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# Loss of skeletal muscle density during neoadjuvant chemotherapy in older women with advanced stage ovarian cancer is associated with postoperative complications

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ABSTRACT

*Objective:* To assess the association between loss of lumbar skeletal muscle mass and density during neoadjuvant chemotherapy (NACT) and postoperative complications after interval cytoreductive surgery (CRS) in older patients with ovarian cancer.

*Materials and methods:* This multicenter, retrospective cohort study included patients aged 70 years and older with primary advanced stage ovarian cancer (International Federation of Gynecology and Obstetrics stage III-IV), treated with NACT and interval CRS. Skeletal muscle mass and density were retrospectively assessed using Skeletal Muscle Index (SMI) and Muscle Attenuation (MA) on routinely made Computed Tomography scans before and after NACT. Loss of skeletal muscle mass or density was defined as >2% decrease per 100 days in SMI or MA during NACT.

*Results:* In total, 111 patients were included. Loss of skeletal muscle density during NACT was associated with developing any postoperative complication ≤30 days after interval CRS both in univariable (Odds Ratio (OR) 3.69; 95% Confidence Interval (CI) 1.57–8.68) and in multivariable analysis adjusted for functional impairment and WHO performance status (OR 3.62; 95%CI 1.27–10.25). Loss of skeletal muscle density was also associated with infectious complications (OR 3.67; 95%CI 1.42–9.52) and unintended discontinuation of adjuvant chemotherapy (OR 5.07; 95%CI 1.41–18.19). Unlike loss of skeletal muscle density, loss of skeletal muscle mass showed no association with postoperative outcomes.

*Conclusion:* In older patients with ovarian cancer, loss of skeletal muscle density during NACT is associated with worse postoperative outcomes. These results could add to perioperative risk assessment, guiding the decision to undergo surgery or the need for perioperative interventions.



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## 1. Introduction

Forty-seven percent of all new epithelial ovarian cancers are diagnosed in patients aged 70 years and older [1]. The percentage of older patients diagnosed with ovarian cancer has increased over time [2] and due to the ageing population this percentage is expected to increase further in the future. Primary treatment of advanced stage ovarian carcinoma (International Federation of Gynecology and Obstetrics (FIGO) stage III-IV) comprises cytoreductive surgery (CRS), followed by six courses of adjuvant platinum and taxane-based chemotherapy. Neoadjuvant chemotherapy (NACT) with interval CRS is offered if primary CRS is considered not feasible due to extent of disease or poor patient condition [3]. Individual perioperative risk assessment can help clinicians and patients in shared decision making. It contributes to the decision whether or not to undergo surgery, or guide the need for perioperative interventions aiming to improve postoperative outcomes, such as prehabilitation [4].

In several studies among older oncological patients, preoperative low skeletal muscle mass and density have been associated with poor postoperative outcomes and chemotoxicity [5]. In younger patients with ovarian cancer, low preoperative skeletal muscle mass has been associated with adverse postoperative outcomes and mortality [6–9]. In a population of older patients with ovarian cancer, low preoperative skeletal muscle density was found to be associated with adverse postoperative outcomes [10]. Low skeletal muscle density indicates enhanced fat infiltration within muscle and reflects low muscle quality, while low skeletal muscle mass is a surrogate for low muscle quantity [11].

In line with low preoperative skeletal muscle mass and density, loss of skeletal muscle mass during NACT could be a useful marker in predicting adverse treatment outcomes in patients with ovarian cancer [12,13], but current evidence is not unanimous yet [14]. Loss of skeletal muscle mass or density could be target points for prehabilitation, to prevent or minimize loss and decreasing the risk for worse postoperative outcomes. The clinical implications of loss of skeletal muscle density have not yet been assessed in this population. Thus far, studies on loss of skeletal muscle mass and density in an older population with ovarian cancer are lacking.

