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par

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TITRE

Quantification de la composition corporelle par scanner à l'aide du logiciel Slice-O-Matic : étude de la reproductibilité inter- et intra-observateur et étude de la valeur pronostique et de l'évolution sous chimiothérapie néo-adjuvante chez des patientes atteintes de cancer de l'ovaire.

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SERMENT D'HIPPOCRATE

En présence des Maîtres de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits à l'indigent,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux et reconnaissant envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert d'opprobre
et méprisé de mes confrères
si j'y manque.

A mes parents

A ma famille et mes proches que j'aime tant

A Monsieur le Professeur Laurent BRUNEREAU

Professeur des Universités – Praticien Hospitalier
(Radiologie et Imagerie médicale)

Vous me faites l'honneur de présider ce jury de thèse, acceptez pour cela mes plus sincères remerciements. Vous avez toujours été bienveillant à mon égard et je vous en suis reconnaissant. Merci pour l'enseignement que vous m'avez donné.

A Monsieur le Professeur Jean-Philippe COTTIER

Professeur des Universités – Praticien Hospitalier
(Radiologie et Imagerie Médicale)

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A Madame le Docteur Aurore BLEUZEN

Praticien Hospitalier
(Radiologie et Imagerie Médicale)

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A Madame le Docteur Adeline DOLLY

Docteur en Science de la Vie et de la Santé

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Je te souhaite bonne continuation dans ta nouvelle vie belge.

A Madame le Professeur Lobna OULDAMER

Professeur des Universités – Praticien Hospitalier
(Gynécologie Obstétrique)

Que dire si ce n'est que sans vous rien n'aurait été possible. Vous m'avez fait l'honneur de diriger ce travail de thèse et je ne saurais vous en remercier assez. Vous m'avez guidé, encadré, aidé, conseillé. Merci pour votre implication sans pareil. Vous êtes assurée de ma gratitude la plus sincère et la plus profonde.

Titre:

Quantification de la composition corporelle par scanner à l'aide du logiciel Slice-O-Matic : étude de la reproductibilité intra- et inter-observateur et étude de la valeur pronostique et de l'évolution sous chimiothérapie néo-adjuvante chez des patientes atteintes de cancer de l'ovaire

Résumé:

La relation entre composition corporelle et pronostic chez les patients atteints de cancers fait l'objet de nombreuses études. L'imagerie est l'outil le plus fiable pour évaluer la distribution des masses musculaire et adipeuse. Au cours de ce travail de thèse, nous nous sommes donné comme objectifs :
i) D'étudier la reproductibilité intra-observateur de la quantification de la composition corporelle par scanner et d'étudier la reproductibilité inter-observateur entre une personne spécialisée en imagerie et une personne non spécialisée en imagerie.
ii) D'évaluer la valeur pronostique des paramètres de composition corporelle dans une cohorte de patientes atteintes de cancer de l'ovaire et d'apprécier l'évolution de ces derniers sous chimiothérapie néo-adjuvante.
Ainsi il apparait qu'en fonction de l'observateur et du tissu analysé, des erreurs de précision existent dans la quantification de la composition corporelle. Les mesures des surfaces de muscle squelettique, de graisse viscérale et de graisse sous-cutanée montrent les meilleures reproductibilités inter-observateur, à l'inverse de la mesure de surface de graisse intermusculaire sujette à plus de variations. La variabilité intra-observateur est très basse.
Dans la cohorte étudiée, un pourcentage important de patientes étaient sarcopéniques et présentaient une faible densité musculaire avant tout traitement. Une perte significative de masse adipeuse était observée au cours des premiers cycles de chimiothérapie néo-adjuvante et celle-ci était associée à une réduction de la survie globale. Il était aussi observé une perte non significative de masse musculaire et une augmentation du nombre de patientes sarcopéniques.

Mots clés:

Scanner – Composition corporelle – Reproductibilité – Masse adipeuse – Muscle squelettique – Chimiothérapie néo-adjuvante – Cancer épithélial de l'ovaire – Sarcopénie

Title:

Assessment of body composition by computed tomography using Slice-O-Matic software: study of inter-observer and intra-observer reproducibility and study of the prognostic value and the evolution of body composition parameters in patients with ovarian cancer undergoing neoadjuvant chemotherapy

Abstract:

The relationship between body composition and prognosis in cancer patients is the subject of many studies. Imaging is the most reliable tool to assess the distribution of muscle and fat mass. In this work, we set ourselves the following objectives:
i) To study the intra-observer reproducibility of the quantification of body composition by scanner and to study the inter-observer reproducibility between a person specialized in imaging and a person not specialized in imaging.
ii) To evaluate the prognostic value of body composition parameters in a cohort of patients with ovarian cancer and to assess the evolution of these under neoadjuvant chemotherapy.
Thus it appears that depending on the observer and the tissue analyzed, precision errors exist in the quantification of body composition. Measurements of skeletal muscle, visceral fat and subcutaneous fat areas show the best inter-observer reproducibility, unlike the inter-muscular fat area measurement subject to more variation. Intra-observer variability is very low.
In the cohort studied, a high percentage of women were sarcopenic and had low muscle attenuation before any treatment. Fat mass loss was observed during the first cycles of neoadjuvant chemotherapy and was significantly associated with overall survival reduction. A non-significant muscle mass loss and an increase of the percentage of sarcopenic women were also observed under treatment.

Keywords:

CT imaging – Body composition – Reproducibility – Fat mass – Skeletal muscle – Neoadjuvant chemotherapy – Epithelial ovarian cancer – Sarcopenia

TABLE DES MATIERES

Préambule

La cachexie cancéreuse est un syndrome multifactoriel caractérisé par une perte progressive du muscle squelettique et parfois aussi du tissu adipeux, qui entraîne une diminution de la qualité de vie, de la réponse aux traitements anticancéreux, et de la survie des patients. De par la complexité physiopathologique de ce syndrome clinique, il n'existe pour le moment aucun traitement curatif contre la cachexie cancéreuse. Malgré de récentes découvertes, les mécanismes à l'origine de la fonte musculaire squelettique ne sont pas clairement élucidés. Jusqu'à présent, une trentaine d'études cliniques ont analysé des biopsies musculaires squelettiques pour explorer les mécanismes sous-jacents à la fonte musculaire caractéristique de la cachexie cancéreuse (Anoveros-Barrera *et al*., 2019). La grande majorité de ces études a inclus des patients atteints de cancers gastro-intestinaux, et leurs résultats soulignent de possibles altérations de la structure des fibres musculaires (Ebhardt *et al*., 2017; Schmitt *et al*., 2007), des voies de la protéolyse (de Castro *et al*., 2019; Aversa *et al*., 2016; Khal *et al*., 2005; Bossola *et al*., 2003) et de la synthèse protéique (Schmitt *et al*., 2007), ainsi que des métabolismes mitochondrial (de Castro *et al*., 2019; Marzetti *et al*., 2017) et lipidique (Stephens *et al*., 2011). D'autre part, il a été montré que le tissu adipeux pouvait être affecté durant le développement de la cachexie cancéreuse, d'un point de vue morphologique et métabolique (Alves *et al*., 2017; Henriques *et al*., 2017; Silvério *et al*., 2017; Petruzzelli *et al*., 2014). La prévalence accrue de l'obésité observée au cours des dernières décennies a fait émerger un nouveau concept d'obésité sarcopénique. Chez les patients obèses, la sarcopénie est masquée par l'accumulation de graisse, ce qui rend le dépistage de la pathologie plus difficile. L'obésité sarcopénique fait l'objet de débats dans la communauté scientifique, quand certains parlent de l'effet paradoxalement protecteur de l'obésité notamment grâce à des réserves adipeuses plus importantes, alors que d'autres pointent du doigt la dangerosité de la fonte musculaire masquée (Prado *et al*., 2016). En plus de la tumeur, les traitements anticancéreux, en particulier la chimiothérapie, peuvent également aggraver l'état nutritionnel

du patient. Chez les patients atteints d'un cancer, l'accès aux scanners de diagnostic et de suivi de la pathologie, a permis la mise en place de très nombreuses études cliniques rétrospectives et prospectives d'évaluation de la composition corporelle en lien avec les traitements chimio-thérapeutiques et la cachexie cancéreuse. L'utilisation de ces scanners a permis d'évaluer les effets propres d'agents chimio-thérapeutiques sur différents paramètres de la composition corporelle, tels que la masse musculaire squelettique (Hopkins and Sawyer, 2018), la densité osseuse (Lee *et al*., 2016; Oostra *et al*., 2015; Cameron *et al*., 2010; Hui *et al*., 2010; Hadji *et al*., 2009) et les Tissus Adipeux Totaux (TAT) (KazemiBajestani *et al*., 2019; Daly *et al*., 2018; Nattenmüller *et al*., 2017; Palmela *et al*., 2017; Awad *et al*., 2012). Ainsi, la chimiothérapie a été associée à des modifications de la composition corporelle dans divers cancers, en fonction du type de tumeur, du type de médicament et de la dose.

Au cours de ce travail de thèse, nous nous sommes donnés comme objectifs :
i) D'étudier la reproductibilité inter-observateur de la quantification de la composition corporelle par scanner entre une personne spécialisée en imagerie et une personne non spécialisée en imagerie et d'étudier sa reproductibilité intra-observateur.
ii) D'évaluer grâce au scanner l'évolution sous chimiothérapie néo-adjuvante des paramètres de composition corporelle dans une cohorte de patientes atteintes de cancers de l'ovaire et d'apprécier sa valeur pronostique.

Ce manuscrit s'articule autour de deux chapitres, consistant chacun en un article à part entière répondant séparément aux objectifs suscités.

Chapitre I

Article - Assessment of body composition by computed tomography using Slice-O-Matic software: Inter-observer and intra-observer reproducibility

Assessment of body composition by computed tomography using Slice-O-Matic software: Inter-observer and intra-observer reproducibility

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ABBREVIATIONS

BMI : Body Mass Index

CT : Computed Tomography

CV : Coefficient of Variation

IMAT : Inter-Muscular Adipose Tissue

SAT : Sub-Cutaneous Adipose Tissue

SD : Standard Deviaton

TAT : Total Adipose Tissue

VAT : Visceral Adipose Tissue

ABSTRACT

Introduction: The relationship between body composition and prognosis in patients with chronic disease has been the subject of numerous clinical studies. Computed tomography (CT) is a reliable technique and is now commonly used to assess body composition. But precision errors exist depending on the machine, the patient and the observer.

Objective: To evaluate and understand better CT imaging inter- and intra-observer variability in muscle and fat distribution measurement using Slice-O–Matic software.

