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Original Research

Can radiomics help to predict skeletal muscle response to chemotherapy in stage IV non-small cell lung cancer?

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Abstract ***Background:*** Muscle depletion negatively impacts treatment efficacy and survival rates in cancer. Prevention and timely treatment of muscle loss require prediction of patients at risk. We aimed to investigate the potential of skeletal muscle radiomic features to predict future muscle loss.
Methods: A total of 116 patients with stage IV non-small cell lung cancer included in a randomised controlled trial (NCT01171170) studying the effect of nitroglycerin added to paclitaxel-carboplatin-bevacizumab were enrolled. In this post hoc analysis, muscle cross-sectional area and radiomic features were extracted from computed tomography images obtained before initiation of chemotherapy and shortly after administration of the second cycle. For internal cross-validation, the cohort was randomly split in a training set and validation set 100 times. We used least absolute shrinkage and selection operator method to select features that were most significantly associated with muscle loss and an area under the curve (AUC) for model performance.
Results: Sixty-nine patients (59%) exhibited loss of skeletal muscle. One hundred ninety-three features were used to construct a prediction model for muscle loss. The average AUC was 0.49 (95% confidence interval [CI]: 0.36, 0.62). Differences in intensity and texture radiomic features over time were seen between patients with and without muscle loss.

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Conclusions: The present study shows that skeletal muscle radiomics did not predict future muscle loss during chemotherapy in non-small cell lung cancer. Differences in radiomic features over time might reflect myosteatosis. Future imaging analysis combined with muscle tissue analysis in patients and in experimental models is needed to unravel the biological processes linked to the radiomic features.

1. Introduction

Cachexia is a frequently observed phenomenon of skeletal muscle and adipose tissue depletion among patients with non-small cell lung cancer (NSCLC) [1,2]. The progressive loss of muscle has a devastating impact on the quality of life [3] and survival rates in patients with NSCLC [2,4–6]. Although both muscle and fat become depleted, there is evidence that body fat is lost more rapidly than muscle [7,8]. Cancer may therefore shift lipid metabolism to a catabolic state, which in turn may affect skeletal muscle. In cancer, depletion of subcutaneous fat is driven by increased lipolysis [9,10]. Experimental research has shown that lipolysis generates fatty acids which are able to transport into myocytes and stimulate protein degradation [11]. Indeed, skeletal muscle of patients with cancer contained more intramyocellular fat than age- and gender-matched controls [12]. However, there are currently no (non-invasive) biomarkers available to predict muscle loss.

Radiomics is a method that quantitatively extracts features, including shape, size, intensity and texture, that are related to pathophysiology, from standard-of-care medical images [13–17]. Until now, radiomics has mainly been applied to extract tumour features in oncologic patients to visualise tumour heterogeneity [17] and to assess prognosis [18–20]. Besides quantitative evaluation of Hounsfield units, radiomics also explores patterns. Given the quantitative and qualitative differences in skeletal muscles of cachectic patients, radiomics might be helpful to predict future muscle loss. Therefore, the primary goal of this exploratory study is to investigate whether baseline skeletal muscle radiomic features are different between patients who develop muscle loss and those who maintain their muscle mass after chemotherapy. We furthermore investigated longitudinally if muscle loss is associated with changes in muscle radiomic features.

2. Material and methods

2.1. Patient cohort

Computed tomography (CT) scans derived from the multicentre randomised phase II trial (NVALT12 trial, NCT01171170) were investigated. In this trial, the effect of nitroglycerin added to paclitaxel-carboplatin-bevacizumab, on progression-free survival in chemotherapy-naïve stage IV non-squamous NSCLC patients was investigated. The methodology and results of this trial have been published previously [21].

