat distribution markers, BMI, and age in n = 316 cervical cancer patients.

	Unadjusted HR (95% CI)	p	Adjusted HR (95% CI)*	p
VAV (L)	1.07 (0.86–1.33)	0.54		
SAV (L)	1.00 (1.00–1.00)	0.17		
TAV (L)	1.00 (1.00–1.00)	0.44		
VAV%	1.07 (1.03–1.09)	**<0.001**	1.04 (1.00–1.08)	**0.03**
WC	0.99 (0.97–1.02)	0.63		
LD (HU)	0.99 (0.98–1.06)	0.29		
Age at primary treatment	1.04 (1.02–1.06)	**<0.001**	1.02 (0.99–1.05)	0.06

Abbreviations: BMI: Body mass index; FIGO: International Federation of Gynecology and Obstetrics; HR: Hazard Ratio; HU: Hounsfield units; LD: Liver density; p: p-values; SAV: Subcutaneous abdominal fat volume; TAV: Total abdominal fat volume; VAV: Visceral abdominal fat volume; VAV%: Visceral fat percentage; WC: Waist circumference.
* Only variables significant in univariable analysis.

Obesity is closely linked to insulin resistance and low-grade chronic inflammation, characterized by activation of inflammatory signaling pathways and abnormal cytokine production [33,34]. Particularly, visceral adipose tissue has increased adipokine production and accumulation of immune cells that produce inflammatory mediators [35–37]. In our study, patients with VAV% ≥29 had tumors with increased inflammatory signaling, such as IFN-α- and -γ signaling. IFN-γ is reported to have a dualistic role, as it may induce both anti- and pro-tumorigenic effects [38–40]. Tumors exposed to high IFN-γ levels have been reported to be less immunogenic and exhibit a phenotype characterized by increased capability of growth and immune escape [38,39]. The present findings that high VAV% predicts high-risk clinical features and associates with increased tumor IFN-γ signaling, suggest a potential association between visceral adiposity and immune escape. However, in contrast to our study, a similar study in endometrial cancer reported an opposite relationship, linking upregulated inflammatory response to low VAV% [12]. This may be an example of the paradoxical tumor protective and -promoting actions of the immune system. The interplay between IFN-γ tumor signaling and visceral adiposity and its relevance for tumor immune escape and -progression, needs to be studied in larger and independent cervical cancer cohorts.

Our study has some limitations. First, the CT-derived obesity markers were acquired from a single timepoint at primary cervical cancer diagnosis. Including previous or subsequent CT scans would allow exploring the importance of the duration of visceral adiposity. However,