Material and methods: A radiologist MD and a scientist without medical formation in radiology independently evaluated whole body composition in women with ovarian and/or endometrial cancer. 55 abdominopelvic cross-sectional images were analysed by these two observers. Skeletal muscle and various fat compartments areas were measured using a single image in axial section at the L3 vertebra.

Results: Inter-observer reliability was high for both fat mass (Visceral adipose tissue (VAT): r=0.98, coefficient of variation (CV): 8.9%; Subcutaneous adipose tissue (SAT): r=0.98, CV: 6.7%; Intra-muscular adipose tissue (IMAT): r=0.72, CV: 28.1%) and skeletal muscle (r=0.92, CV: 3.3%). CV of VAT and SAT measurements were significantly influenced by Body Mass Index categories. The intra-observer discordance was less than or equal to 1% for nearly all body composition parameters studied, except for IMAT.

Conclusion: Upon comparing analysis performed by two observers with different levels of experience, our results confirm that precision errors do exist depending on the observer and the tissue analysed. Measurement of skeletal muscle, VAT and SAT areas shows high inter-observer reproducibility, while IMAT area measurement is subject to larger variations. Intra-observer variability was also very low. CT measurements can be safely performed by different observers.

Keywords: CT imaging – Body composition – Reproducibility – Fat mass – Skeletal muscle

INTRODUCTION

The prognostic value of body composition parameters (skeletal muscle mass and/or fat mass) for survival, recurrence, and surgical outcome in patients with chronic disease has been the subject of numerous studies in the past few years.

Different methods exist to assess body composition (1,2). Anthropometric measurements such as waist circumference, weight or Body Mass Index (BMI) are commonly used to describe body mass, height, shape and adiposity. However, these traditional indices are not sufficient to accurately estimate the volumes of body composition compartments, particularly adipose tissue (3–6). Impedancemetry is also a popular technique which indirectly evaluate body composition, but its clinical value is questioned in the literature (7). Imaging is proving to be the most reliable tool to analyse body fat and fat-free mass distribution (1,8,9). Cross-sections of CT (Computed Tomography) Scanners or, less frequently, MRI (Magnetic Resonance Imaging) (9–11) are generally used. Validation of the use of DXA (Dual energy X-ray Absorptiometry), particularly for measuring muscle mass, requires further studies (12).

Analysis of total muscle and adipose tissue cross-sectional areas at the third lumbar vertebra has been thoroughly validated in the literature (6,13–15). A correlation has indeed been demonstrated between skeletal muscle area (including psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique, and rectus abdominis muscles) and whole body lean mass. Total adipose tissue area at this level also highly correlates with whole body fat mass.

A critical point in the evaluation of body composition on CT images is the repeatability of measurements (depending on the device and patient positioning) and the reliability of analyses (intra- and inter-observer errors). In their review of the literature, MacDonald *et al.* highlighted that precision errors could vary between 0.4 and 1.5% depending on the machine,

the patient and the operator (9), proving the very high reliability of this technique. The analyses were performed using different imaging software, most common ones being Image J and Slice-O-Matic (Tomovision). Van Vugt *et al.* also shown that the measurements of skeletal muscle and adipose tissue cross-sectional areas on CT-Scanners using vFatSeg, OsiriX, ImageJ or Slice-O-Matic software, were similar, as were the inter- and intra-observer variability rates (16).

The aim of our study was to re-evaluate inter- and intra-observer reproducibility rates and identify the precision error of body composition parameters measurements on single-slice CT-Scanners images, using Slice-O-Matic software. We compared the results obtained by a radiologist to those of an observer with pure scientific background and no medical training in radiology. Repetitive calculations on several CT images by the same observer were also compared.

PATIENTS AND METHODS

Study design and patients

We included 55 patients who participated in a monocentric prospective study, sponsored by the university teaching hospital of Tours (France), from 01/03/2017 to 16/07/2019 (METERMUS-IMC, NCT03027479). This study was in accordance with the code of ethics of the World Medical Association. The objective of this pilot clinical study was to explore alterations in skeletal muscular energetic metabolism in ovarian and/or endometrial cancer patients with malnutrition and/or cachexia, depending on BMI. Inclusion criteria were: adult patients with histologically confirmed ovarian or endometrial tumor, and who were eligible for surgery. Exclusion criteria included: unbalanced diabetes; chronic neuromuscular disease as well as any severe uncontrolled medical condition.

CT-Scan analyses

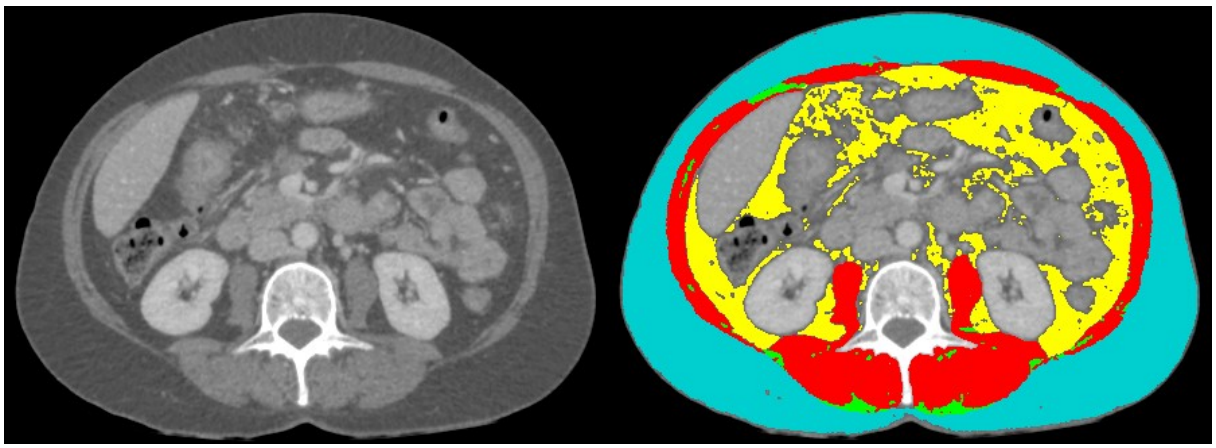
Diagnostic abdominopelvic CT images were used to determine body composition. Images were acquired using a standard protocol. One axial image of the 3rd lumbar vertebra (L3) was selected for analysis of total muscle and fat cross-sectional areas (6,11,14). CT image parameters included: contrast-enhanced, 1 to 5 mm slice thickness, 100 to 140 kVp, and ~100 to 500 mA. Tissues were identified anatomically and quantified within pre-specified Hounsfield unit (HU) ranges (HU) (11,14,17,18): muscle (−29 to +150 HU); subcutaneous adipose tissue (SAT) (-190 to -30 HU); inter-muscular adipose tissue (IMAT) (-190 to -30 HU); visceral adipose tissue (VAT) (-150 to -50 HU), using Slice-O–Matic software (v.5.0; Tomovision, Magog, Canada). An example of compartments segmentation is shown in *Figure 1*. Measurements were performed simultaneously by two observers: a radiologist and a researcher without medical training in radiology. In addition to the overall benchmark of the

level of the third lumbar vertebra, the precise selection of the cut level was left to the discretion of the two observers and was performed independently by them, blind to each other.

Statistical analyses

Data were recorded on Microsoft Excel. Statistical analyses were performed using R statistical program. Data are expressed as mean ± standard deviation (SD). Coefficients of variation (CV) defined as the ratio of the standard deviation to the mean multiplied by 100, were also calculated by the radiologist observer. To evaluate intra-observer reproducibility, the radiologist performed five repeated measures on several CT images within two months. Inter-observer reliability was assessed using Pearson's correlation coefficient. Intra-observer and inter-observer reproducibility were assessed using Bland-Altman method. We considered $p \leq 0.05$ to be statistically significant.

Figure 1. Example of compartments segmentation using Slice-O-Matic software



Muscle: -29 to +150 HU **SAT:** -190 to -30 HU **IMAT:** -190 to -30 HU **VAT:** -150 to -50 HU

RESULTS

Patient characteristics

The majority of the 55 women included had ovarian cancer (65%), 25% had endometrial cancer and 10% had borderline ovarian tumour. Mean age was 67 ± 10.8 years (interquartile range (IQR): 24-86). Mean BMI was 28.2 ± 6.8 (IQR: 17.5-50), 4% of the participants were underweight (< 18.5 kg/m^2), 29% had normal BMI (18.5 to 24.9 kg/m^2), 36% were overweight (25 to 29.9 kg/m^2) and 31% were obese (> 30 kg/m^2).

Body composition measurements

Mean abdominal fat areas as calculated by the radiologist were: VAT 122.5 ± 90.17 cm^2, SAT 248.2 ± 133.4 cm^2 and IMAT 16.3 ± 11.1 cm^2. Mean abdominal fat areas as calculated by the scientist were: VAT 118.7 ± 90.5 cm^2, SAT 236.5 ± 133.1 cm^2 and IMAT 14.9 ± 9.5 cm^2.

Mean abdominal skeletal muscle area as calculated by the radiologist was: 107.4 ± 17.3 cm^2, while mean abdominal skeletal muscle area as calculated by the scientist was: 109.1 ± 17.1 cm^2.

Intra- and inter-observer reproducibility

Based on the 55 CT-Scans analysed, we obtained an inter-observer CV of:

- 28.1% for IMAT (44% for underweight women, 22.5% for normal BMI, 30% for overweight women and 28% in case of obesity, p=0.65).

- 8.9% for VAT (30.7% for underweight women, 10% for normal BMI, 7.8% for overweight women and 6.3% in case of obesity, p=0.02).

- 6.7% for SAT (36.3% for underweight women, 7.9% for normal BMI, 4.3% for overweight women and 4.6% in case of obesity, $p<0.001$).

- and 3.3% for skeletal muscle (1% for underweight women, 3.1% for normal BMI, 2.8% for overweight women and 3.7% in case of obesity, $p=0.57$).

Surface measurements performed by the 2 observers are listed in Table 1. Correlation coefficient was r=0.98 for VAT ($p<0.0001$), r=0.98 for SAT ($p<0.0001$), r=0.72 for IMAT ($p<0.0001$) and r=0.92 for the skeletal muscle ($p<0.0001$). The intra-observer CV was 5.8% for IMAT, 0.4% for VAT, 0.3% for SAT and 1% for the skeletal muscle. The measurements performed by the radiologist observer to determine intra-observer CV are listed in Table 2.

