Supplementary Material

Radiomics: the bridge between medical imaging and personalized medicine

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Description of the digital phantom image data

To compare different software implementations for radiomic feature extraction algorithms, we provide CT data of the primary tumor region (i.e. a 5 cm margin around the tumor volume) and the corresponding tumor contours of 4 lung cancer cases, to serve as “real life” digital phantoms (figure 1). The images have an in plane pixel spacing of 0.977 mm and a slice thickness of 3 mm. The data is provided both in original and pre-processed form. Using the pre-processed image data, we calculated a set of commonly used features, for which the details are given below, to serve as a reference feature dataset.

All image and contour data is provided in DICOM format and is publicly available (http://dx.doi.org/10.17195/candat.2016.08.1). The data was generated in Matlab R2014a (The Mathworks, Natick, MA) using an adapted version of CERR [1]. The reference feature data is provided in spreadsheet form (Microsoft Excel and comma separated values).

Results for other features, or features calculated with different pre-processing (e.g. features after image filtration, such as Laplacian of Gaussian or Wavelets, or using a different intensity discretization scheme) can be provided upon request. In this regard, the original CT data can be used. The DICOM RTSTRUCTs, containing the contour coordinates, may be used to compare different implementations to create 3D binary masks from polygon data.
**Figure 1**: (a) Representative image of a digital phantom CT image, with the tumor delineation shown outlined in green. (b) A 3D rendering of the tumor region.

**Image pre-processing**

To be able to correctly compare between different implementations of feature extraction algorithms, resulting feature values should not be affected by differences in segmentation and intensity discretization, which are part of image pre-processing. To ensure that the same region of interest (ROI) is used for feature calculations—eliminating dependency of feature values on segmentation—the delineation of the primary tumor (GTV) has been converted to a 3D binary ([0,1]) mask image \( I_M \) (figure 2a) and applied to the original image.

We provide two pre-processed images per digital phantom: \( I_O \) (figure 2b), the original image with an offset of +1000 Hounsfield Units (HU), eliminating negative values (air = 0 HU), and \( I_B \) (figure 2c) a gray value image discretized into equally spaced bins, with a bin width of 25 HU. Resampling intensity values into bins with an intensity resolution of \( B = 25 \text{ HU} \) was performed using:

\[
I_B(x) = \left\lfloor \frac{I(x)}{B} \right\rfloor - \min \left( \left\lfloor \frac{I(x)}{B} \right\rfloor \right) + 1
\]

Where term \( \left\lfloor \min (I(x)/B) \right\rfloor + 1 \) ensures that the bin count starts at 1. Since differences in intensity discretization affect the resulting feature values [2], the gray values of the pre-processed images should therefore be used as-is. Voxels outside the ROI, which should be ignored for feature
calculations, are set to -1000 for both $I_D$ and $I_B$. The in plane pixel spacing and slice thickness have not been altered.

Figure 2: (a) The 3D binary mask $I_M$. (b) The pre-processed image with an offset of + 1000 HU ($I_D$). (c) The pre-processed gray value image with a bin width of 25 HU ($I_B$).

Reference radiomic features

First order statistics (N=18) describe the histogram of voxel intensity values contained within the ROI and were calculated on $I_D$. Geometric features (N=16) describe the 3D shape and size of the ROI and were calculated on the 3D (binary) mask $I_M$ of the ROI (i.e. not the original contour coordinates). Textural features describing the spatial distribution of voxel intensities were calculated from gray-level co-occurrence (GLCM) [3], gray-level run-length (GLRLM) [4], gray-level size-zone (GLSZM) [5], gray-level distance-zone (GLDZM) [6], neighborhood gray tone difference (NGTDM) [7] and neighboring gray level dependence (NGLDM) [8] texture matrices. All texture matrices were determined on $I_B$, considering 26 connected voxels (i.e. voxels were considered to be neighbors in all 13 directions in three dimensions) at a distance of 1 voxel. The dependency coarseness parameter ($a$) for NGLDM was set to 0. Features derived from GLCM and GLRLM were calculated by averaging their value over all 13 directions. In total, 44 textural features (26 GLCM, 16 GLRLM, 16 GLSZM, 16 GLDZM, 5 NGTDM and 16 NGLDM) were calculated.

See Tables 1–8 for an overview of calculated features and how they appear in the provided spreadsheets of feature values. Mathematical definitions for the calculated features are described below in the section Definition of reference radiomic features [9, 10].
Table 1: Calculated first order (histogram) statistics.