2.2. Image analysis

CT scans made at baseline and after the second cycle of chemotherapy, as part of a secondary end-point, were used [22]. To evaluate whether or not patients lost skeletal muscle, cross-sectional measurements of skeletal muscle areas were made on transverse images at the third lumbar level using Slice-O-matic software, version 5.0 (Tomovision, Montreal, Canada). One slice at the third lumbar level in each scan was selected for each patient. During anatomical land marking, the first image at the third lumbar level with both vertebral transverse processes clearly visible was used for analysis. Skeletal muscle cross-sectional area was quantified on the basis of pre-established thresholds of Hounsfield units (−29 to 150). Boundaries were corrected manually when necessary. It is of note that this delineation excludes intramuscular fat. Changes in muscle cross-sectional areas between CT scans were expressed as a percentage. A measurement error of 1.3% was adopted, based on previous reported literature [2,4]. Changes greater than or equal to −1.3% were considered as 'loss of skeletal muscle', while changes less than −1.3% were considered 'maintenance of skeletal muscle'. In addition, the mean Hounsfield units of the muscle cross-sectional area (CSA) were assessed, as a measure for muscle fat deposits. Low values reflect increased muscle fat.

Then, to evaluate radiomic features, skeletal muscle cross-sectional area was delineated at the third lumbar level using the same thresholds of Hounsfield units as described previously. Now, it was extended one slice in the cranial direction and one slice in the caudal direction using Mirada software (Mirada Medical, Oxford, UK), to be able to calculate three-dimensional image features. Segmentation for radiomics was a semi-automatic process which was manually adjusted if needed. Image features were calculated on both baseline and follow-up scans, using an adapted version of computational environment for radiotherapy research extended with in-house developed radiomic image analysis software

(Matlab 2014a; The Mathworks, Natick, MA). Before the extraction of features, a grey-level discretisation using a bin width of 25 Hounsfield units was applied. To minimise the possible effect of the variation in image parameters, all scans were resampled to a voxel size of $1 \times 1 \times 3$ mm^3 using a cubic interpolation as recommended in the study by Larue et al. [23]. Although collection of the CT scans was predefined in the clinical trial, the analysis of muscle mass and radiomics was not part of the pre-registered outcomes of the original trial. Because of this well-defined randomised patient cohort, with CT scans executed according to study protocol—predefined time points, this was an appropriate data set to explore our hypothesis.

2.3. Radiomic feature selection and statistics

Intensity and texture features were analysed. Shape and size features were excluded because the volumes of interest has been segmented manually, which might influence the outcome of these feature categories. In addition, a three-dimensional wavelet transformation was applied to the CT scan to create filtered, next to the unfiltered intensity and texture features. Features without a range (i.e. features with an exact similar value in all patients), which were not able to discriminate patients, were excluded.

Spearman's correlation coefficient (ρ) was used to assess the correlation between all texture and intensity radiomic features. Of each feature pair with $\rho > 0.85$, the feature that was strongest correlated to all other features was excluded. This process was repeated until no feature pair with all $\rho > 0.85$ was remaining.

To calculate to which extent the variation among the radiomic features on baseline scans is explained by muscle loss, a logistic least absolute shrinkage and selection operator (LASSO) regression model adopting a 100-fold Monte Carlo cross-validation in Matlab 2017b was applied (The Mathworks, Natick, MA).

The cohort was randomly split into a training set (approximately two-third) and a validation set (approximately one-third). Patients were randomised such that the ratio between patients with and without skeletal muscle loss was similar in each group. Features in the training and validation sets were standardised by subtracting the respective mean feature value in the training set and dividing by the feature standard deviation in the training set. The logistic LASSO model was used to reduce the number of features and estimate regression coefficients for the remaining features. The model-intrinsic parameter λ was estimated using an internal fivefold cross-validation on the training set. The out-of-sample area under the curve (AUC) of the receiver operating characteristic curve (ROC) was computed on the validation set to assess the prognostic power. This process was repeated 100 times, each time with a different randomisation of the patients into training and validation sets, and the average AUC over the hundred different models was calculated. This analysis was carried out for the radiomic texture and intensity features of the baseline scan and for the absolute difference in feature values between the baseline scan and the follow-up scan (delta features). For all radiomic features that were selected at least once in the LASSO feature selection procedure, the difference in feature value between patients with and without muscle loss was compared by plotting a heatmap. For the heatmap, all radiomic features were normalised to have values between 0 and 1. A hierarchical clustering was applied on the same heatmap to identify clusters of patients with different radiomic texture and intensity values.