In this study, we investigated the association between loss of skeletal muscle mass and density during NACT and postoperative outcomes after interval CRS in older patients with advanced ovarian cancer. We hypothesized that patients experiencing loss of skeletal muscle mass or density during NACT suffer from postoperative complications more often than patients who are able to maintain or improve skeletal muscle status.

## 2. Materials and methods

### 2.1. Study design and setting

In this multicenter, retrospective cohort study patients aged ≥70 years who were treated with NACT and interval CRS for primary ovarian carcinoma FIGO stage III or IV were included from three hospitals in the Netherlands (The Netherlands Cancer Institute (NKI), Amsterdam; University Medical Center Groningen (UMCG); and Reinier de Graaf (RDG), Delft). Patient selection in UMCG was based on the local, prospectively registered OncoLifeS [15] database, including patients who consented to participate in OncoLifeS between January 2016 and August 2019. In NKI and RDG, patients receiving interval CRS between January 2014 and January 2017 were selected from the local Dutch Gynecological Oncology Audit (DGOA) databases [16]. Two preoperative CT scans (one before start and one after ≥2 cycles of NACT) had to be available for each patient to be included in the analysis. Patients receiving combined surgery for ovarian cancer and a second malignancy were excluded. The Medical Research Ethics Committee stated that the study was not subject to the Dutch Medical Research Involving Human Subjects Act and local approval was obtained from all participating centers. The study was performed in compliance with the Declaration of Helsinki and Good Clinical Practice guidelines.

### 2.2. Data collection

Data was collected from OncoLifeS, the local DGOA database and the electronic medical records. We registered age, living situation, preoperative American Society of Anesthesiologists (ASA) score [17], preoperative WHO performance status [18], Body Mass Index (BMI), comorbidity using the Charlson Comorbidity Index [19] (applying a cut-off score of ≥2), history of abdominal surgery and polypharmacy (daily use of ≥5 different medicaments). A standardized geriatric risk questionnaire, conducted at hospital admission before surgery of all older patients in the Netherlands, was used to collect 1) patient- or caregiver-reported memory problems or history of confusion during illness or hospital admission [20]; 2) fall risk (≥1 fall incident in the last six months [20]); 3) risk for malnutrition (Short Nutritional Assessment Questionnaire score ≥2 [21] or Malnutrition Universal Screening Tool score ≥1 [22]); 4) functional impairment (score of ≥2 [20] in the Katz Index of Independence in Activities of Daily Living (KATZ-ADL) [23]); and 5) use of a walking aid. We collected tumor histology and grade, FIGO stage, preoperative involvement of a geriatrician, completeness of CRS (no macroscopic residual disease, ≤1 cm residual disease or >1 cm residual disease), performance of bowel surgery, intraoperative blood loss >1000 cc, and intraoperative injury (lesions of the bowel, bladder, ureters or major blood vessels).

#### 2.2.1. Skeletal muscle mass and density

Contrast enhanced abdominal CT scans (in the portal venous phase), performed as part of standard clinical care before and after ≥2 cycles of NACT, were used to determine skeletal muscle mass and density. We extracted transversal slices on the level of the midpoint of L3 from every included CT scan. In this slice, skeletal muscle was manually outlined by an experienced, board-certified radiologist who was blinded for all outcomes. Within these contours, muscle voxels were defined by radiodensity ranging from −29 to +150 Hounsfield Units (HU) [24]. Next, the Skeletal Muscle Index (SMI) was calculated by dividing the total muscle surface area on level L3 by the square of the length of the patient ($cm^2/m^2$) [25]. Skeletal muscle density was defined as the mean Muscle Attenuation (MA) in HU of the muscle voxels in this slice. All CT scan assessments were executed using in-house developed analysis software (SarcoMeas version 0.60) [26].