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<td>Mean absolute deviation</td>
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<td>Median</td>
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Table 2: Calculated geometric features

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Table 3: Calculated GLCM features. Abbreviations: Informational measure of correlation 1 (IMC1), Informational measure of correlation 2 (IMC2), Inverse difference moment normalized (IDMN), inverse difference normalized (IDN).

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Table 4: Calculated GLRLM features. Abbreviations: Short Run Emphasis (SRE), Long Run Emphasis (LRE), Gray-Level Nonuniformity (GLN), Run Length Nonuniformity (RLN), Gray-Level Nonuniformity Normalized (GLNN), Run Length Nonuniformity Normalized (RLNN), Low Gray-Level Run Emphasis (LGRE), Short Run Low Gray-Level Emphasis (SRLGE), Short Run High Gray-Level Emphasis (SRHGE), Low Run Low Gray-Level Emphasis (LRLGE), Low Run High Gray-Level Emphasis (LRHGE), Gray Level Variance (GLV), Run Length Variance (RLV), Run Entropy (RE)

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Table 5: Calculated GLSZM features. Abbreviations: Small Area Emphasis (SAE), Large Area Emphasis (LAE), Intensity Nonuniformity (IN), Size Zone Nonuniformity (SZN), Intensity Nonuniformity Normalized (INN), Size Zone Nonuniformity Normalized (SZNN), Zone Percentage (ZP), Low Intensity Emphasis (LIE), High Intensity Emphasis (HIE), Low Intensity Small Area Emphasis (LISAE), High Intensity Small Area Emphasis (HISAE), Low Intensity Large Area Emphasis (LILAE), High Intensity Large Area Emphasis (HILAE), Intensity Variance (IV), Size Zone Variance (SZV), Zone Entropy (ZE).

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Table 6: Calculated GLDZM features. Abbreviations: Small Distance Emphasis (SDE), Large Distance Emphasis (LDE), Intensity Nonuniformity (IN), Distance Zone Nonuniformity (DZN), Intensity Nonuniformity Normalized (INN), Distance Zone Nonuniformity Normalized (DZNN), Zone Percentage (ZP), Low Intensity Emphasis (LIE), High Intensity Emphasis (HIE), Low Intensity Small Distance Emphasis (LISDE), High Intensity Small Distance Emphasis (HISDE), Low Intensity Large Distance Emphasis (LILDE), High Intensity Large Distance Emphasis (HILDE), Intensity Variance (IV), Distance Zone Variance (DZV), Distance Zone Entropy (DZE).

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Table 7: Calculated NGTDM features.

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Table 8: Calculated NGLDM features. Abbreviations: Small Dependence Emphasis (SDE), Large Dependence Emphasis (LDE), Gray-Level Nonuniformity (GLN), Dependence Nonuniformity (DN), Gray-Level Nonuniformity Normalized (GLNN), Dependence Nonuniformity Normalized (DNN), Low Gray-Level Emphasis (LGE), High Gray-Level Emphasis (HGE), Low Gray-Level Small Dependence Emphasis (LGSDE), High Gray-Level Small Dependence Emphasis (HGSDE), Low Gray-Level Large Dependence Emphasis (LGLDE), High Gray-Level Large Dependence Emphasis (HGLDE), Gray-Level Variance (GLV), Dependence Variance (DV), Dependence Entropy (DE), Second Moment (SM).

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<tr>
<td>123.</td>
<td>HGSDE</td>
<td>NGLDM,HGSDE</td>
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<tr>
<td>124.</td>
<td>LGLDE</td>
<td>NGLDM,LGLDE</td>
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<td>125.</td>
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<td>128.</td>
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<td>129.</td>
<td>SM</td>
<td>NGLDM,SM</td>
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Definition of reference radiomic features

First-order gray-level statistics

First-order gray-level statistics describe the distribution of gray-values within the volume. Let $X$ denote the three dimensional image matrix with $N$ voxels, $P$ the first order histogram, $P(i)$ the fraction of voxels with intensity level $i$ and $N_i$ the number of discrete intensity levels.

1. **Energy**

$$
energy = \sum_{i=1}^{N} X(i)^2
$$

Energy is also known as the sum of squares.

