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Reliability of PET/CT shape and heterogeneity features in functional and morphological components of Non-Small Cell Lung Cancer tumors: a repeatability analysis in a prospective multi-center cohort

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Short title: PET/CT texture features repeatability

ABSTRACT

Purpose: The main purpose of this study was to assess the reliability of shape and heterogeneity features in both Positron Emission Tomography (PET) and low-dose Computed Tomography (CT) components of PET/CT. A secondary objective was to investigate the impact of image quantization.

Material and methods: A Health Insurance Portability and Accountability Act -compliant secondary analysis of deidentified prospectively acquired PET/CT test-retest datasets of 74 patients from multi-center Merck and ACRIN trials was performed. Metabolically active volumes were automatically delineated on PET with Fuzzy Locally Adaptive Bayesian algorithm. 3DSlicer^{TM} was used to semi-automatically delineate the anatomical volumes on low-dose CT components. Two quantization methods were considered: a quantization into a set number of bins ($quantization_B$) and an alternative quantization with bins of fixed width ($quantization_W$). Four shape descriptors, ten first-order metrics and 26 textural features were computed. Bland-Altman analysis was used to quantify repeatability. Features were subsequently categorized as very reliable, reliable, moderately reliable and poorly reliable with respect to the corresponding volume variability.

Results: Repeatability was highly variable amongst features. Numerous metrics were identified as poorly or moderately reliable. Others were (very) reliable in both modalities, and in all categories (shape, 1st-, 2nd- and 3rd-order metrics). Image quantization played a major role in the features repeatability. Features were more reliable in PET with $quantization_B$, whereas $quantization_W$ showed better results in CT.

Conclusion: The test-retest repeatability of shape and heterogeneity features in PET and low-dose CT varied greatly amongst metrics. The level of repeatability also

depended strongly on the quantization step, with different optimal choices for each modality. The repeatability of PET and low-dose CT features should be carefully taken into account when selecting metrics to build multiparametric models.

Key words: PET/CT, texture analysis, radiomics, repeatability

INTRODUCTION

The crucial role of positron emission tomography/computed tomography (PET/CT) with fluorine-18 fluorodeoxyglucose (FDG) for diagnosis and staging of non-small cell lung cancer (NSCLC) is established *(1)*. Tumor metabolism is usually quantified with standardized uptake value (SUV) metrics (*e.g.,* maximum and mean) in PET, whereas the low-dose CT component's role is limited to PET attenuation correction and anatomical localization.

Radiomics denotes the extraction of intensity, shape and heterogeneity features from medical images *(2)*. Its application to PET *(3)* and CT *(4)* has gained interest for characterizing NSCLC tumors quantitatively, with potentially higher value than standard metrics, with the opportunity to combine features from both PET and low-dose CT components *(5)*.

A first challenge is that numerous features can be calculated, most of which are sensitive to image noise, segmentation or reconstruction settings *(7–11)*. Their use for therapy response monitoring and early prediction faces another challenge: repeatability. Because metrics calculated in pre-, mid- and post-therapy images need to be compared, test-retest repeatability allows determining the cut-off above which a change is attributed to response or progression. This has been estimated at ±15% to 30% for SUV and volume *(12,13)*. Regarding shape and heterogeneity metrics, several studies have investigated their repeatability in PET with FDG or fluorine-18 fluorothymidine *(8,14–17)* and in diagnostic CT *(18,19)*, dosimetry CT *(4,18)*, contrast-enhanced CT (CE-CT) *(18,20)* or cone-beam CT (CBCT) *(21)*. These studies exploited small single-center cohorts [n=8 CE-CT *(20)*, n=10 CBCT *(21)*, n=11 FDG-PET *(8,15,17)*, n=11 fluorine-18 fluorothymidine-PET *(16)*, n=16 FDG-PET *(14)*, n=20 CT and 13 CE-CT *(18)* and n=31 CT *(4,19)*] and never reported on the repeatability of

features from the low-dose CT from PET/CT, which is important when combining features from both components *(5)*.