Low skeletal muscle mass was defined as a SMI <38.50 $cm^2/m^2$, as suggested by a systematic review and meta-analysis on sarcopenia and survival in ovarian cancer [9]. The cut-off for low MA was defined as one standard deviation (SD) below the mean (if normally distributed) or the lowest quartile of MA (if non-normally distributed) [9]. BMI-dependent cut-off points as suggested by Martin et al. [27] could not be applied to our population, since BMI is often influenced by ascites in patients with advanced ovarian cancer.

We assessed changes in SMI and MA between the first and second CT scan. The individual percentage change was divided by the number of days between scans and multiplied by 100 days (percent change per 100 days), because time between CT scans was not equal for all patients [12,28]. Changes between −2% and +2% were determined as maintenance of skeletal muscle mass or density. A measurement error of 2% was used based on previously reported accuracy of CT for muscle and fat tissue analysis [12,28]. Loss/gain of skeletal muscle mass or density was defined as >2%

decrease/increase per 100 days, in line with Rutten et al. [12] and Ubachs et al. [14].

#### 2.2.2. Outcomes

Our primary outcome was any postoperative complication ≤30 days of CRS (i.e. cardiac complications, infections, wound defects, postoperative hemorrhage or hematomas, thromboembolisms, kidney or liver dysfunction, urinary retention, ileus, other systemic complications and death). Intraoperative blood loss, injuries or technical problems were not included as postoperative complication.

The secondary outcome measures composed severe complications (Clavien-Dindo classification ≥ grade 3 [29], including only the complication with the highest grade per patient); infectious complications; postoperative delirium; extended hospital stay (>14 days); discharge to a care facility previously not residing in (indicating functional decline); readmission ≤30 days after discharge; unintentional discontinuation of adjuvant chemotherapy; and 30-day, 6-months and 12-months mortality (calculated from the date of surgery to date of death). Linkage with the Dutch Personal Records Database provided data on mortality. If linkage was not possible, information on mortality was retrieved from the electronic medical records. Patients with inadequate follow-up were not included in the mortality analyses.

### 2.3. Statistical analysis

Differences in baseline characteristics and outcomes between groups with and without loss of skeletal muscle mass or density were compared using a Fisher's exact test for binominal variables, a Fisher-Freeman-Halton exact test for nominal or ordinal data, an unpaired T-test for normally distributed continuous variables or a Mann-Whitney *U* test for not normally distributed continuous variables. Absolute changes between pre- and post-NACT skeletal muscle mass and density were assessed using a Wilcoxon signed-rank test. The association between loss of skeletal muscle mass and density during NACT and the outcome measurements was determined using univariable logistic regression analysis. Multivariable analysis was performed if skeletal muscle mass or density was associated with postoperative complications in univariable analysis.

We considered the following factors that were collected before, during or after NACT as potential confounders: age [30]; comorbidity [31]; polypharmacy [31]; WHO performance status ≥2 [31]; ASA classification [31]; functional impairment [31]; living situation; fall risk; pre-existing memory problems; history of confusion during illness; malnutrition risk; use of a walking aid; and pre-NACT skeletal muscle mass and density. We added performance of bowel surgery and completeness of CRS as measures of surgical complexity. To be included in the multivariable analysis, potential confounders had to be associated with both loss of skeletal muscle density or mass and the outcome ($p < 0.30$) in univariable analysis. Confounders were kept in the model if they altered the regression coefficient of the determinant with more than 10%. Only complete cases were included in the analysis.

Level of statistical significance was defined as $p < 0.05$. all statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS), version 23.0.

## 3. Results

### 3.1. Participants and baseline characteristics

One hundred eleven of the 123 patients that met the inclusion criteria were included in the final analysis. In eleven patients only one CT scan was available and one patient had simultaneous surgery for a second malignancy.