3. Results

3.1. Patients and characteristics

In total, 223 patients were enrolled in the randomised controlled trial. One hundred three patients were excluded because of unavailability of one or both CT scans, two patients were excluded because L3 was not evaluable, one patient was excluded because of lacking overall survival (OS) data and one was excluded for insufficient quality of the scans. After exclusion, CT scans from 116 patients were eligible. The mean age was

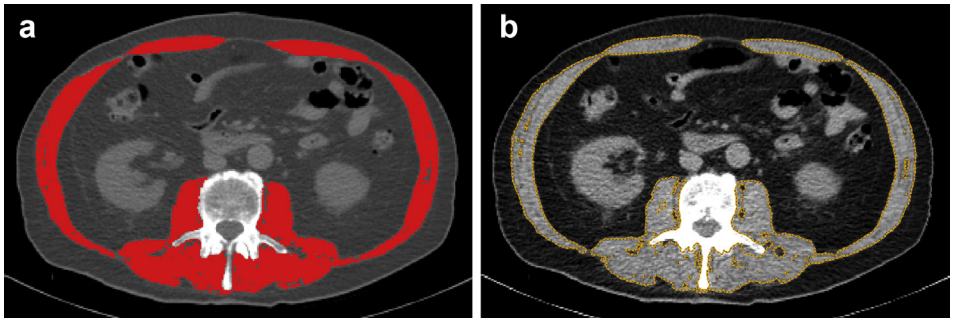
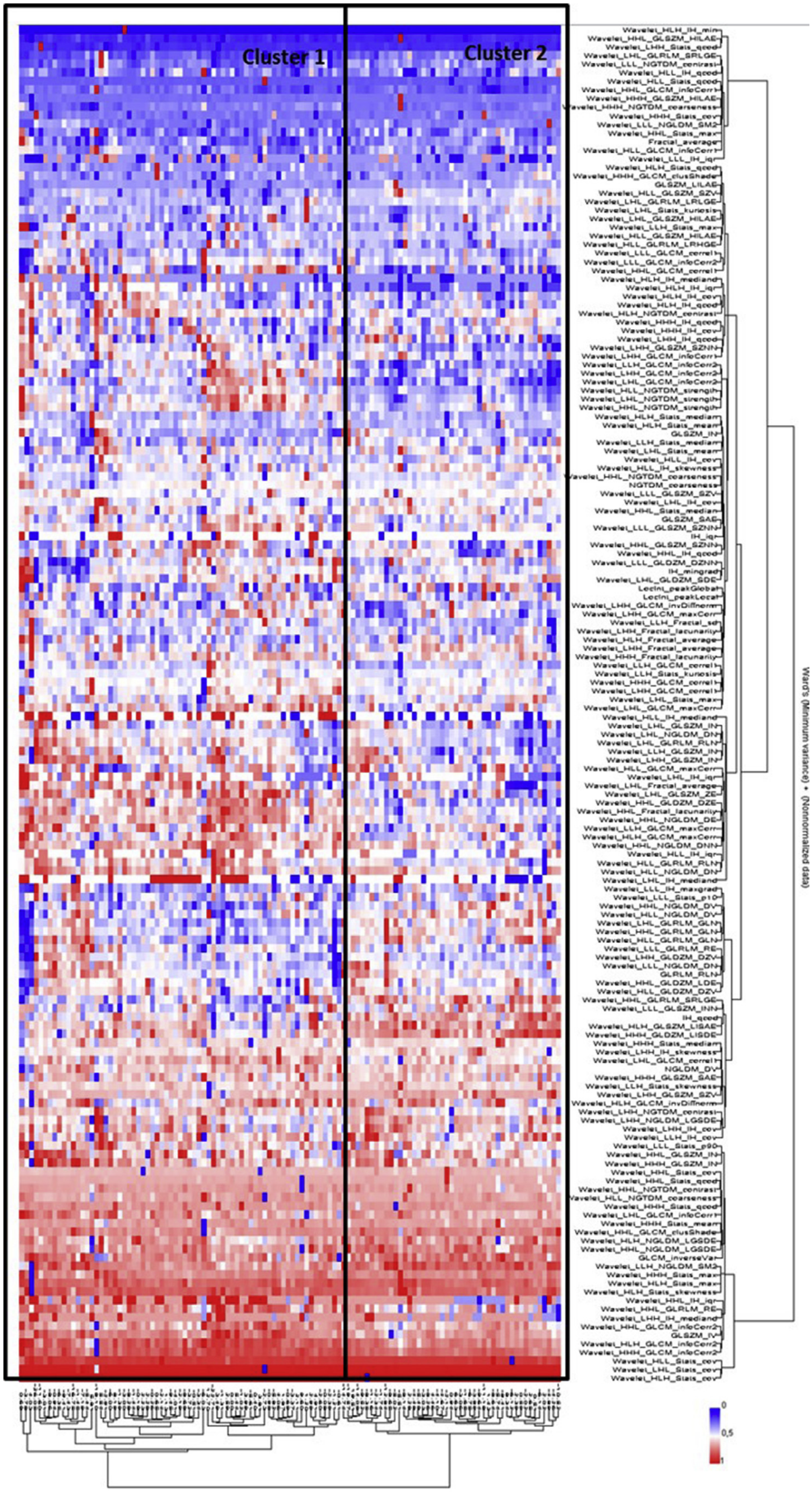