Table 1. Body composition parameters measurements performed by the 2 observers and inter-observer reproducibility coefficients of variation

	RADIOLOGIST				NON RADIOLOGIST							
	Areas (cm²)				Areas (cm²)				Coefficients of variation (%)			
N° patient	VAT	SAT	IMAT	MUSCLE	VAT	SAT	IMAT	MUSCLE	VAT	SAT	IMAT	MUSCLE
1	136,8	231,8	8,665	112,6	121,8	220	10,18	105,4	8,203094909	3,6936078	11,36924143	4,670797087
2	112,7	267	25,29	103,4	110,6	266,8	42,56	113,8	1,329981407	0,05298665	35,99626857	6,771556652
3	88,63	214,2	0,4833	99,29	86,49	206,7	20,14	101,6	1,728196108	2,5199814	134,7930338	1,626180163
4	33,59	144,1	3,602	121,6	38,64	138	6,773	120,7	9,887551558	3,05803004	43,22381886	0,525295999
5	194,1	173,8	13,79	95,61	196,4	157	20,2	89,63	0,832955491	7,18222124	26,6699292	4,565427069
6	216,9	180,4	6,855	120,8	193	161,1	30,25	120,9	8,245841459	7,99248075	89,16729899	0,058511111
7	57,53	250,8	22,47	131,8	59,38	245,4	19,25	128,6	2,237871089	1,53904741	10,91507112	1,737896851
8	109,6	206,5	14,63	101,5	97,34	205,2	17,37	104,5	8,378398702	0,4465576	12,10920363	2,059534314
9	89,07	133,7	13,13	101,3	80,89	124,5	7,586	100,1	6,806464427	5,03902586	37,84707468	0,842629729
10	34,2	226,7	3,792	118,5	34,26	224,4	3,279	118	0,123945097	0,72105768	10,26009839	0,298988068
11	113,9	297,2	22,41	99,23	89,17	292,2	21,06	93,52	17,22238706	1,19970611	4,391967585	4,189447181
12	288,2	309,2	33,22	94,53	283,6	288,3	27,73	98,7	1,137702411	4,94678886	12,73836334	3,051943567
13	64,71	335,7	6,24	103,6	64,94	329,1	19,86	109,2	0,250882468	1,40400263	73,7991905	3,721614638
14	25,31	87,07	8,794	91,69	15,14	46,16	6,669	91,59	35,55637065	43,4252622	19,4348045	0,077161369
15	208,6	304,5	21,62	104,7	191,9	301	19,38	106,4	5,89697041	0,81746449	7,726435072	1,13887402
16	117,5	168,3	23,19	75,53	117,8	158,3	13,27	81,34	0,180307722	4,33010889	38,47777986	5,237828009
17	25,14	192,8	12,29	108,8	18,42	159,9	19,72	115,5	21,81706873	13,1918418	32,82601302	4,22435616
18	5,337	62,83	15,42	96,04	4,915	61,07	16,49	114,9	5,821284855	2,00889094	4,742113794	12,64438598
19	164,1	64,92	11,97	85	153,7	62,69	10,27	88,14	4,628011658	2,4713551	10,81008568	2,564762958
20	120	230,3	15,16	116,9	125,2	241	12,7	115,8	2,999147848	3,21071189	12,48731286	0,668515221
21	121,5	327	4,527	103,7	118,1	323	8,984	106,2	2,006813903	0,87028527	46,65198614	1,684389665
22	3,29	45,44	1,433	105,2	3,481	42,81	2,933	125,3	3,989289476	4,21459679	48,5872731	12,33218768
23	63,65	140,4	10,07	96,82	58,18	127,3	5,838	97,92	6,34962504	6,92050716	37,62227682	0,798826599
24	257,3	373,7	7,76	140,2	224	407,6	3,195	145,9	9,784606613	6,13616278	58,93094397	2,817552361
25	6,733	39,07	0,212	88,08	9,76	59,5	0,62	90,61	25,95540201	29,3115381	69,35085739	2,002328229
26	168	289,5	33,78	79,4	164,9	290,5	29,64	81,79	1,316930623	0,24382992	9,231857692	2,09688592
27	252,6	590,3	23,81	106,7	215,6	571,4	18,87	118,8	11,17597219	2,30082089	16,36882614	7,588463018
28	95,25	132,4	6,034	86,97	70,88	129,3	4,757	86,34	20,745431	1,67522432	16,73571235	0,51408144
29	72,41	165,8	22,35	91,46	61,81	196,8	24,82	107,4	11,16872579	12,0906289	7,405358277	11,3358967
30	56,43	295,9	20,55	107,4	45,62	197,1	20,41	121,7	14,98054739	28,341643	0,483373776	8,82726056
31	166,6	294,6	10,05	132,3	164,9	297,2	10,57	128,1	0,725237724	0,62131721	3,566396957	2,280989617
32	291,7	434,6	41,6	100,5	280,2	427,4	38,95	102,6	2,843758693	1,18124567	4,652595829	1,462259223
33	153,4	419	33,43	108,1	150,9	398	22,36	115,9	1,161858004	3,63506546	28,06120117	4,924493655
34	21,9	173,7	19,28	97,02	8,224	86,38	9,839	99,65	64,20390612	47,481209	45,8518158	1,891178964
35	113,9	174,6	14,37	84,75	106,8	165,9	12,07	87,39	4,549576934	3,6134091	12,30216034	2,168888001
36	34,47	83,75	7,826	115,4	34,13	89,76	7,733	111,9	0,700922174	4,89852084	0,845310504	2,177627571
37	47,6	306,1	14,72	137,4	30,83	309,4	6,104	151	30,23889002	0,75822985	58,51356153	6,668968255
38	103,5	194,9	11,66	77,34	95,81	186,2	10,17	74,55	5,456475989	3,2284592	9,652671589	2,597706129
39	152,3	267,5	21,16	114,9	131,3	263,6	5,944	113,7	10,4719622	1,03849235	79,39298098	0,742369324
40	120,1	416,7	7,399	105,8	120,1	341	7,182	104,4	0	14,1290704	2,104686531	0,941911983
41	84,89	170,2	7,31	119,1	75,88	164,3	4,791	119,5	7,925647942	2,49442751	29,4389221	0,237085258
42	22,35	251,6	15,58	82,82	19,27	249,6	10,2	85,54	10,46558811	0,56433103	29,51306814	2,284783137
43	8,987	44,2	4,193	95,13	9,888	45	3,351	90,69	6,750762488	1,26835297	15,78430302	3,379134763
44	48,33	204,8	7,356	124,5	66,35	193,9	8,902	113,3	22,22194663	3,86629742	13,44798971	6,66071989
45	267,4	265,5	8,929	117,2	300	216,5	4,913	117,3	8,125372248	14,3768599	41,03078794	0,060307615
46	336,7	712,3	30,17	149,7	361,9	689,3	27,33	147,5	5,101371568	2,32069863	6,984985247	1,046860645
47	164,9	248,7	13,43	118,8	168,2	224,6	7,34	110,9	1,401052163	7,20104518	41,46634855	4,863860315
47	367,7	493,5	47,38	122,1	321,2	536,4	34	134,4	9,545787582	5,89084006	23,25163119	6,781608896
48	93,2	410,4	48,73	144,5	104,5	351,9	23,69	124,8	8,083264165	10,8528786	48,89796686	10,34534244
50	165,6	256,4	12,52	110,5	179,3	273,3	17,54	109,2	5,61749081	4,51202741	23,6172724	0,836812759
51	283,3	347,1	25	141,3	327,7	344,3	15,64	136,9	10,27677286	0,57272172	32,57145409	2,236714477
52	129,5	282,1	18,48	104,4	147,6	220,7	18,8	104,8	9,237555207	17,2698315	1,213917221	0,270404123
53	102,2	268	22,44	118,2	101,1	268	15,94	120,5	0,765191795	0	23,95098529	1,362669122
54	129,8	364,7	22,45	93,1	141,3	361,4	16,51	87,44	5,999061589	0,64273582	21,56167495	4,433615134
55	23,57	85,22	15,52	105,9	25,79	72,04	13,98	106,1	6,36052291	11,8525593	7,38267419	0,133416374
								MEAN	**8,9**	**6,6**	**28,1**	**3,3**

Table 2. Body composition parameters measurements performed by the radiologist observer and intra-observer reproducibility coefficients of variation

	Measurements n°1				Measurements n°2							
	Areas (cm²)				Areas (cm²)				Coefficients of variation (%)			
N° patient	VAT	SAT	IMAT	MUSCLE	VAT	SAT	IMAT	MUSCLE	VAT	SAT	IMAT	MUSCLE
1	98,46	199	13,69	102,1	98,59	198,3	13,59	101	0,0933	0,249169	0,518407	0,765945
2	79,32	244,4	11,57	127,2	77,88	242,6	13,26	131,5	1,295463	0,522707	9,625537	2,350645
3	119,3	333,1	6,626	132,9	118,8	332,5	7,37	131,5	0,296979	0,127483	7,517683	0,748827
4	125,3	151,8	13,14	104,2	125	151	14,05	104,1	0,169502	0,373636	4,733116	0,067893
5	184	377,1	8,295	100,4	184	376,7	9,127	101,6	0	0,075044	6,753677	0,840127
								MEAN	**0,4**	**0,3**	**5,8**	**1,0**

DISCUSSION

The objective of our study was to evaluate inter- and intra-observer reproducibility of different body composition parameters measurements on single-slice CT-Scans images, using Slice-O-Matic software, when one observer was a radiologist and the other one, a scientist with no medical training in radiology.

Expected inter-observer discordance was observed for VAT and SAT parameters: between 5 and 10% variability. It could have been lower if the two observers had chosen exactly the same level of cut to the nearest millimetre. Apart from the overall reference point of the third lumbar vertebra, the precise choice of the cut was made independently by the two observers, blind to each other. For the VAT, one can imagine that a shift in the choice of section (at different levels of the L3) could expose to variations due to the different positioning of the intra-abdominal viscera (in particular the digestive elements which are very mobile), in addition to variations linked to the observer himself. This explanation is less valid, in our opinion, for SAT, for which the distribution seems to remain homogeneous from one level to another throughout the vertebra (although the presence of skin folds at the chosen cut level may also stain the results of some variations). This seems to be confirmed upon considering the discrepancies observed: 6.7% for SAT *vs* 8.9% for VAT.

Regarding IMAT, we observed a significant discordance between the two observers measurements (28.1%). Of all body composition parameters, IMAT usually has the lowest surface observed on CT images. Therefore, even the smallest measurement difference could result in high percentage of variation. This also seems to be confirmed by the intra-observer discordance coefficient for this fat compartment, which is the highest of all reproducibility rates. Furthermore, according to the two observers, IMAT measurement involves the most subjectivity: in fact the anatomical limits on CT-scan images between fat belonging to the

intra-muscular compartment and extra-muscular fat are sometimes difficult to identify precisely.