Table 1 shows the baseline characteristics of all included patients distributed by loss of skeletal muscle density. Supplementary table A1 presents the baseline characteristics of all included patients distributed by loss of skeletal muscle mass. Median age at surgery was 76.6 years (IQR 73.6–78.7). Tumor and treatment characteristics were equally distributed between patients with and without loss of skeletal muscle mass or density. Most patients (n = 88; 80%) lived at home without professional care. Fall risk was available for 89 patients (80%), of whom thirteen patients (15%) were known to be at risk for falls. For 80% of patients a KATZ-ADL score was available, and eight patients (9%) had functional impairment. For 59 patients (53%) risk for malnutrition was available, of whom 18 patients (31%) were actually at risk. Use of a walking aid was known for 93 patients, of whom fourteen patients indeed used a walking aid (15%). Five patients (6%) reported pre-existing memory problems and 6% had a history of confusion during illness or hospital admission, which were both known in 90 patients (81%). Twenty-nine patients (26%) had polypharmacy, which differed significantly between patients with and without loss of skeletal muscle density (42% and 19%, respectively).

### 3.2. Skeletal muscle mass and density

Median interval time between CT scans was 66 days (IQR 53–96 days). Table 2 shows median pre-NACT and preoperative skeletal muscle mass and density and the median changes in skeletal muscle mass and density during NACT. In 27 patients (24%), low skeletal muscle density (<26.10 HU, < lowest quartile) was present before the start of NACT. Pre-NACT low skeletal muscle density was not significantly associated with postoperative complications within 30 days after surgery (OR 2.26; 95%CI 0.92–5.55). Thirty-six participants (32%) had a decrease in skeletal muscle density, eight patients (7%) maintained skeletal muscle density, and 67 patients (60%) gained skeletal muscle density during NACT.

Before start of NACT, 50 patients (45%) had a low skeletal muscle mass. Pre-NACT low skeletal muscle mass was not significantly associated with postoperative complications within 30 days after surgery (OR 1.12; 95%CI 0.50–2.53). Seventy-six patients (69%) had a decrease in skeletal muscle mass, 11 patients (10%) maintained skeletal muscle mass, and 24 patients (22%) gained skeletal muscle mass during NACT.

### 3.3. Primary and secondary outcomes

Table 3 shows the incidence of all outcome variables. Thirty-four patients (31%) had a postoperative complication. Twenty-three patients (21%) had one complication, eight patients (7%) had two complications, one patient had three complications and two patients had four complications.

#### 3.3.1. Loss of skeletal muscle density

Table 3 shows the results from univariable and multivariable analysis for loss in skeletal muscle density. Loss of skeletal muscle density during NACT was significantly associated with developing any postoperative complication within 30 days after surgery both in univariable (OR 3.69; 95%CI 1.57–8.68) and in multivariable analysis (OR 3.62; 95%CI 1.27–10.25) adjusted for KATZ-ADL ≥2 and WHO performance status ≥2. Loss of skeletal muscle density was also associated with the secondary outcomes infectious complications within 30 days (OR 3.67; 95%CI 1.42–9.52) and unintended discontinuation of adjuvant chemotherapy (OR 5.07; 95%CI 1.41–18.19) in univariable analysis. Because of the low frequency of events, multivariable analysis of the secondary outcome measures was not performed.

**Table 1**
Characteristics of patients included in the analysis for loss of skeletal muscle density during neoadjuvant chemotherapy.