Finally, it has been shown recently that the image quantization step in the calculation of textural features can have an impact on the relationship to other parameters *(3)* and on the repeatability *(17,22)*.

The primary goal of the present work was to evaluate the repeatability of shape and heterogeneity metrics from both PET and low-dose CT components in a large prospective multi-center cohort. A secondary goal was to evaluate the impact of the quantization step.

MATERIALS AND METHODS

Patient cohort and imaging

Patients with stage IIIB-IV NSCLC were prospectively included in the multi-center Merck MK-0646-008 (40 patients in 17 sites) and American College of Radiology Imaging Network (ACRIN) 6678 (34 patients in 14 sites) trials (NCT00424138 and NCT00729742, respectively) *(23)*. Centers had to conform to the criteria of ACRIN PET qualification (www.acrin.org/6678_protocol.aspx) to participate. Merck used a similar accreditation program. PET/CT protocols were designed in accordance with National Cancer Institute guidelines *(24)*. The institutional review board of each participating site approved the study, and all subjects signed a written informed consent form. The whole cohort of 74 patients has been previously included in *(23)*, but only SUV measurements were analyzed whereas in this present analysis, texture features and shape parameters were also computed both on PET and CT images. The present secondary analysis of deidentified PET/CT images from these

trials was approved by ACRIN and was performed in compliance with the Health Insurance Portability and Accountability Act.

PET and CT analysis

In both test-retest datasets, the PET and the low-dose CT images were processed independently. In PET, the metabolically active volumes (MAV) of the primary tumor and up to three additional lesions were segmented with the Fuzzy Locally Adaptive Bayesian algorithm previously validated for accuracy and robustness *(25,26)*. In low-dose CT, the anatomical volume (AV) of primary tumors were delineated with a validated semi-automatic approach using 3D Slicer™ *(27)*. Additional lesions were analyzed if they could be reliably delineated.

The following metrics were calculated on the delineated volumes. Table 1 contains a glossary. All features are described with their calculation formulae *(3)* in the Supplemental Material.

3D shape descriptors were included, such as sphericity, irregularity or major axis *(4,28)*.

1st-order metrics (not accounting for spatial distribution of voxels) in both Hounsfield units (low-dose CT) and SUV (PET) include maximum and mean values, as well as histogram-derived skewness, kurtosis, energy, $entropy_{HIST}$ or the area under the curve of the cumulative histogram (CH_{AUC}) *(29)*. These metrics do not require quantization as a prior step. Quantization (not to be confused with quantification) is an intensity resampling step applied to the image prior to building textures matrices on which 2nd and 3rd order features rely. These matrices dimensions are determined by the number of intensity values obtained after this resampling. Several different quantization approaches have been proposed *(3)*.

2nd-order metrics from grey-level co-occurrence matrix (GLCM) and neighborhood grey-tone difference matrix (NGTDM), and 3rd-order metrics from grey-level zone size matrix were calculated in a single matrix considering all 13 orientations simultaneously *(30,31)*. Quantization was performed in a set number of bins B (denoted from here onwards $quantization_B$), as previously recommended *(14,18,30,32)* using equation 1:

$$I_B = B \times \frac{I - I_{min}}{I_{max} - I_{min}} \quad (1)$$

Where I_{max} and I_{min} denote maximum and minimum intensity (Hounsfield units in low-dose CT and SUV in PET), and B is the number of bins (here B=64). Choosing a different B value can have an impact on the repeatability of features *(14)*. Results obtained with B=8 to 128 are in the Supplemental Material. It has been suggested that an alternative quantization using fixed-width bins (*e.g.,* 0.5 SUV) can have an important impact *(17,22)*. Results using this approach (denoted from here onwards $quantization_w$) following equation 2 were also generated.

$$I_W = \left\lceil \frac{I_O}{W} \right\rceil - \min\left(\left\lceil \frac{I_O}{W} \right\rceil \right) + 1 \quad (2)$$

Where W is the bin width (here 0.5 SUV for PET *(22)* and 10 Hounsfield units for low-dose CT). Note that W=0.25 SUV and W=5 Hounsfield units were also tested but no significant differences were observed. Supplemental Figure 1 shows a NSCLC tumor with both PET and low-dose CT, and the corresponding quantization results and histograms.