The inter-observer CV reported in this study for adipose tissues are much higher than those reported in the literature (9,16). We believe that the independent choice of cross-sections by the observers in our study may explain this result. Another explanation would be the small tissue areas, for which the smallest difference can give a large percentage variation. The smallest inter-observer CV is that of the skeletal muscle (3.3%), which is closer to the values reported in literature (9,16). Even truer than for SAT, the distribution of skeletal muscle remains very homogeneous from one level to another. It should also be remembered that the measurements were performed by two observers with different training and experience levels, one specialized in imaging and the other not. Thus it is possible that the inter-observer CV would have been lower if the comparison had been made between two people with imaging training.

It should be noted that intra-observer reproducibility is excellent for all compartments studied (less than or equal to 1%), with the exception of IMAT, which is more difficult to quantify precisely for the reasons mentioned above.

CONCLUSION

Considering our inter- and intra-observer reproducibility rates, skeletal muscle area appears to be the most reliable parameter among all body composition parameters quantified on single-slice CT Scans. Fat compartments measurements seem to be subject to a little more variation, especially IMAT.

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Declaration of interest

The authors declare that they have no conflicts of interest in connection with this article.

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Chapitre II

Article - Evolution of body composition parameters assessed by computed tomography and its prognostic value in patients with epithelial ovarian cancer undergoing neoadjuvant chemotherapy

Evolution of body composition parameters assessed by computed tomography and its prognostic value in patients with epithelial ovarian cancer undergoing neoadjuvant chemotherapy

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ABBREVIATIONS

AUC : Area Under the Curve

BMI: Body Mass Index

CT: Computed Tomography

EOC: Epithelial Ovarian Cancer

FFM: Fat Free Mass

FIGO:

FM: Fat Mass

HGSOC: High Grade Serous Ovarian Cancer

HU: Hounsfield Unit

IMAT: InterMuscular Adipose Tissue

IQR: InterQuartile Range

NAC: NeoAdjuvant Chemotherapy

OS: Overall Survival

RFS: Recurrence Free Survival

SAT: Subcutaneous Adipose Tissue

SD: Standard Deviaton

SMM: Skeletal Muscle Mass

TAT: Total Adipose Tissue

VAT: Visceral Adipose Tissue

ABSTRACT

Introduction: Patients diagnosed with ovarian cancer generally experience cachexia, defined as pathological weight loss and skeletal muscle wasting with or without loss fat loss. Treatments, especially chemotherapy, may also worsen the patient's nutritional status.

Objective: To assess the evolution of body composition parameters using CT images in a cohort of women treated with neoadjuvant chemotherapy (NAC) for advanced epithelial ovarian cancer (EOC) and to determine if these changes have a prognostic impact.

Material and methods: This retrospective unicentric study included 53 patients with FIGO III-IV stage EOC. CT-scans produced at diagnosis (C0), after 3-4 cycles (C3) and after 6 cycles (C6) of NAC were used to assess body composition. Fat mass (FM), fat free mass (FFM) and skeletal muscle mass (SMM) were calculated. Changes in tissue composition were normalized and expressed as change/100 days to account for variation in the exact duration of CT-scan intervals.

Results: 26 women (49%) underwent surgery after 3 to 4 cycles of chemotherapy and 12 patients (22.6%) after 6 cycles. Before any treatment, 40% of women were sarcopenic and 70% had low muscle attenuation ; these percentages increased along NAC : 55% and 80% respectively at C6. A significant FM loss (-5.24% ; -1.41 kg) occured during the first cycles of treatment and was significantly associated with overall survival (OS) reduction (p=0.04). OS tended to be reduced in women with low MA. SMM was also observed although not significant.

Conclusion: This study suggestes that FM loss has a predictive value in patients treated with NAC for advanced EOC. NAC may also worsen sarcopenia. An early and well-conducted nutritional intervention is imperative in this category of patients.

Keywords: CT imaging – Fat mass – Neoadjuvant chemotherapy – Ovarian cancer – Sarcopenia

INTRODUCTION

Epithelial ovarian cancer (EOC) is mostly diagnosed at advanced stage. Optimal management with better survival is achieved through complete macroscopic debulking surgery and chemotherapy. Neoadjuvant chemotherapy (NAC) has been introduced for patients who are not candidates for primary debulking surgery (unresectable disease) to decrease tumor load and perform a unique complete surgery (1). The overall 5-year survival is around 50% (2). The International Federation of Gynecology and Obstetrics (FIGO) stage and residual disease are well-recognized prognostic factors but are also unmodifiable at the time of diagnosis.

Cancer cachexia is a complex multifactorial syndrome characterized by involuntary and pathological weight loss, mainly due to skeletal muscle wasting, with or without loss of adipose mass. In 2011, a consensus of international experts established a clinical definition for cancer cachexia based on body weight loss and body mass index (BMI). In 2019, the “Haute Autorité de Santé” (HAS) subsequently validated these diagnosis criteria based on weight loss and/or quantified reduction in muscle mass and/or function (3). However, recent studies have demonstrated the importance of updating these clinical criteria, taking into account the evolution of overweight and obesity prevalence, as well as the advanced age of most cachectic patients. In patients with EOC, the diagnosis of cancer cachexia can be missed if weight loss is masked by ascites accumulation: an analysis of body composition more accurate than weight or BMI alone is therefore essential to avoid these pitfalls; such detailed analysis can be provided by computed tomography (CT) imaging.

In the cancer context, the initial status of body composition parameters is important, but so is its evolution in time: along the course of cancer treatment, associations between muscle and fat loss and outcome have already been demonstrated in patients with foregut cancers for instance (4). Oncological therapies, especially chemotherapy, can indeed worsen the patient's

nutritional status in addition to the presence of the tumor itself. CT-scans performed at diagnostic and during follow-up are easily accessible and their availability allowed the realization of a large number of retrospective and prospective clinical studies dealing with body composition changes under treatment. This way, specific effects of chemotherapeutic agents on various parameters of body composition, such as skeletal muscle mass (SMM) (5) and total adipose tissues (TAT) (4,6–9) could be evaluated. Chemotherapy has thereby been associated with changes in body composition in various cancers, depending on tumor type, drug type, and dose. Regarding ovarian malignancies, there are to our knowledge only two studies dealing with body composition and outcome : in 2013 Torres *et al.* showed that a combined low subcutaneous adipose tissue (SAT) and intermuscular adipose tissue (IMAT) at diagnosis was associated with poorer overall survival (OS) and longer hospital stay in a retrospective study of patients undergoing surgery as primary treatment (10) ; in 2016, Rutten *et al.* retrospectively highlighted that skeletal muscle loss during neoadjuvant chemotherapy (NAC) was significantly associated with diminished survival and that the assessment of skeletal muscle at a specific and isolated point in time had no prognostic value (11). In this later publication, the drug and the protocol used in NAC were not specified however.

Given the low number of research in this specific area to date, we aimed to assess in the present study the evolution of body composition parameters using CT images in a cohort of women treated with neoadjuvant chemotherapy for advanced epithelial ovarian cancer and to determine wether these changes have a prognostic impact or not.

PATIENTS AND METHODS

Study population

From January 2016 to December 2019, the data of all women who were managed for EOC were retrospectively abstracted from our prospectively maintained database (Tours University hospital). All the women had presumed advanced-stage EOC and final 2009 FIGO (12) stage III-IV cancer. The research protocol was approved by the institutional review board.

Neoadjuvant chemotherapy regimen

Patients who were not eligible for primary debulking surgery received neoadjuvant chemotherapy which consisted in carboplatine (AUC 5) plus paclitaxel (175 mg/m²) every 21 days. Women under 65 years old did not receive more than 750 mg of paclitaxel per cycle and women above 65 years old did not receive more than 600 mg per cycle. If patients were still not eligible for complete surgery after 3 to 4 cycles, NAC was continued for a total of 6 cycles.

Body composition assessment

Abdominopelvic CT images at diagnostic were used to determine body composition. Images were acquired using CT-scanner with a standard protocol. One axial image of the 3rd lumbar vertebra (L3) was selected for analysis of total muscle and fat cross-sectional areas (13–15). CT image parameters included: contrast-enhanced, 1 to 5 mm slice thickness, 100 to 140 kVp, and ~100 to 500 mA. Tissues were identified anatomically and quantified within pre-specified Hounsfield Unit (HU) ranges (14–17) : skeletal muscle (−29 to +150 HU); subcutaneous adipose tissue (SAT) (-190 to -30 HU); intermuscular adipose tissue (IMAT) (-190 to -30 HU); visceral adipose tissue (VAT) (-150 to -50 HU), using Slice-O–Matic software (v.5.0; Tomovision, Magog, Canada). Measurements were performed by a radiologist. An example

of muscle and fat compartments segmentation is shown in *Figure 1*. TAT area was considered as the sum of VAT, SAT and IMAT areas. Mean muscle attenuation (MA) in HU was automatically calculated by the software after measurement of the skeletal muscle compartment area. Analysis of body composition was repeated on CT-scans performed after the third-fourth cycle (C3) and after the sixth and last cycle (C6) of NAC if applicable. The median duration between diagnosis CT-scan (C0) and interval CT-scan performed after C3 was 103 days (IQR: 83 to 132 days). The median duration between CT-scan at C0 and CT-scan performed after C6 was 170 days (IQR: 154 to 197 days). To account for variation in the exact duration of scan intervals, changes in tissue composition along the course of NAC are expressed as change/100 days.