| Patient/treatment characteristics | Patient group[a] | | *p*-value |
|---|---|---|---|
| | Loss of Skeletal Muscle Density[b] (n=36) | No loss of Skeletal Muscle Density (n=75) | |
| Age in years (median; IQR) | 76.6 (72.9–79.2) | 76.3 (74.0–78.3) | 0.97 |
| Living situation (n=110) | | | 0.83 |
| *Independent at home* | 28 (77.8) | 60 (81.1) | |
| *At home with help* | 7 (19.4) | 11 (14.9) | |
| *Care facility* | 1 (2.8) | 3 (4.1) | |
| Charlson Comorbidity Index ≥2[c] | 9 (25.0) | 25 (33.3) | 0.51 |
| History of abdominal surgery | 24 (66.7) | 42 (56.0) | 0.31 |
| Body Mass Index (median; IQR) | 24.5 (22.3–28.3) | 23.7 (21.9–25.7) | 0.16 |
| Polypharmacy[d] | 15 (41.7) | 14 (18.7) | **0.02** |
| ASA classification[e] | | | 0.77 |
| *1* | 7 (19.4) | 13 (17.3) | |
| *2* | 21 (58.3) | 49 (65.3) | |
| *3* | 8 (22.2) | 13 (17.3) | |
| Pre-NACT Low Skeletal Muscle Density[f] | 8 (22.2) | 19 (25.3) | 0.82 |
| Pre-NACT Low Skeletal Muscle Mass[g] | 15 (41.7) | 35 (46.7) | 0.69 |
| Preoperative Low Skeletal Muscle Density[h] | 18 (50.0) | 9 (12.0) | **<0.001** |
| Preoperative Low Skeletal Muscle Mass[g] | 24 (66.7) | 44 (58.7) | 0.53 |
| Fall risk | 6 (16.7) | 7 (9.3) | 0.49 |
| *Missing* | 6 (16.7) | 16 (21.3) | |
| KATZ-ADL ≥2 | 4 (11.1) | 4 (5.3) | 0.58 |
| *Missing* | 7 (19.4) | 15 (20.0) | |
| Risk for malnutrition | 6 (16.7) | 12 (16.0) | 0.45 |
| *Missing* | 14 (38.9) | 38 (50.7) | |
| History of confusion during illness or hospital admission | 0 (0.0) | 5 (6.7) | 0.29 |
| *Missing* | 6 (16.7) | 15 (20.0) | |
| Pre-existing memory problems | 0 (0.0) | 5 (6.7) | 0.29 |
| *Missing* | 6 (16.7) | 15 (20.0) | |
| Use of walking aid | 4 (11.1) | 10 (13.3) | 0.53 |
| *Missing* | 4 (11.1) | 14 (18.7) | |
| WHO performance status (n=106)[i] | | | 0.37 |
| *0* | 30 (83.3) | 49 (70.0) | |
| *1* | 4 (11.1) | 9 (12.9) | |
| *2* | 1 (2.8) | 9 (12.9) | |
| *3* | 1 (2.8) | 3 (4.3) | |
| FIGO stage | | | 0.67 |
| *III* | 25 (69.4) | 48 (64.0) | |
| *IV* | 11 (30.6) | 27 (36.0) | |
| Tumor grade (n=106) | | | 0.16 |
| *Well differentiated* | 0 (0.0) | 3 (4.3) | |
| *Moderately differentiated* | 0 (0.0) | 3 (4.3) | |
| *Poorly differentiated* | 35 (97.2) | 64 (91.4) | |
| *Undifferentiated* | 1 (2.8) | 0 (0.0) | |
| Tumor histology (n=108) | | | |
| *Serous* | 35 (100.0) | 71 (97.3) | 1.00 |
| *Endometrioid* | 0 (0.0) | 1 (1.4) | 1.00 |
| *Mixed epithelial* | 0 (0.0) | 1 (1.4) | 1.00 |
| Number of cycles of NACT (median; IQR) | 3.0 (3.0–4.0) | 3.0 (3.0–3.3) | 0.74 |
| Involvement of geriatrician preoperatively | 2 (5.6) | 5 (6.7) | 1.00 |
| Result of cytoreductive surgery | | | 0.81 |
| *No residual disease* | 15 (41.7) | 30 (40.0) | |
| ≤1 cm *residual disease* | 15 (41.7) | 28 (37.3) | |
| >1 cm *residual disease* | 6 (16.7) | 17 (22.7) | |
| Bowel surgery | 7 (19.4) | 11 (14.7) | 0.59 |
| Intraoperative blood loss >1000 cc | 6 (16.7) | 17 (22.7) | 0.62 |
| Intraoperative injury | 2 (5.6) | 4 (5.3) | 1.00 |
| Days between CT scans (median; IQR) | 68.0 (54.0–100.3) | 65.0 (52.0–88.0) | 0.42 |

IQR = Inter Quartile Range; SD = Standard Deviation; ASA = American Society of Anesthesiologists; NACT = Neoadjuvant Chemotherapy; KATZ-ADL = Six-item Katz Index of Independence in Activities of Daily Living; FIGO = International Federation of Gynecology and Obstetrics.
Boldface data are statistically significant. Missing patients were included in the analysis if missing n >5. If a variable has ≤5 missing values, the number presented behind a variable represents the number of patients included in this analysis.