Statistical analysis

Statistical analyses were performed with MedCalc™ (MedCalc Software, Belgium). The repeatability of each metric was assessed with Bland-Altman analysis by reporting the mean and standard deviation (SD) of the differences between the two measurements. Lower and upper repeatability limits were calculated as ±1.96×SD after log-transformation when not normal. Bland-Altman analysis was preferred over intra-class correlation coefficients based on previous recommendations *(33)*. Intra-class correlation coefficients are nonetheless provided in the Supplemental Material.

Correlations between metrics were assessed with Spearman rank coefficients (rs).

Each metric was also categorized with respect to the repeatability (SD) of the corresponding volume of interest ($VOI_{rep}SD$): very reliable (≤0.5×$VOI_{rep}SD$), reliable (>0.5×$VOI_{rep}SD$ and ≤1.5×$VOI_{rep}SD$), moderately reliable (>1.5×$VOI_{rep}SD$ and ≤2×$VOI_{rep}SD$) and poorly reliable (>2×$VOI_{rep}SD$).

RESULTS

The analysis was performed in 73 datasets because one was not available. In the PET images, 73 primary tumors and 32 additional lesions (nodal or distant metastases) were analyzed. Mean MAV was 47.8 cm^3 (median 24.9 cm^3, SD 55.4 cm^3). In the low-dose CT, 2 patients were excluded because visual assessment of images indicated that repeatable volume delineation could not be ensured (Supplemental Fig. 2). Seventy-one primary tumors and 5 additional lesions were analyzed. Mean AV was 52.4 cm^3 (median 37.5 cm^3, SD 53.0 cm^3). .

Figure 1 displays repeatability results of volume determination in both modalities, while Figures 2, 3 and 4 display repeatability of 1st-order metrics and shape descriptors, 2nd- and 3rd-order textural features, respectively. Tables containing all results with also other quantization values are in the Supplemental Material.

PET and low-dose CT volumes

As shown in Figure 1, MAV determination had a repeatability of -1.4±11.1%, with upper and lower repeatability limits of +20.3% and -23.2%, which was dependent on MAV, smaller volumes exhibiting significantly (rs=-0.41, p<0.0001) poorer repeatability. The AV determination had a similar repeatability of -0.4±10.5%, with upper and lower repeatability limits of +20.3% and -21.0%. Repeatability was less dependent on volume (rs=-0.32, p=0.006).

PET (respectively low-dose CT) features were thus categorized with similar thresholds for reliability: ≤5.6% (respectively 5.3%), >5.6% (respectively 5.3%) and ≤16.7% (respectively 15.8%), >16.7% (respectively 15.8%) and ≤22.2% (respectively 21%) and >22.2% (respectively 21.0%).

PET features

Shape descriptors and 1st-order metrics

Overall, the shape features in PET were very repeatable (Fig. 2). Irregularity and sphericity were very reliable, with only 4.8% SD. 3D surface and major axis were reliable although with higher variability (9.0% and 8.4%, respectively). Amongst intensity-based 1st-order features, the most repeatable were CH_{AUC} (-0.2 ± 3.6%) and $entropy_{HIST}$ (-0.2 ± 3.6%), whereas the least repeatable were energy (-1.2 ± 23.8%) and skewness (-1.1 ± 33.7%). Mean (SUV_{mean}) and max (SUV_{max}) values were moderately reliable, with upper and lower repeatability limits of -30.4% and 36.3%, and -34.3% and 41.3%, respectively.