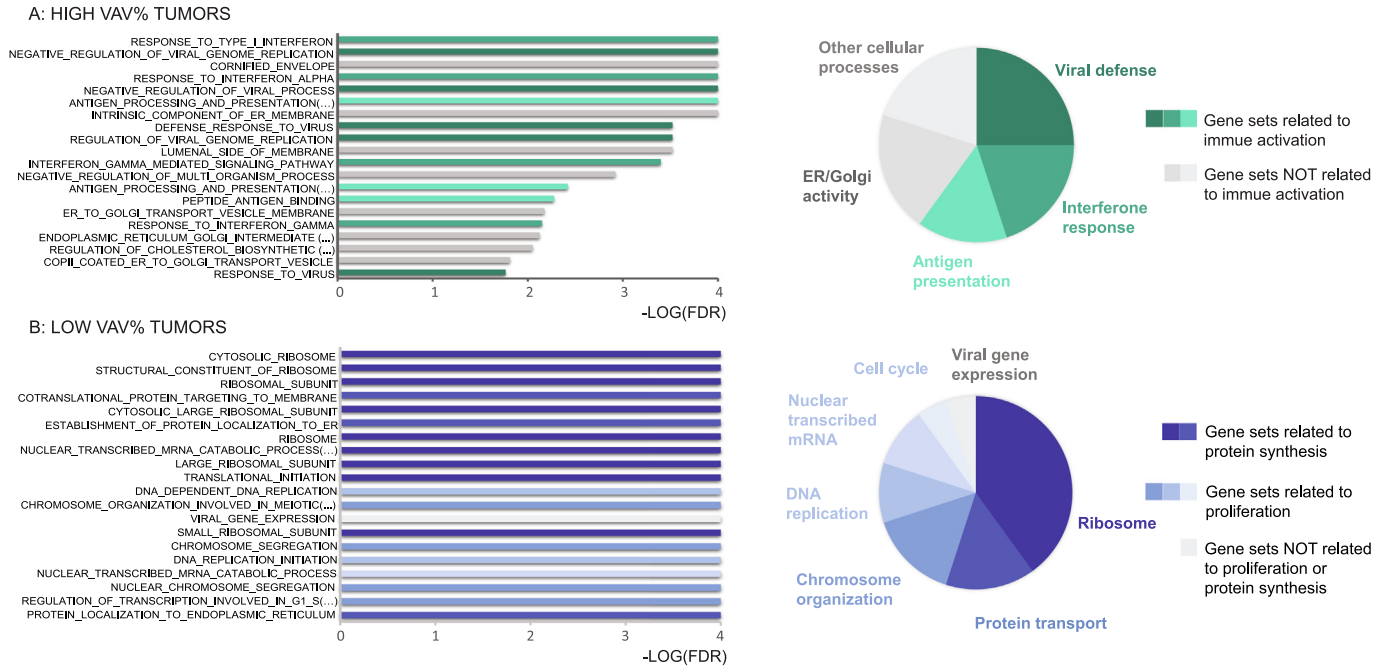

Fig. 2. Tumor gene sets enriched in a subset of $n = 108$ cervical cancer patients with high VAV% and low VAV%.
A: Patients with VAV% ≥29% had tumors with upregulated gene expression within gene sets related to inflammatory signaling and immune response. 60% (12/20) of the top ranked ontology (C5) gene sets were related to interferon signaling, viral and immune response (FDR < 0.05).
B: Patients with VAV% <29% had tumors with upregulated gene expression within gene sets related to protein synthesis and proliferation. 60% (12/20) of the top-rated ontology (C5) gene sets were related to protein synthesis, while 35% (7/20) were related to proliferation (FDR <0.05).

many patients did not have previous or follow-up CT scans or information about BMI history, making exploration of temporal adiposity unfeasible in this cohort. Furthermore, only a subset of patients had tumors available for GSEA, which may have partly biased our results. Finally, the quite homogeneous patient population in this study precludes assessing to what extent CT obesity marker profiles are related to ethnicity or other demographic patient features. Thus, the proposed cut-offs for the CT derived obesity markers for predicting DSS, may not necessarily be generalizable to a different patient population.

In this large patient cohort, we have linked CT-assessed visceral adiposity (i.e., high VAV%) to high-risk clinical features and poor prognosis in cervical cancer. Furthermore, patients with high VAV% have primary tumors exhibiting upregulated inflammatory signaling and immune cell infiltration, suggesting that visceral adiposity may be associated with immune escape and promote tumor progression in cervical cancer. The possible role of CT-derived visceral adiposity markers for prognostication and predicting immune-related targets for treatment, needs to be further studied and validated in independent cervical cancer patient cohorts.

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Authors' contributions

Agnes J. Eide: Conceptualization, Data curation, Investigation, Formal analysis, Writing- Original draft preparation. **Mari K. Halle:** Data curation, Formal analysis, Resources, Investigation, Writing- Original draft preparation. **Njål Lura:** Data curation, Formal analysis, Writing- review and editing. **Kristine E. Fasmer:** Investigation, Writing- review and editing. **Kari Wagner-Larsen:** Data curation, Writing- review and editing. **David Forsse:** Resources, Writing- review and editing. **Bjørn I. Bertelsen:** Resources, Writing- review and editing. **Øyvind Salvesen:** Formal analysis, Writing- review and editing. **Camilla Krakstad:** Conceptualization, Investigation, Formal analysis, Funding acquisition, Resources, Writing- Original draft preparation, Supervision, Project Administration. **Ingfrid S. Haldorsen:** Conceptualization, Investigation, Formal analysis, Funding acquisition, Writing- Original draft preparation, Supervision, Project administration. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by the Regional Ethical Committee for Medical and Health Research Ethics (REK 2015/2333, REK2018/591 and REK 2014/1907), according to Norwegian legislation and regulation. All participants gave written informed consent at primary diagnosis in this retrospective study with prospectively collected data.

Consent for publication

Not applicable.

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Data availability

Not applicable.

Declaration of Competing Interest

The authors declare no competing interests.

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