[a] Number (valid %) of patients, unless indicated otherwise.
[b] Loss of skeletal muscle density is defined as >2% decrease per 100 days in skeletal muscle density during neoadjuvant chemotherapy [12,14].
[c] A high Charlson Comorbidity Index (CCI) was defined as a score ≥2.
[d] Polypharmacy was defined as the daily use of ≥5 different medicines.
[e] The ASA classification (measured before surgery) ranges for 1 to 6, with higher scores indicating a worse physiological status and a higher operative risk [17].
[f] Low pre-NACT skeletal muscle density is defined as a mean Muscle Attenuation (MA) <26.10 HU (lowest quartile).
[g] Low skeletal muscle mass is defined as a skeletal muscle index (SMI) <38.50 $cm^2/m^2$ [9].
[h] Low preoperative skeletal muscle density is defined as a mean Muscle Attenuation (MA) <26.36 HU (lowest quartile).
[i] The WHO/ECOG performance status (measured before surgery) ranges from 0 to 4, with higher scores indicating a worse level of functioning [18].

**Table 2**
Changes in skeletal muscle mass and density during neoadjuvant chemotherapy[a]

| | Pre-NACT (baseline) | Post-NACT[b] (preoperative) | Absolute change between pre- and post-NACT | *p*-value[c] | Percent change per 100 days between pre- and post-NACT |
|---|---|---|---|---|---|
| Skeletal Muscle Density (MA in HU) | 30.2 (26.1–35.1) | 32.1 (26.4–37.6) | 1.60 (−1.8-5.2) | **0.004** | 6.3 (−7.1-27.6) |
| Skeletal Muscle Mass (SMI in $cm^2/m^2$) | 39.1 (36.3–43.1) | 37.2 (34.7–40.5) | −1.8 (−3.7-0.2) | **<0.001** | −6.0 (−14.6-1.1) |

NACT = Neoadjuvant Chemotherapy; MA = Muscle Attenuation; HU = Hounsfield Units; IQR = Inter Quartile Range; SMI = Skeletal Muscle Index.
[a] All values represent median (IQR).
[b] After ≥2 courses of neoadjuvant chemotherapy.
[c] Wilcoxon signed-rank test for absolute change between pre and post NACT skeletal muscle mass or density.

**Table 3**
Results from univariable and multivariable analysis of the primary and secondary outcomes for loss of skeletal muscle density during neoadjuvant chemotherapy.

| Outcome | Number of events | Univariable Analysis | | | Multivariable Analysis[a] (n=85) | | |
|---|---|---|---|---|---|---|---|
| | Total cohort (n=111) n (%) | Odds Ratio | 95% Confidence Interval | *p*-value | Odds Ratio | 95% Confidence Interval | *p*-value |
| Any postoperative complication within 30 days | 34 (30.6) | 3.69 | 1.57-8.68 | **0.003** | 3.62 | 1.27-10.25 | **0.02** |
| Severe complications[b,c] | 10 (9.0) | 1.44 | 0.38-5.45 | 0.59 | | | |
| Infectious complications[c] | 23 (20.7) | 3.67 | 1.42-9.52 | **0.007** | | | |
| Postoperative delirium | 6 (5.4) | 4.56 | 0.80-26.19 | 0.09 | | | |
| Extended length of hospital stay (>14 days) | 9 (8.1) | 0.57 | 0.11-2.90 | 0.50 | | | |
| Discharge to care facility without living there preoperatively | 10 (9.0) | 0.26 | 0.61-8.37 | 0.22 | | | |
| Readmission within 30 days | 4 (3.6) | 2.15 | 0.29-15.89 | 0.45 | | | |
| 30-day mortality | 0 (0.0) | NA | NA | NA | | | |
| 6-month mortality | 6 (5.4) | 1.04 | 0.18-5.98 | 0.96 | | | |
| 12-month mortality (n=105) | 19 (18.1) | 0.67 | 0.22-2.03 | 0.60 | | | |
| Unintentional discontinuation of adjuvant chemotherapy | 12 (10.8) | 5.07 | 1.41-18.19 | **0.01** | | | |