2nd-order metrics

As shown in Figure 3, with $quantization_B$, amongst GLCM features, $entropy_{GLCM}$ (-0.1 ± 2.6%), sum entropy (-0.2 ± 2.1%) and difference entropy (-0.2 ± 3.0%) were the most repeatable, whereas most other features fell in the reliable category. Five were categorized as moderately reliable and 3 as unreliable. For correlation the very poor repeatability is due to a few outliers for values around zero, to which Bland-Altman is very sensitive. After excluding them, correlation had reproducibility limits below ±20% and could be re-categorized as moderately reliable. The five NGTDM features were less repeatable than the best GLCM features although still categorized as reliable, all achieving SD ~14-17%, except $contrast_{NGTDM}$ (27.6%).

The use of the alternate $quantization_W$ changed both the above hierarchy and the absolute repeatability of the features. Overall, features calculated after $quantization_W$ were much less reliable with notably more outliers, all exhibiting a higher variability than MAV.

3nd-order metrics

As shown in figure 4, amongst 3rd-order metrics, quantization had a similar impact: with $quantization_W$ all grey-level zone size matrix features were categorized as poorly reliable, whereas with $quantization_B$ two were very reliable (small zone size emphasis and zone size percentage with SD <4%) and 3 reliable (large zone size emphasis, gray-level non-uniformity and zone size non-uniformity with SD ~11-14%). Amongst the least repeatable features were those focusing on small zones and/or low grey values (*e.g.*, LZLGE, SZLGE and LGLZE).

Low-dose CT features

Shape descriptors and 1st-order metrics

As shown in Figure 2, morphological irregularity, sphericity and 3D surface were the most repeatable (SD 3.3%, 10.0% and 11.6%, respectively). Major axis was less reliable (3.8 ± 18.4%).

On the one hand, four histogram metrics showed poor reliability such as maximum (4.7 ± 38.6%) and mean (-4.2 ± 43.6%) intensity, kurtosis (4.8 ± 37.4%) and skewness (11.1 ± 202.2%). On the other hand, $entropy_{HIST}$ and CH_{AUC} were very reliable (-0.1 ± 2.5% and 0.7 ± 9.1%).

2nd-order metrics

The repeatability depended strongly on the quantization, $quantization_w$ improving the repeatability compared to $quantization_B$ (Fig. 3). Amongst GLCM metrics, the most repeatable (for $quantization_B$ *vs.* $quantization_w$, respectively) were $entropy_{GLCM}$ (-1.9 ± 12.0% *vs.* -0.4 ± 5.2%), sum entropy (-1.4 ± 10.0% *vs.* 0.1 ± 0.4%) and difference entropy (-2.3 ± 13.1% *vs.* -0.3 ± 1.9%). To a lesser extent, the same was observed for NGTDM, with higher repeatability using $quantization_w$. Complexity was the only parameter with variability <15.8% and categorized as reliable (0.5 ± 14.3% and -0.5 ± 12.3% with $quantization_B$ and $quantization_w$, respectively).

3nd-order metrics

The quantization method also had an important impact (Fig. 4). Eight parameters were categorized as moderately reliable or better with $quantization_w$ and only two with $quantization_B$. Small zone size emphasis (-0.6 ± 4.8% *vs.* -0.5 ± 2.6% with $quantization_B$ and $quantization_w$, respectively) and zone size emphasis (-2.8 ± 17.4% *vs.* -0.9 ± 11.9%) were the most repeatable features (Figs. 4D and 4E).