2. **Entropy**

$$
entropy = \sum_{i=1}^{N_i} P(i) \log_2 P(i)
$$

3. **Kurtosis**

$$
kurtosis = \frac{1}{N} \left( \sum_{i=1}^{N} (X(i) - \bar{X})^4 \right) - \left( \frac{1}{N} \sum_{i=1}^{N} (X(i) - \bar{X})^2 \right)^2
$$

where $\bar{X}$ is the mean of $X$.

4. **Maximum**

The maximum intensity value of $X$.

$$
maximum = \max (X)
$$

5. **Mean**

The mean gray-value of $X$.

$$
mean = \frac{1}{N} \sum_{i=1}^{N} X(i)
$$
6. **Mean absolute deviation**

The mean of the absolute deviations of all voxel intensities around the mean intensity value.

\[
\text{mean absolute deviation} = \frac{1}{N} \sum_{i=1}^{N} |X(i) - \bar{X}|
\]

where \(\bar{X}\) is the mean of \(X\).

7. **Median**

The sample median of \(X\), or the 50th percentile of \(X\).

8. **Minimum**

The minimum intensity value of \(X\).

\[
\text{minimum} = \min(X)
\]

9. **Range**

The range of intensity values of \(X\).

\[
\text{range} = \max(X) - \min(X)
\]

10. **Root mean square (RMS)**

The quadratic mean, or the square root of the mean of squares of all voxel intensities.

\[
RMS = \sqrt{\frac{\sum_{i=1}^{N} X(i)^2}{N}}
\]

11. **Skewness**

\[
\text{skewness} = \frac{1}{N} \frac{\sum_{i=1}^{N} (X(i) - \bar{X})^3}{\left(\frac{1}{N} \sum_{i=1}^{N} (X(i) - \bar{X})^2\right)^{3/2}}
\]

where \(\bar{X}\) is the mean of \(X\).

12. **Standard deviation**

\[
\text{standard deviation} = \left(\frac{1}{N-1} \sum_{i=1}^{N} (X(i) - \bar{X})^2\right)^{1/2}
\]

where \(\bar{X}\) is the mean of \(X\).
13. Robust mean absolute deviation

The mean absolute deviation (0) of only those voxels in $X$ with a gray-value between the 10th and 90th percentile.

14. 10th percentile

The 10th percentile of $X$, a robust alternative to the minimum gray-value (8).

15. 90th percentile

The 90th percentile of $X$, a robust alternative to the maximum gray-value (4).

16. Interquartile range

The interquartile range is defined as the 75th minus the 25th percentile of $X$.

17. Uniformity

$$\text{uniformity} = \sum_{i=1}^{N_1} P(i)^2$$

18. Variance

$$\text{variance} = \frac{1}{N-1} \sum_{i=1}^{N} (X(i) - \bar{X})^2$$

where $\bar{X}$ is the mean of $X$. Variance is the square of the standard deviation (12).
**Geometric features**

Geometric features describe the shape and size of the volume of interest. Let $V$ be the volume and $A$ the surface area of the volume of interest. Let $N$ be the total number of voxels, $X = \{\vec{x}_1, \vec{x}_2, ..., \vec{x}_N\}$ the set of $N$ Cartesian coordinate vectors and $I = \{I_1, I_2, ..., I_N\}$ the corresponding intensity values.

19. **Asphericity**

\[
\text{asphericity} = \left( \frac{1}{36\pi} \frac{A^3}{V^2} \right)^{\frac{1}{3}} - 1
\]

20. **Centroid distance**

The centroid distance is the Euclidean distance between the geometric centroid ($C_g$) and the centroid weighing each voxel by its intensity value ($C_i$). The centroid distance is a measure of how close the high intensity values are to the geometric center.

\[
C_g = \frac{1}{N} \sum_{i=1}^{N} \vec{x}_i
\]

\[
C_i = \frac{\sum_{i=1}^{N} I_i \vec{x}_i}{\sum_{i=1}^{N} I_i}
\]

\[
\text{centroid distance} = \|C_g - C_i\|
\]

21. **Compactness 1**

Compactness is a measure of how much the volume resembles a sphere, as described by Aerts *et al.* [10].

\[
\text{compactness 1} = \frac{V}{\sqrt{\pi A^3}}
\]

22. **Compactness 2**

\[
\text{compactness 2} = 36\pi \frac{V^2}{A^3}
\]