NA = Not Applicable.
Boldface data are statistically significant. If a variable has missing values, the number presented behind an outcome variable represents the number of patients included in this analysis.
[a] Multivariable analysis adjusting for KATZ-ADL ≥2 and WHO performance status ≥2.
[b] Complications ≥ Clavien-Dindo grade 3.
[c] Also included in 'any postoperative complication within 30 days'.

### 3.3.2. Loss of skeletal muscle mass

Supplementary table A2 shows the results of univariable analysis for loss of skeletal muscle mass. Loss of skeletal muscle mass during NACT was not associated with development of any postoperative complications within 30 days after surgery (OR 1.42; 95%CI 0.58–3.47), nor with any of our secondary outcome measurements.

## 4. Discussion

To the best of our knowledge this is the first study to evaluate the relation between loss of skeletal muscle density and post-operative complications in patients with interval CRS after NACT in ovarian cancer. Single measured preoperative low skeletal muscle density has been shown to be more strongly associated with negative outcomes than low skeletal muscle mass in gynecologic cancer [6] [–] [10]. Only one recent study evaluated the change in skeletal muscle density during NACT for ovarian cancer [32]. This retrospective cohort study reported that skeletal muscle density significantly increased during NACT, while SMI significantly decreased. These findings are in line with our study. We were able to additionally assess the impact of loss of skeletal muscle mass and density on postoperative outcomes.

Sarcopenia and cachexia are frequent problems in older patients with cancer [5]. It is difficult to distinguish between sarcopenia and cancer cachexia with CT measurements only, since both conditions overlap in diagnostic criteria as assessed using CT. The definition of sarcopenia focusses on low muscle strength with reduced muscle quality or quantity and/or low physical performance [33]. Cancer cachexia is defined as ongoing muscle wasting with or without loss of fat mass [34]. Preoperative low skeletal muscle density is associated with both the inflammatory and the nutritional component of cachexia [35] and evidence suggests that skeletal muscle density may be of equal or greater value than skeletal muscle mass in assessing cachexia [36]. Thus, loss of skeletal muscle density during NACT might reflect ongoing sarcopenia as well as cancer cachexia, although both conditions cannot be diagnosed without clinical

assessments.

Even though the underlying mechanisms of sarcopenia and cachexia differ, current treatment strategies have similar goals: to improve muscle mass, muscle function, patient function and physical performance [5]. Therefore, loss of skeletal muscle density during NACT could be treated similarly in a prehabilitation program containing at least physical exercise and adequate protein intake. To design an effective prehabilitation program, it is highly relevant to identify patients at risk for skeletal muscle density loss (in another way than using pre-NACT low skeletal muscle density) and to investigate how to achieve muscle density maintenance or gain during chemotherapy in future studies. These studies should incorporate measures on quality of life, physical exercise and food intake. We hypothesize that the increase of skeletal muscle density during NACT could be caused by improved physical condition after start of chemotherapy. It is well known among clinicians that patients with ovarian cancer often feel better after the first cycle(s) of chemotherapy, due to tumor response and loss of ascites. A quality of life analysis comparing primary cytoreductive surgery versus neoadjuvant chemotherapy also showed that after three cycles of NACT various symptoms, for example appetite loss and pain, improved [37]. This can make patients feel better, eat better and exercise more. Currently, two clinical trials, the PADOVA trial and the TRAINING-Ovary 01 trial, are investigating prehabilitation during NACT in patients with ovarian cancer [38,39]. It would be very interesting to additionally assess loss of skeletal muscle density in relation to prehabilitation and outcomes within these trials as well.