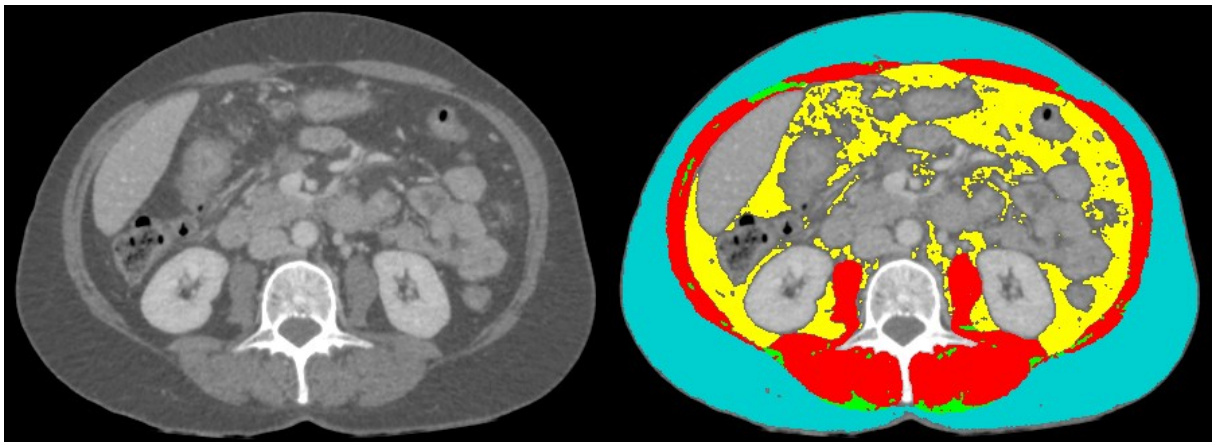
After quantifying skeletal muscle areas, we calculated the estimates for skeletal muscle index (SMI), skeletal muscle volume (SMV), and skeletal muscle mass (SMM) using the previously published formulas (15,18). We also calculated total body fat mass (FM) and total body fat free mass (FFM) using the previously published equations (13). SMM, FM and FFM changes were categorized into loss (decrease <−2%), stable (change between −2% and +2%), or gain (>2% SMM increase).

BMI was dichotomized on the basis of current World Health Organization (WHO) definition: patients were classified as underweight (BMI < 18.5 kg/m2), normal weight (18.5 ≤ BMI < 25 kg/m2), overweight (25 ≤ BMI < 30 kg/m2) and obese (BMI ≥ 30 kg/m2). Sarcopenia was defined on the basis of current “Haute Autorité de Santé” (HAS) definition as a skeletal muscle index <38.5 cm^2/m^2 for any BMI for females. That definition was first established by Prado et al. (19) and was widely used in subsequent publications later on (7,20–22) as these values showed an association with mortality in patients with solid tumors. In accordance with previous publications, low MA was defined as MA <41 HU in patients with a BMI <25 kg/m^2 and <33 HU in those with a BMI ≥25 kg/m^2 (4,23).

Statistical analyses

The women, tumours and treatment characteristics were analysed using Chi-square statistics or Fisher's exact test in case of categorical and the t-test or analysis of variance (ANOVA) for continuous variables. Kaplan-Meier estimates were used to estimate the event-time distributions, and log-rank test was used to compare the differences among the risk groups in terms of recurrence free survival (RFS) and overall survival (OS). We assessed the multivariate effects of covariates with Cox proportional hazards models. Values of $p<0.05$ were considered to denote significant differences. Data were managed with an Excel database (Microsoft, Redmond, WA, USA) and analysed using the R 2.15 software, available online.

Figure 1. Example of muscle and fat compartments segmentation using Slice-O-Matic software



Muscle: -29 to +150 HU **SAT:** -190 to -30 HU **IMAT:** -190 to -30 HU **VAT:** -150 to -50 HU

RESULTS

Characteristics of the study population

During the study period, 53 women with available CT scans who received NAC for advanced EOC (FIGO stage III and IV), were included. 26 women (49%) underwent surgery after 3 to 4 cycles of chemotherapy and 12 patients (22.6%) after 6 cycles. 15 women (28.4%) were not eligible for complete surgery after 6 cycles of NAC. Median follow up was 18 months (IQR: 9-25; range: 4-64). Median age was 68 years (range: 23-84). 33 women (62.3%) were under 70 years. 8 women (15.1%) were premenopausal. Median weight at diagnosis was 64 kg (range: 44-120) and mean weight was 65.8 kg (SD=13.7). 17 patients (32.1%) lost weight during the past 2-6 months: mean weight loss was 5.8 kg (SD=5.6) and median weight loss was 5 kg (range: 2-25). Median BMI was 24.7 kg/m^2 (range: 15.0-39.7); 3 women (5.7%) were underweight, 25 (47.2%) had normal BMI, 17 (32.1%) were overweight and 8 (15.1%) were obese. 21 patients (39.6%) had ascites removal during the study: mean and median quantity of ascites removed was 3.7 litres (range: 0.1-10.5). Regarding tumor histology: 43 women (81.1%) had pure high grade serous ovarian cancer (HGSOC) and 10 (18.9%) had EOC types (2 women had HGSOC mixed with undifferentiated type, 2 had carcinosarcomas, 2 had endometrioid type and 3 had clear cell carcinoma type).

Patient characteristics are presented in *Table 1*.

Baseline body composition parameters

Briefly, 21 women (40%) were already sarcopenic before NAC implementation. At the time of diagnosis, the distribution of sarcopenic women significantly differed according to BMI category (p=0.01): 100% of underweight women, 40% of normal weight and 47.1% of overweight women were sarcopenic and there was no sarcopenic woman in the obese

category. There was no statistical difference in the number of sarcopenic patients according to age above or below 70 years.

37 women (70%) met the criteria for low muscle attenuation at diagnosis. The distribution of women with low MA did not differ significantly according to BMI category (p=0.05): 76% of normal weight, 70.1% of overweight and 75% of obese women were sarcopenic but underweight women had all normal MA.

Baseline body composition parameters are all listed in *table 2*.

Changes in body composition under NAC

Table 3 illustrates the changes in the proportion of sarcopenic women and women with low MA along the course of NAC. Those results underscore a constant increase in the percentage of sarcopenic women from diagnosis (40%) to the end of NAC (55%). When analysing by BMI categories we noticed that this increase mainly concerned normal weight women (40% of sarcopenic women at diagnosis to 70% after NAC completion). There was also an increase in the proportion of women with low MA during NAC. We remind this percentage was already very high at diagnosis (70%) and reached 80% at the end of NAC.

In *table 4* are presented the longitudinal changes in body composition parameters. Between C0 and C3, there was a mean loss of -1.9 cm^2 (-1.3%) in skeletal muscle area, a mean loss of -0.57 kg (-1.19%) in FFM and a mean loss of -0.34 kg (-1.24%) in SMM. In accordance with the previous definition, changes in SMM and FFM were therefore considered stable (loss <2%). However, when analyzing by BMI categories, we highlighted a significant -3.61% (-0.82 kg) loss of SMM and -3.42% (1.41 kg) loss of FFM in obese women. Regarding fat parameters, changes between C0 and C3 were more obvious with a mean loss of -33.7 cm^2 (-10.3%) in TAT area and a mean loss of -1.41 kg (-5.24%) in FM, with as significant loss in all BMI categories for this later parameter.

Changes between C0 and C6 are less important: there was a mean loss of -1.3 cm² (-0.82%) in skeletal muscle area, a mean loss of -0.73 kg (-1.52%) in FFM and a mean loss of -0.23 kg (-0.77%) in SMM. As for fat parameters, there was a mean loss of -6.7 cm² (-0.62%) in TAT area and a loss of 0.28 kg (-0.65%) in FM. Analysis according to BMI categories did not show changes >2% in between C0 and C6 (results not shown).

Outcome

Overall survival tended to be reduced in women with low MA (p=0.07) : 100% versus 70.3% of women alive at the end of follow-up (*figure 2*). Overall survival was significantly different according to FM loss between C0 and C3 (higher loss: 4e quartile versus others; p=0.007) : 100% versus 65.7% of women alive at the end of follow-up (*figure 3*). The difference was also significant (p=0.04) when we used a higher percentage loss of TAT: 100% versus 67.8% of women alive at the end of follow-up (*figure 4*). RFS tended to be different according to percentage of loss of TAT (higher loss :4e quartile versus others) between C0 and C3 (p=0.06) : 51.1% versus 0% of women alive withtout recurrence at the end of follow-up.

Table 1. Patient characteristics

	Total *n* = 53
Age	
median (range), *years*	68 (23-84)
< 70 years, *n* (%)	33 (62.2)
> 70 years, *n* (%)	20 (37.8)
Menopausal status	
premenopausal, *n* (%)	8 (15.1)
Body mass index (kg/m²)	
median (range)	24.7 (15.1-39.7)
underweight (≤ 18.5), *n* (%)	3 (5.7)
normal (18.5-24.9), *n* (%)	25 (47.2)
overweight (25-29.9), *n* (%)	17 (32.1)
obese (≥30.0), *n* (%)	8 (15.1)
Weight at diagnosis (kg)	
median (range)	64 (44-120)
mean (SD)	65.8 (13.7)
Weight loss during the past 2-6 months	
n (%)	17 (32.1)
weight loss median (kg) (range)	5 (2-25)
weight loss mean (kg) (SD)	5.8 (5.6)
Ascites punction	
n (%)	21 (39.6)
median quantity of ascites removed (l) (range)	3.7 (0.1-10.5)
mean quantity of ascites removed (l)	3.7
Histology, *n* (%)	
pure HGSOC	43 (81.1)
other cancer types	10 (18.9)
Treatment, *n* (%)	
surgery after 3-4 cycles of chemotherapy	26 (49.1)
surgery after 6 cycles of chemotherapy	12 (22.6)
non operable at anytime	15 (28.3)
Follow up (months)	
median (IQR)(range)	18 (9-25)(4-64)

HGSOC, high grade serous ovarian cancer; IQR, interquartile range; SD, standard deviation

Table 2. Baseline body composition parameters, values expressed as mean (standard deviation), unless stated otherwise

Characteristic	Total *n* = 53
Muscle parameters	
Skeletal muscle area (cm²)	103.5 (16.9)
Skeletal muscle index (cm²/m²)	40.4 (6.8)
Sarcopenia, *n* (%)	21 (39.6)
underweight, *n* (%)	3 of 3 (100)
normal BMI, *n* (%)	10 of 25 (40)
overweight, *n* (%)	8 of 17 (47.1)
obese, *n* (%)	0 of 8 (0.0)
Estimated FFM (kg)	37.12 (5.0)
Estimated SMM (kg)	20.5 (2.9)
Muscle attenuation (HU)	32.8 (9.8)
Low muscle attenuation, *n* (%)	37 (69.8)
underweight, *n* (%)	0 of 3 (0.0)
normal BMI, *n* (%)	19 of 25 (76)
overweight, *n* (%)	12 of 17 (70.1)
obese, *n* (%)	6 of 8 (75.0)
Fat parameters	
VAT area (cm²)	87.9 (86.5)
VAT index (cm²/m²)	34.5 (33.1)
SAT area (cm²)	199.9 (117.6)
SAT index (cm²/m²)	78.5 (46.5)
TAT index (cm²/m²)	303.7 (194.4)
Estimated FM (Kg)	23.96 (8.17)