Fig. 1. Skeletal muscle area on transverse CT images at the third lumbar level, using (**a**) Slice-O-Matic for evaluation of cross-sectional area and (**b**) Mirada software for extraction of radiomic features. CT, computed tomography.


Cluster 1
Cluster 2
Ward's (Minimum variance) • (Nonnormalized data)
0
0,5
1

61 years, and 64 patients (55%) were male; survival was comparable with the whole study group of 223 patients.

3.2. Muscle maintenance and muscle loss

Delineations of skeletal muscle CSA made using Slice-O-Matic for CSA and using Mirada for extraction of radiomic features are shown in Fig. 1. Analysis of skeletal muscle CSA at baseline and during follow-up revealed that in the whole cohort, skeletal muscle decreased with mean (±standard deviation) 2.9 ± 6.7%. Of those, 69 patients (59%) exhibited loss of skeletal muscle.

3.3. Radiomic features

A total of 1298 radiomic features were extracted. For analysis of baseline radiomic features, those which had no range (n = 9) were excluded. After removing the redundant features using the spearman correlation method, 193 radiomic features, 11 unfiltered and 182 filtered, could be used for the analysis.

Fig. 2 shows a heatmap in which radiomic features that are selected at least once in the LASSO models are plotted against the patients ranked in descending order of the decrease in muscle mass. The upper half of the graph shows the patients with muscle loss, and the lower half of the graph, the patients with a stable muscle mass. No difference in radiomic features is seen between those with maintenance of muscle and those with muscle loss. The average AUC over 100 repetitions for radiomic features of the baseline scan, with muscle loss as outcome, is 0.49 (95% CI: 0.36, 0.62). In addition, no differences were observed in muscle mass changes between patients treated with and without nitroglycerin. A list with the selected radiomic features in alphabetic order can be found in the Supplementary data Table A.

We also analysed the delta features (differences in feature values between the baseline scan and the follow-up scan) with muscle loss as outcome. The average AUC was 0.68 (95% CI: 0.51–0.84). In this model, the grey-level co-occurrence matrix (GLCM) was most often selected (data not shown).

4. Discussion

To the best of our knowledge, this is the first exploratory study evaluating the potential of skeletal muscle radiomics to predict skeletal muscle loss. Some cross-sectional studies show that baseline low CT-derived muscle mass is an important prognostic factor for OS [4,24], which contradicts to other studies [25,26]. The lack of properly validated and population-specific cut-off values for CT-derived low muscle mass may explain this discrepancy. We therefore were interested to know if radiomic features of baseline skeletal muscle are prognostic for longitudinal muscle loss. In this study, baseline radiomic features had no discriminatory value with regard to longitudinal skeletal muscle changes. However, longitudinal differences in radiomic features were seen between those who lost muscle and those who maintained muscle mass.