Impact of quantization method

Overall, the inverted impacts of the quantization method observed in PET and low-dose CT can be explained by the different correlative relationships between the features and the corresponding volume and maximum intensity. In PET, we observed that $quantization_W$ features were correlated with SUV_{max} and not with MAV. On the contrary, features calculated with $quantization_B$ were correlated with MAV but not SUV_{max}. The higher repeatability obtained with $quantization_B$ can thus be explained by the fact that MAV repeatability was much higher than that of SUV_{max}. Contrary to PET, features in low-dose CT were correlated with both volume and maximum intensity using $quantization_B$, whereas they were less or not correlated with either volume or intensity using $quantization_W$. Because maximum intensity had a much worse repeatability than volume in CT, $quantization_B$ thus led to worse repeatability. This is illustrated in Figure 5 for the feature dissimilarity. Note the relative inversion of relationships with volume and SUV_{max} for $quantization_B$ compared to $quantization_W$ in the case of the PET component. On the contrary for the low-dose CT component, $quantization_B$ led to a higher correlation with maximum intensity than volume, but $quantization_W$ led to lower correlation with volume and non-significant correlation with maximum intensity.

DISCUSSION

In the present work, 73 test-retest PET/CT acquisitions from 31 centers (17 for ACRIN in the USA and 14 for Merck in Asia and Europe) were analyzed for repeatability.

A similar variability of volume delineations was observed for both modalities. MAV from PET were slightly smaller than AV measured in CT, mostly due to the fact that more lymph nodes and metastases were delineated in PET than in CT, and some

large CT volumes had parts without FDG uptake. Regarding SUV_{mean} and SUV_{max}, our results differ slightly from those previously published in the same cohort *(23)*. Only lesions with SUV_{max}>4 were included in the previous analysis, whereas we did not restrict it. By restricting to SUV_{max}>4, our test-retest results for SUV_{max} were similar to those previously reported.

Regarding shape and heterogeneity features, our results confirm prior findings in PET *(8,14–17)*. To the best of our knowledge, our study is the first to report on the repeatability of these features in the low-dose CT component.

Overall, the geometric features (shape descriptors) were found reliable (some with high repeatability) in both modalities, which can be related to the high repeatability of segmentation. This is in line with previous findings for PET *(8,17)* and with morphological shape in other CT modalities *(4)*. We emphasize that only one segmentation by one expert was considered. The variability might be higher when considering different segmentation approaches and/or several observers.

Regarding 1st-order metrics and textural higher-order features, our results confirm that the repeatability varies greatly amongst metrics. On the one hand, several features were confirmed to be unreliable in both modalities and should be systematically avoided, *e.g.,* 1st-order skewness, 2nd-order Angular Second Moment, $contrast_{GLCM}$ and $contrast_{NGTDM}$, and 3rd-order metrics quantifying low grey values and/or small zones. On the other hand, it should be emphasized that several features were identified as reliable, in all three categories and for both modalities. In between, other features with moderate repeatability should be used with caution as they exhibit larger variability than the corresponding volume determination.

We compared two different quantization methods. $Quantization_B$ is most often used. The impact of choosing another B value has been evaluated previously *(14)* and our results confirm these findings. Although B=64 is a good compromise and most features exhibited similar repeatability with different values, repeatability of some metrics depended on B. We observed a different impact in PET and low-dose CT for $quantization_W$, as it led to worse repeatability in PET but better repeatability in low-dose CT. This was explained by the different relationships between the features and the corresponding volume and maximum intensity. With more control over data acquisition and higher repeatability of SUV_{max}, $quantization_W$ may lead to higher repeatability. These results highlight the major impact of the quantization step and its variable impact depending on image modality that should thus not be overlooked.

Our results confirm that studies building clinical models by combining features from PET/CT images should carefully account for repeatability. This is mandatory when calculating evolution of features across pre-, mid- and/or post-therapy images. This is nonetheless an important factor when building models based on single time-point images, as models built using robust and repeatable features are more likely to be generalizable and achieve good performance in external/testing cohorts. Repeatability is not the only criterion on which feature selection needs to be based, as discriminative power, robustness and redundancy have to be considered also.