FFM, fat free mass; FM, fat mass; SAT, subcutaneous adipose tissue; SMM, skeletal muscle mass; TAT, total adipose tissue; VAT, visceral adipose tissue

Table 3. Changes in the proportion of women with sarcopenia and low MA during NAC

	C0 (n=53)	**C3-C4 (n=53)**	**C6 (n=20)**
Sarcopenia, *n* (%)	21 (39.6)	28 (52.8)	11 (55)
underweight, *n* (%)	3 of 3 (100)	3 of 3 (100)	0 of 0 (0)
normal BMI, *n* (%)	10 of 25 (40)	15 of 25 (60)	7 of 10 (70)
overweight, *n* (%)	8 of 17 (47.1)	10 of 17 (58.8)	4 of 7 (57.1)
obese, *n* (%)	0 of 8 (0.0)	0 of 8 (0.0)	0 of 3 (0)
Low muscle attenuation, *n* (%)	37 (69.8)	38 (71.7)	16 (80)
underweight, *n* (%)	0 of 3 (0.0)	2 of 3 (66.6)	0 of 0 (0)
normal BMI, *n* (%)	19 of 25 (76)	19 of 25 (76.0)	9 of 10 (90)
overweight, *n* (%)	12 of 17 (70.1)	12 of 17 (70.1)	4 of 7 (57.1)
obese, *n* (%)	6 of 8 (75.0)	5 of 8 (62.5)	3 of 3 (100)

C0, at diagnosis (before initiation of NAC); C3-C4, after completion of 3 to 4 cycles of NAC (interval);
C6 after completion of 6 cycles of NAC (end of NAC)

Table 4. Changes in body composition parameters per 100 days between C0 and C3 and between C0 and C6. Changes according to BMI are also shown between C0 and C3.

	Mean change per 100 days	Mean relative change per 100 days (%)
C0 - C3		
Skeletal muscle area (cm²)	−1.90	−1.3
underweight	+0.46	+0.10
normal BMI	−2.13	−1.49
overweight	−0.69	−0.11
obese	−4.71	−4.02
FFM (kg)	−0.57	−1.19
underweight	+0.14	+0.15
normal BMI	−0.64	−1.32
overweight	−0.21	−0.17
obese	−1.41	−3.42
SMM (kg)	−0.34	−1.24
underweight	+0.08	+0.14
normal BMI	−0.37	−1.38
overweight	−0.12	−0.15
obese	−0.82	−3.61
TAT area (cm²)	−33.7	−10.3
underweight	−9.30	−2.91
normal BMI	−25.2	−10.8
overweight	−25.9	−7.17
obese	−85.7	−18.3
FM (kg)	−1.41	−5.24
underweight	−0.39	−2.22
normal BMI	−1.05	−4.65
overweight	−1.09	−3.82
obese	−3.60	−11.2
C0 - C6		
Skeletal muscle area (cm²)	−1.3	−0.82
FFM (kg)	−0.73	−1.52
SMM (kg)	−0.23	−0.77
TAT area (cm²)	−6.7	−0.62
FM (kg)	−0.28	−0.65

C0, at diagnosis (before initiation of NAC); C3, after completion of 3 to 4 cycles of NAC (interval); C6 after completion of 6 cycles of NAC (end of NAC); FFM, fat free mass; FM, fat mass; SMM, skeletal muscle mass; TAT, total adipose tissue;

Figure 2. Overall survival according to muscle attenuation (Kaplan-Meier estimator; p=0.07)

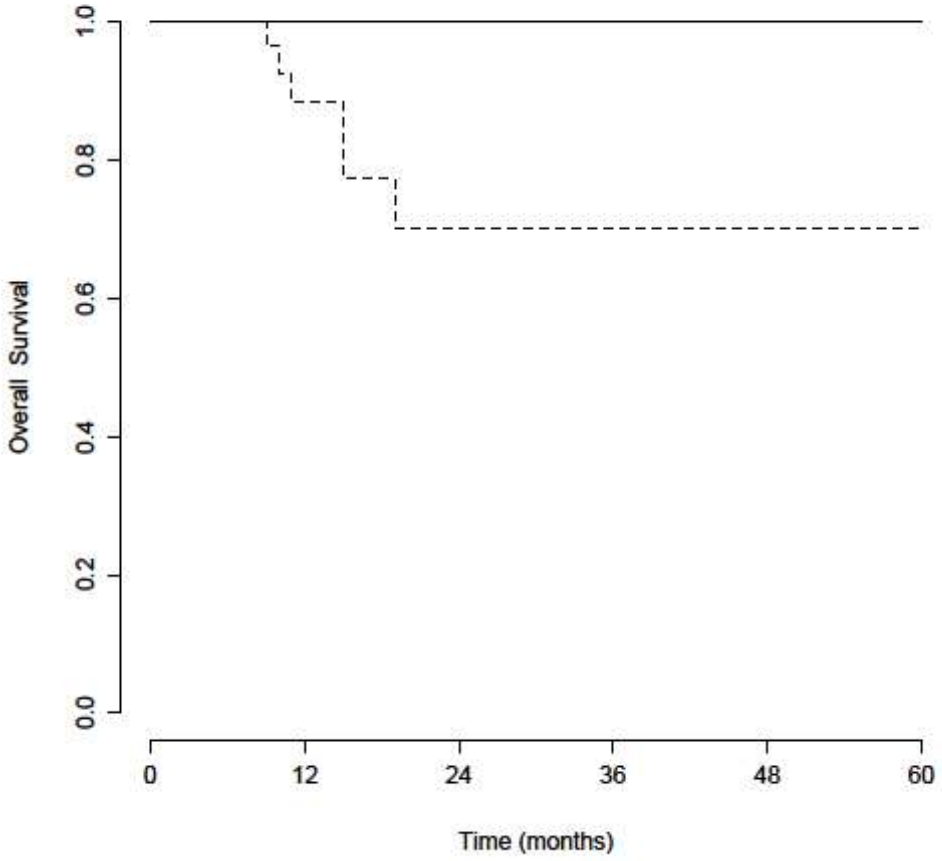


Figure 3. Overall survival according to fat mass loss between C0 and C3 (Kaplan-Meier estimator; p=0.04)

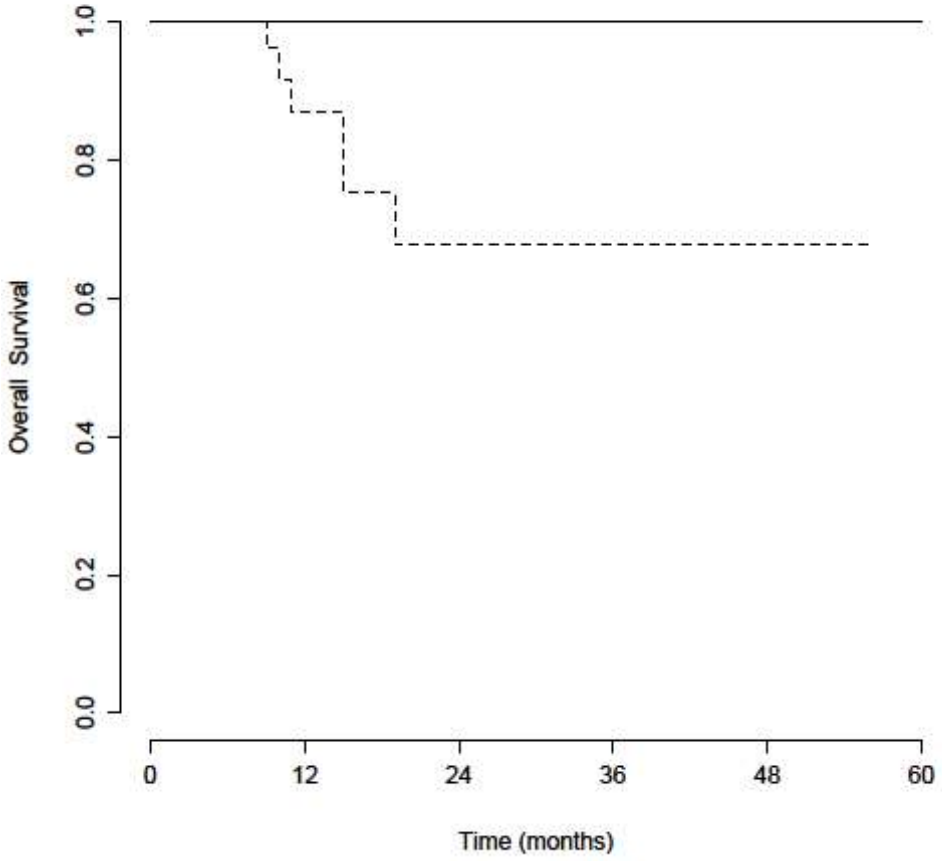


Figure 4. Overall survival according to higher percentage loss of total adipose tissue between C0 and C3 (Kaplan-Meier estimator; p=0.007)