The most distinct delta radiomic feature was a feature in the GLCM category. To calculate the GLCM, each pixel in an image is assigned a numerical value depending on the combination of grey-level intensity values in two neighbouring pixels. Second-order statistics calculate mathematical algorithms to derive textural homogeneity, contrast, variance, etc. [27]. GLCM features depend on the grey-level pattern, which might implicate that patients with muscle loss develop more muscle fat deposits, leading to a more heterogeneous grey-level intensity pattern (as low grey levels reflect increased intramuscular fat). Indeed, analysis of muscle biopsies demonstrated that compared with controls, patients with cancer exhibited increased numbers of lipid droplets in skeletal muscle. Moreover, the amount of lipid droplets increased with progression of weight loss [28]. Muscle fat depots assessed by muscle radiation attenuation on CT are associated with poor survival in cancer [4]. A phantom study showed concordance between radiation attenuation and muscle lipid content [29]; therefore, reduced muscle radiation attenuation is believed to reflect fat infiltration. However, it is unclear if this radiation attenuation indicates intramyocellular or extramyocellular lipids. Therefore, the aetiology and prognostic significance of muscle lipids in cachexia progression is object for further research.

While the strength of our study comes from the well-defined randomised patient cohort, with CT scans executed according to study protocol—predefined time points, there are some limitations. Pre-treatment changes in muscle mass are unknown. Patients currently identified as having 'muscle maintenance' could have exhibited muscle loss before the first CT scan, which may influence radiomic features. The NVALT12 trial is a multicentre study. Consequently, the CT scans included in this analysis are performed in different hospitals on different CT scanners. Although all scans were low-dose CT scans, there might be differences in scan acquisition and the use of contrast. A phantom study showed that slice thickness variability influenced radiomic features; however, this variability can be reduced by resampling to a standardised voxel size [23]. While it is known that different exposures do not influence the radiomic features values [23], the impact of use of contrast is unknown.

Fig. 2. Heatmap of the normalised selected delta radiomics features in alphabetic order (list of features can be found in the supplementary material). Patients are ranked according to the descending difference in muscle mass; upper half are the patients with muscle depletion, and lower half, patients with stable muscle mass.

5. Conclusion

In conclusion, the present study shows that baseline skeletal muscle radiomics did not predict future muscle loss in patients with metastatic NSCLC. Nevertheless, longitudinal differences in intensity and texture muscle radiomic features are detected, which slightly differ between patients with muscle loss from patients without muscle loss. Future research in experimental models and human radiomics combined with muscle tissue analysis is required to unravel the biological processes linked to the radiomic features.

Conflict of interest statement

E.E.C.d.J., K.J.C.S., T.M.D., W.v.E., A.J., J.E.v.T., J.H.R.J.D. and A.M.W.J.S. declare that they have no conflict of interest. R.T.H.L. reports personal fees and other from OncoRadiomics SA, outside the submitted work. In addition, he has a patent EP3207521A1. A-M.C.D. reports personal fees from Roche, Boehringer Ingelheim, Eli Lily, Takeda and BMS, outside the submitted work. P.L. reports grants/sponsored research agreements from Oncoradiomics and ptTheragnostic outside the submitted work, from Health Innovation Ventures, DualTpharma and ptTheragnostics. He received an advisor (SAB)/presenter fee and/or reimbursement of travel costs/external grant writing fee and/or in kind manpower contribution from Oncoradiomics, outside the submitted work, from BHV and Convert pharmaceuticals. P.L. has shares in the company Oncoradiomics and, outside the submitted work, Convert pharmaceuticals and is the co-inventor of two patents on radiomics (PCT/NL2014/050248, PCT/NL2014/050728) licenced to Oncoradiomics and outside the submitted work, one patent on mtDNA (PCT/EP2014/059089) licenced to ptTheragnostic/DNAmito, three non-patentable inventions (softwares), licenced to ptTheragnostic/DNAmito, Oncoradiomics and Health Innovation Ventures. This study is performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejca.2019.07.023.

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