This study is the first study to investigate the effect of loss of skeletal muscle mass and density in a cohort consisting exclusively of older patients with advanced stage ovarian cancer receiving interval CRS, thus a population with an elevated surgical risk. It is of added value that we have identified a preoperative risk factor. Future studies on prehabilitation programs to lower the risk for postoperative complications could further investigate which patients are prone for muscle density loss, how to prevent decline in skeletal muscle density and whether this is effective in preventing postoperative complications. Furthermore, we used the same method to define loss of skeletal muscle mass and density as the largest of the three currently available studies [12] [–] [14] on CT-measured changes in body composition among patients treated with NACT for ovarian cancer, facilitating the ability to compare results. Also, all CT measurements were executed by a board certified radiologist with extensive experience [26]. Lastly, complications can negatively impact quality of life and functional status. Since older patients often prevail preservation of independence over improved survival [40], we studied a highly relevant primary outcome for these patients.

Nevertheless, this study has some limitations. Since CT protocols were not completely standardized for this study, slight variation in contrast enhancement could be present between the different hospitals. However, since all scans were acquired in the portal venous phase, only minimal influence on skeletal muscle density is expected [41]. Due to retrospective data collection we also encountered missing data in some baseline characteristics and secondary outcomes. Next, we could not further elaborate the relationship between loss of skeletal muscle density and discontinuation of adjuvant chemotherapy in multivariable analysis due to the small number of events. It would be of interest to evaluate this outcome in larger studies. Additionally, confounders adjusted for in the multivariable analysis were assessed during the preoperative phase, mostly during or after NACT. We considered those suitable to represent pre-NACT frailty, however changes during the preoperative phase cannot be excluded. Furthermore, pre-NACT skeletal muscle density showed no association with loss of skeletal muscle density ($p > 0.30$) and was therefore not included in the multivariable analysis, while this theoretically could have affected the extend of change in skeletal muscle density during NACT. This influence is possibly diluted by a ground effect of patients with low pre-NACT skeletal muscle density. This could have reduced the association between loss of skeletal muscle density and postoperative complications we found. Lastly, patients who did not receive CRS after NACT were not included in the current study. To extrapolate our results to all patients for whom interval CRS is considered, this subgroup should be included in future studies.

## 5. Conclusions

Loss of skeletal muscle density during NACT for ovarian cancer in older patients is associated with occurrence of postoperative complications after CRS and discontinuation of adjuvant chemotherapy. Further research should elaborate which patients lose, maintain, or gain skeletal muscle density during NACT and how this is affected, with the ultimate goal to develop successful prehabilitation strategies to improve surgical outcomes.

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## CRediT authorship contribution statement

**Vera van der Zanden:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Neeltje J. van Soolingen:** Conceptualization, Methodology, Validation, Formal analysis, Investigation, Data curation, Writing – original draft, Writing – review & editing, Visualization, Project administration. **Alain R. Viddeleer:** Conceptualization, Methodology, Validation, Software, Investigation, Writing – review & editing. **Johannes W. Trum:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision. **Frédéric Amant:** Writing – review & editing. **Marian J.E. Mourits:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision. **Johanneke E.A. Portielje:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision. **Astrid Baalbergen:** Resources, Writing – review & editing. **Esteban T.D. Souwer:** Conceptualization, Methodology, Validation, Writing – review & editing. **Barbara C. van Munster:** Conceptualization, Methodology, Validation, Writing – review & editing, Supervision.

## Declaration of competing interest

None.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejso.2021.10.015.

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