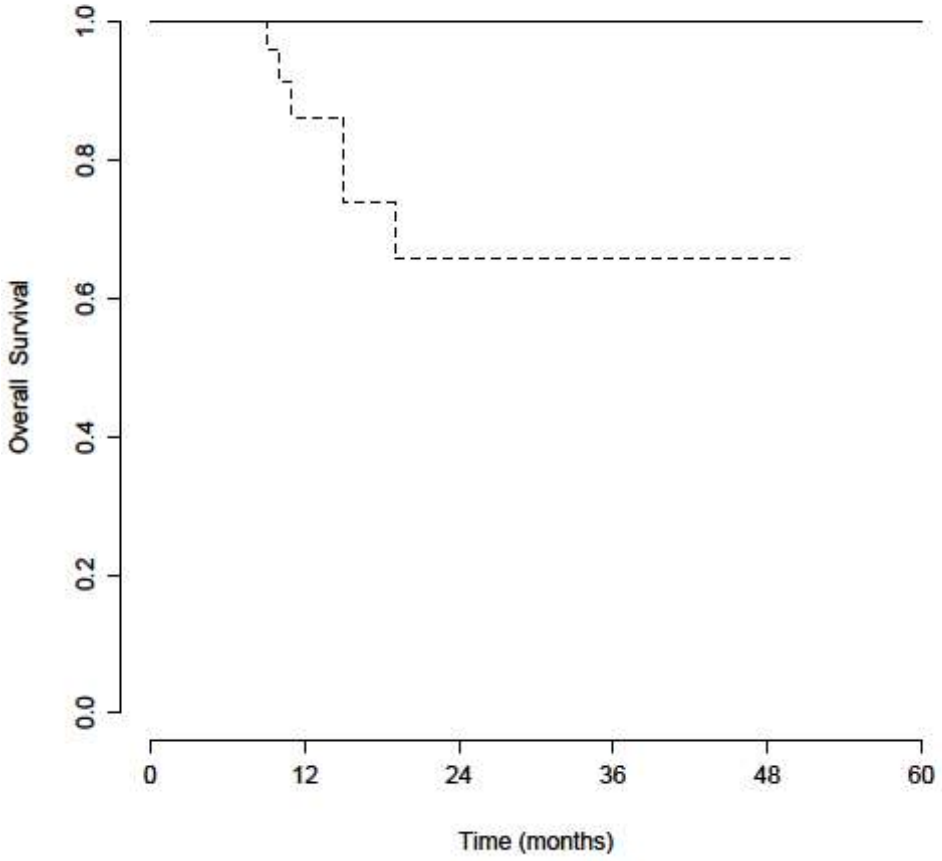
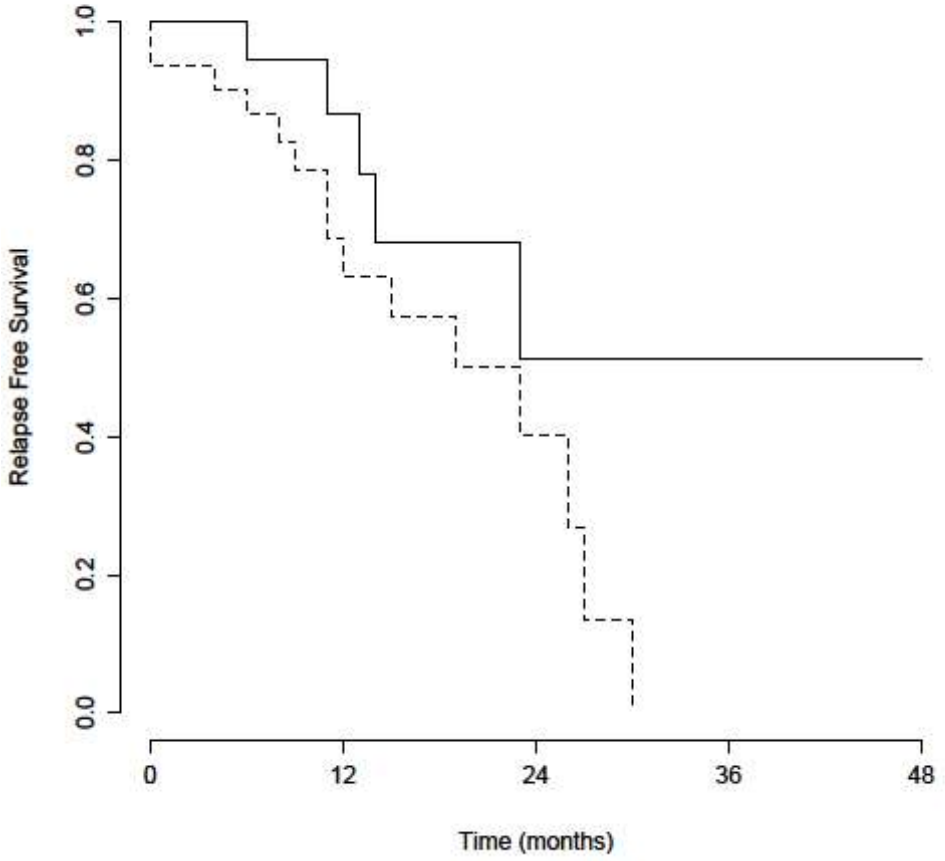


Figure 5. Recurrence free survival according to percentage of loss of total adipose tissue between C0 and C3 (Kaplan-Meier estimator; p=0.06)



DISCUSSION

Our aim was to assess the evolution of body composition parameters using CT images in women treated with neoadjuvant chemotherapy for advanced ovarian epithelial cancer and to evaluate whether these changes had a prognostic impact or not. When studying baseline body composition parameters we first highlited that 40% of women were already sarcopenic before treatment implementation while only 5.7% were considered underweight according to BMI, underlining once again that BMI is not a good indicator of body composition. This is even more true in our study, where women are prone to ascites accumulation that can easily skew weight measurements. Thereby, we notice that 40% of normal weight and 47% of overweight women were actually sarcopenic. It was also intereting to see that, on the contrary, none of the obese women included were sarcopenic at diagnosis nor became sarcopenic during NAC. Ovarian cancers are asymptomatic for a long time and most often discovered at an advanced stage. The women in our cohort all had FIGO III-IV stages of disease and we can imagine that the ovarian malignancy had therefore been promoting a pro-inflammatory state and muscle catabolism pathways for a long time, explaining the high percentage of sarcopenic women at diagnosis. We remind that we choose in this study the 38.5 cm^2/m^2 cut-off to define sarcopenia accordingly with the definition of the French “Haute Autorité de Santé” (High Authority of Health) but the percentage of sarcopenic women could have even been higher if we had decided to choose the 41 cm^2/m^2 cut-off, most often used in Anglo-Saxon publications. That result underscores the highest need for an early and well-conducted nutritional intervention in this category of patients from the very beginning of management. Along the course of NAC, there was a moderate but constant increase in the percentage of sarcopenic women (from 40% at diagnosis, to 53% at C3 and 55% at C6) suggesting that the drugs, doses and protocol used in NAC worsens sarcopenia. This idea is reinforced by the fact

that this increase is clearly found and even more obvious in the normal weight women (40% at diagnosis, 60% at C3 and 70% at C6) which was the most represented BMI category in our study (47.2% of all women). Also, we observed a loss of SMM and FFM during NAC, more marked between C0 and C3, although not significant (<2%) except in the obese women. Thus, altough there were no sarcopenic women in the obese category, obese women are the ones who experienced the higest muscle mass loss and are not protected from sarcopenia occurrence ultimately.

Baseline body composition analysis showed that 70% of women had low MA at diagnosis. Muscle attenuation correponds to the muscle density on CT images measured in HU. It reflects the fatty infiltration of the muscle within the inter- and intra-myocellular spaces on a microscopic scale (24) : muscle density decreases with the increase of its triglyceride content and the term “myosteatosis” is frequently employed to describe this phenomenon. These histological changes in muscle composition can therefore lead to muscle function impairment which in turn causes a decrease in physical activity (25), maintaining a vicious circle of muscle alteration. During NAC, we observed a 10% increase in the percentage of women with low MA (from 70% at C0 to 80% at C6), suggesting that NAC could worsen this phenomenon. Otherwise, OS tended to be reduced in women with low MA. Our findings are consistent with those found in literature : for instance, Van Dijk *et al.* showed in a prospective study that MA is a predictor of survival in patients operated for cancer of the head of the pancreas (26). Rollins at al showed that, in a population of patients with pancreatic cancers or non operable distal chlolangiocarcinomas, low MA was correlated with shorter survival (27). Myosteatosis has also been associated with poor outcome in patients with renal cell carcinomas, melanomas, gastrointestinal and lung tumors (19,23,28).

As to fat parameters, we observed a marked FM loss (-5.24% ; -1.41 kg) between C0 and C3 which was significanltly associated with reduced OS ; RFS also tended to decrease. In

literature, fat loss has been reported in patients treated with neoadjuvant therapy for potentially resectable pancreatic cancer (29) or in patients with locally advanced pancreatic cancer receiving chemoradiation (21). Fat loss has also been associated with poor outcome in the trajectory of cancer (30,31) and we can imagine that this can be explained by the depletion of body energy tanks.

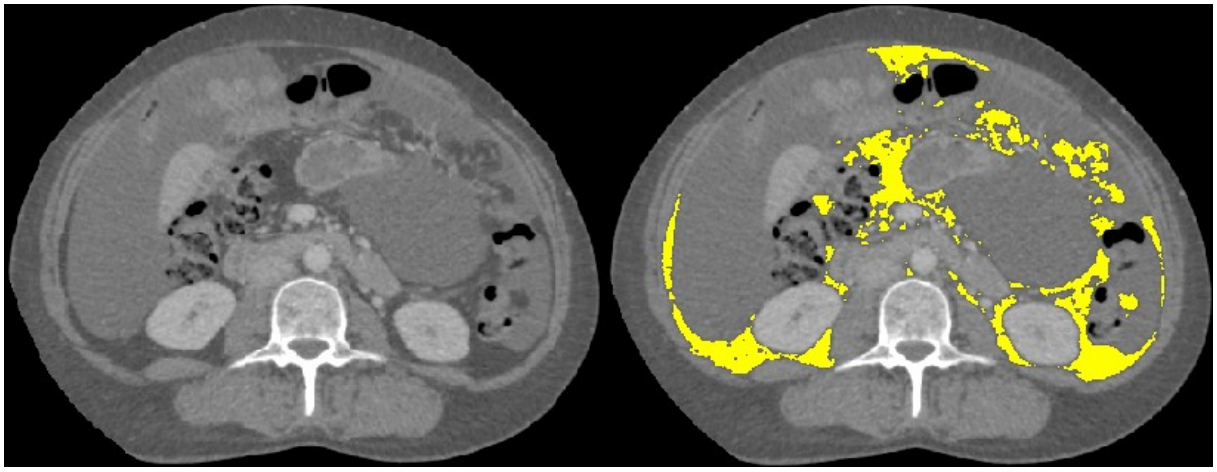
Among the strengths of our work, we can mention the homogeneity and the representativeness of our cohort in several aspects : all patients had advanced stage III-IV FIGO EOC, while publications addressing body composition and oncological outcome often tend to mix cancers types in order to increase the size of the sample studied for better statistical power, leading to generalization issues of the results ; as to treatment, patients all benefited from the same drugs with the same doses and the same protocol for they were all treated in the same center. All measurements were performed by the same observer, reducing measurements variability. Finally, changes in tissue composition over time were normalized and expressed as change/100 days to account for variation in the exact duration of CT-scan intervals.

This study also have limits : its retrospective nature to begin with. After 3-4 cycles of NAC, the size of our sample was highly reduced to only 20 women at 6 cycles. The obese and especially the underweight BMI categories were under-reprenseted with respectively 8 and 3 women included. The presence of abundant ascites on CT images can falsely reduce VAT area measurements. Drying of ascites (due to the therapeutic effect of chemotherapy and/or by manual removal) on subsequent CT examinations leads to volume re-expansion of VAT compartment: it can thus appear on calculations as fat mass stability or even fat gain when compared to previous CT images. An example is shown in *Figure 6*. We remind that in our study, 21 women had manual ascites removal with 3.7 liters of ascites removed in average.