Our study has limitations. Low-dose CT and PET images were analyzed separately using different segmentation processes performed independently on the test and re-test images. The repeatability evaluation therefore includes the intrinsic repeatability of the segmentation. We used robust segmentation approaches that should minimize variability. Another approach would consist in defining the volume on the test image and register it on the re-test image, which however requires accurate

registration and raises other issues *(34)*. In a clinical environment, the use of less accurate and less robust segmentation could lead to a lower repeatability, especially for volume-correlated features.

We chose to categorize the repeatability levels of each metric with respect to that of the corresponding volume. The repeatability acceptance was similar for both modalities (reliability in PET was defined as SD below 16.5%, compared to 15.8% for low-dose CT). These thresholds are arbitrary and choosing different values would change the categorization of several metrics, but without changing their hierarchy.

Finally, respiratory gating was not applied. In NSCLC this may lead to different levels of quantitative bias between the test and retest images, as well as between PET and low-dose CT. The repeatability we reported are therefore larger than what could ideally be obtained in other body regions where motion is less important, or if respiratory motion correction was applied *(35)*.

CONCLUSION

Test-retest repeatability of shape and heterogeneity features in both components of PET/CT varied greatly amongst metrics. The repeatability also depended on the quantization step, with different optimal choices for PET or low-dose CT, because of different relationships of the metrics with volume or intensity. The repeatability of PET/CT features should be carefully accounted for when choosing metrics to combine in multiparametric models.

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Table 1. Glossary

MAV	Metabolically active volume (PET)
AV	Anatomical volume (low-dose CT)
CH_{AUC}	Area Under the Curve of the Cumulative Histogram
ASM	Angular Secondary Moment
IDM	Inverse Different Moment
ID	Inverse Difference
SOSV	Sum Of Square Variance
SAVE	Sum AVErage
SVAR	Sum VARiance
SENT	Sum ENTropy
DVAR	Difference VARiance
DENT	Difference ENTropy
IC	Information Correlation
TS	Texture strength
CP	Cluster Prominence
SZSE	Small Zone Size Emphasis
LZSE	Large Zone Size Emphasis
ZSNU	Zone Size Non-Uniformity
GLNU	Gray-Level Non-Uniformity
ZSP	Zone Size Percentage
LGLZE	Low Grey Level Zone Emphasis
HGLZE	High Grey Level Zone Emphasis
SZLGE	Small Zone / Low Grey Emphasis
SZHGE	Small Zone / High Grey Emphasis
LZLGE	Large Zone / Low Grey Emphasis
LZHGE	Large Zone High Grey Emphasis

FIGURE CAPTIONS

Figure 1: Bland-Altman analysis and correlation between volume and repeatability for MAV and AV determination.

Figure 2: Repeatability of 1st-order metrics and 3D shape descriptors measured on FDG PET (left) and low-dose CT (right). Features are ranked from highest (left) to lowest (right) repeatability. VR = very reliable ; R = reliable ; MR = moderately reliable ; PR = poorly reliable.

Figure 3: Repeatability of 2nd-order metrics measured on FDG PET (first row) and low-dose CT (second row), using either $quantization_B$ (first column) or $quantization_W$ (second column). Features are ranked from highest (left) to lowest (right) repeatability. VR = very reliable ; R = reliable ; MR = moderately reliable ; PR = poorly reliable.

Figure 4: Repeatability of 3rd-order metrics measured on FDG PET (first row) and low-dose CT (second row), using either $quantization_B$ (first column) or $quantization_W$ (second column). Features are ranked from highest (left) to lowest (right) repeatability. VR = very reliable ; R = reliable ; MR = moderately reliable ; PR = poorly reliable.

Figure 5: Illustration of correlative relationships between a textural feature (dissimilarity from GLCM) and volume (first row) or maximum intensity (second row), in both PET (first column) and low-dose CT (second column) components, depending on the quantization approach.