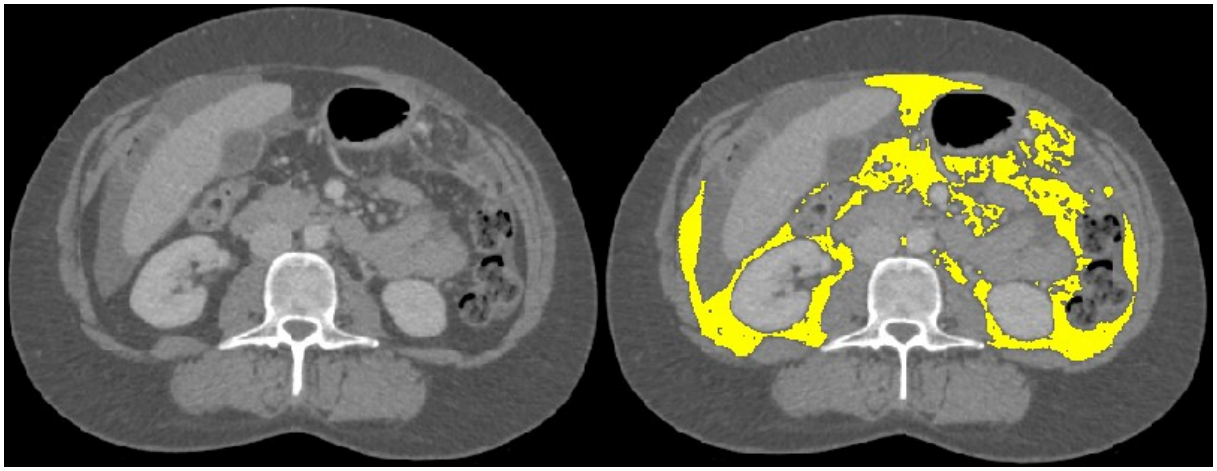
SAT area measurements could also have been plagued with errors linked to skin folds that vary with the positioning of patients when acquiring CT images on different occasions; that point is illustrated in *figure 7*. Some authors have proposed to rigidly align the different scans of a same patient using a fusion method in order to reduce those types of variations (32). Such methods haven't been used in our study and could have helped to improve our measurements quality. For obese patients, SAT was sometimes cut on CT-images, leading once again to measurement biases, as shown in *figure 8*.

In conclusion, this study highlights that in women with advanced EOC, a high percentage are already sarcopenic and have low MA at diagnosis before any treatment. FM loss is observed during the first cycles of NAC and is significantly associated with OS reduction. Although not significant, the SMM loss observed along treatment suggests that NAC have sarcopenic effects, as well as the increase of the percentage of sarcopenic women.

Figure 6. Example of VAT compartment re-expansion after reduction of ascites in time

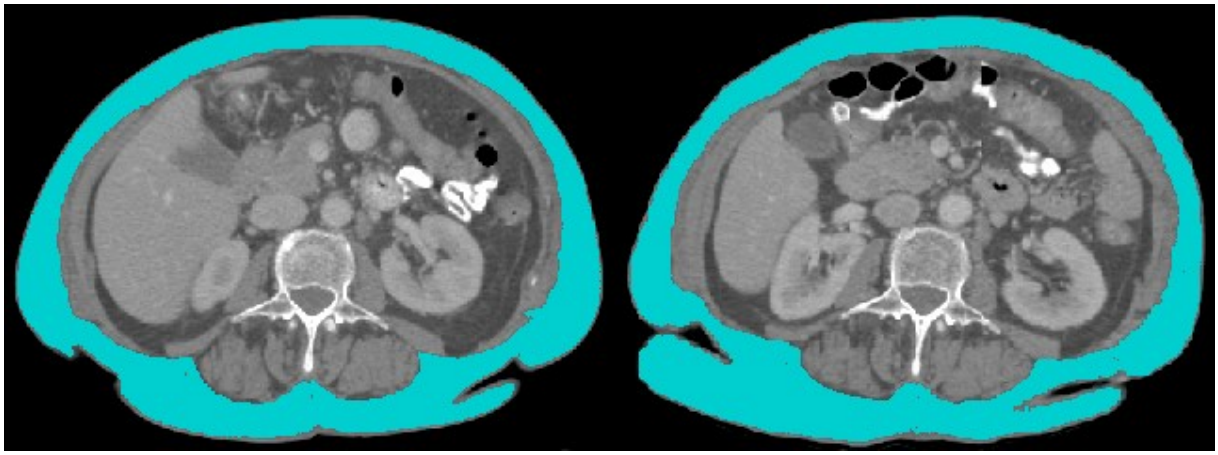


a. VAT area after 3 cycles of NAC is 49.1 cm². Ascites is abundant.



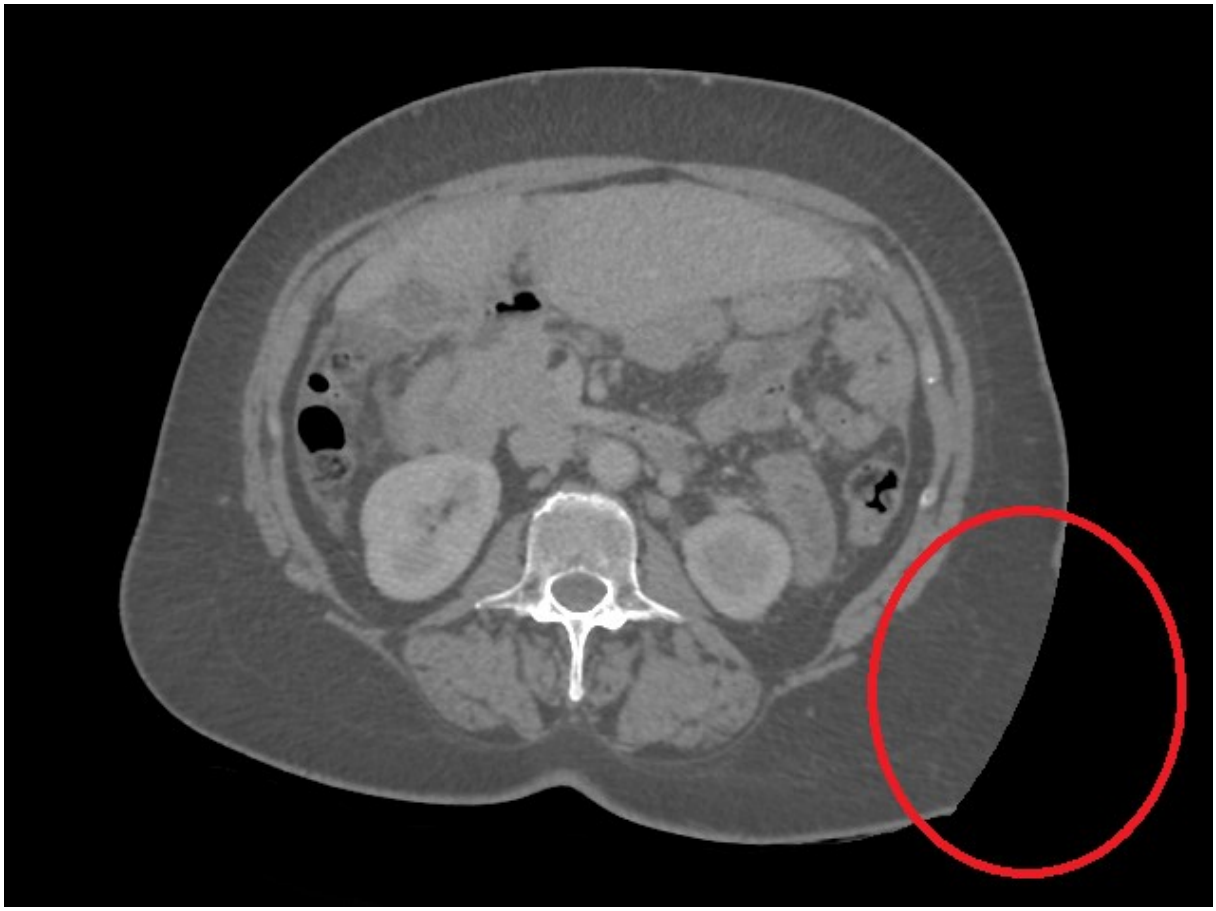
b. After completion of the 6 cycles of NAC, VAT area is now measured 69.7 cm². Ascites volume has reduced, allowing VAT compartment to expand again.

Figure 7. Example of skin folds variations on repetitive CT examinations for the same patient.



Axial CT images acquired at the L3 vertebra at C3 (right) and C6 of NAC (left). SAT area is measured 165.5 cm^2 at C3 and 159.2 cm^2 at C6.

Figure 8. Example of SAT compartment cut on a CT image in an obese patient.



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Declaration of interest

The authors declare that they have no conflicts of interest in connection with this article.

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70 pages – 6 tableaux – 9 figures

Résumé :
La relation entre composition corporelle et pronostic chez les patients atteints de cancers fait l'objet de nombreuses études. L'imagerie est l'outil le plus fiable pour évaluer la distribution des masses musculaire et adipeuse. Au cours de ce travail de thèse, nous nous sommes donnés comme objectifs :
i) D'étudier la reproductibilité intra-observateur de la quantification de la composition corporelle par scanner et d'étudier la reproductibilité inter-observateur entre une personne spécialisée en imagerie et une personne non spécialisée en imagerie.
ii) D'évaluer la valeur pronostique des paramètres de composition corporelle dans une cohorte de patientes atteintes de cancer de l'ovaire et d'apprécier l'évolution de ces derniers sous chimiothérapie néo-adjuvante.
Ainsi il apparait qu'en fonction de l'observateur et du tissu analysé, des erreurs de précision existent dans la quantification de la composition corporelle. Les mesures des surfaces de muscle squelettique, de graisse viscérale et de graisse sous-cutanée montrent les meilleures reproductibilités inter-observateur, à l'inverse de la mesure de surface de graisse inter-musculaire sujette à plus de variations. La variabilité intra-observateur est très basse.
Dans la cohorte étudiée, un pourcentage important de patientes étaient sarcopéniques et présentaient une faible densité musculaire avant tout traitement. Une perte significative de masse adipeuse était observée au cours des premiers cycles de chimiothérapie néo-adjuvante et celle-ci était associée à une réduction de la survie globale. Il était aussi observé une perte non significative de masse musculaire et une augmentation du nombre de patientes sarcopéniques.

Mots clés : Scanner – Composition corporelle – Reproductibilité – Masse adipeuse – Muscle squelettique – Chimiothérapie néo-adjuvante – Cancer épithélial de l'ovaire – Sarcopénie

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