23. **Compactness 3**

\[
\text{compactness 3} = \frac{V}{\sqrt{\pi A^2}^3}
\]

A dimensionless alternative to Compactness (21), as described by Aerts *et al.* [10]
24. **Maximum diameter**

The maximum diameter is the largest pairwise difference between voxels on the surface of the volume, in 3D and for each plane separately. The following diameters are calculated:

24.1. The maximum three-dimensional tumor diameter.

24.2. The maximum two-dimensional diameter of all transversal planes.

24.3. The maximum two-dimensional diameter of all sagittal planes.

24.4. The maximum two-dimensional diameter of all coronal planes.

25. **Major axis length**

Axis lengths are measures of the extent of the volume along its three principle axis. Principle component analysis (PCA) on the x, y and z coordinates of all voxels within the volume is used to determine the three orthogonal eigenvectors and corresponding eigenvalues ($\lambda_{max}$, $\lambda_{minor}$, $\lambda_{min}$).

The major axis length is the largest eigenvalue ($\lambda_{max}$) as determined by PCA.

26. **Minor axis length**

The largest eigenvalue ($\lambda_{minor}$) as determined by PCA.

27. **Least axis length**

The smallest eigenvalue ($\lambda_{min}$) as determined by PCA.

28. **Elongation**

\[
elongation = \frac{\lambda_{minor}}{\lambda_{max}}
\]

29. **Flatness**

\[
flatness = \frac{\lambda_{min}}{\lambda_{max}}
\]
30. **Spherical disproportion [11]**

Spherical disproportion is a measure of how much the volume resembles a sphere.

\[
spherical \ proportion = \frac{A}{4\pi R^2}
\]

Where \( A \) is the surface area and \( R \) is the radius of a sphere with the same volume as the tumor, obtained through:

\[
R = \left( \frac{3V}{4\pi} \right)^{\frac{1}{3}}
\]

31. **Sphericity [11]**

Sphericity is a measure of how much the volume resembles a sphere.

\[
sphericity = \frac{\pi^3 (6V)^{\frac{2}{3}}}{A} = \frac{(36\pi V^2)^{\frac{1}{3}}}{A}
\]

32. **Surface area**

The surface area is calculated by triangulation (i.e. dividing the surface into connected triangles, which define the isosurface enclosing the volume) and is defined as:

\[
surface \ area = \sum_{i=1}^{N} \frac{1}{2} |a_i b_i \times a_i c_i |
\]

Where \( N \) is the total number of triangles covering the surface and \( a, b \) and \( c \) are edge vectors of the triangles.

33. **Surface to volume ratio**

\[
surface \ to \ volume \ ratio = \frac{A}{V}
\]

34. **Volume**

The volume is defined as the number of voxels within the volume multiplied by the voxel volume.

\[
volume = Nv
\]

Where \( v \) is the volume of a single voxel.
Gray-Level Co-Occurrence Matrix based features

Gray level co-occurrence matrix (GLCM) based features, as originally described by Haralick et al. [3].

A normalized GLCM is defined as $P(i, j; \delta, \alpha)$, a matrix with size $N_g \times N_g$ describing the second-order joint probability function of an image, where the $(i,j)$th element represents the number of times the combination of intensity levels $i$ and $j$ occur in two pixels in the image, that are separated by a distance of $\delta$ pixels in direction $\alpha$, and $N_g$ is the maximum discrete intensity level in the image. Let:

$P(i,j)$ be the normalized (i.e. $\sum P(i,j) = 1$) co-occurrence matrix, generalized for any $\delta$ and $\alpha$ ,

$p_x(i) = \sum_{j=1}^{N_g} P(i,j)$,

$p_y(j) = \sum_{i=1}^{N_g} P(i,j)$,

$\mu_x$ be the mean of $p_x$, where $\mu_x = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} iP(i,j)$

$\mu_y$ be the mean of $p_y$, where $\mu_y = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} jP(i,j)$

$\sigma_x$ be the standard deviation of $p_x$, where $\sigma_x^2 = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i - \mu_x)^2 P(i,j)$

$\sigma_y$ be the standard deviation of $p_y$, where $\sigma_y^2 = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (j - \mu_y)^2 P(i,j)$

$p_{x+y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} P(i,j)(i+j = k), k = 2,3,...,2N_g$,

$p_{x-y}(k) = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} P(i,j)(|i-j| = k), k = 0,1,...,N_g-1$,

$HXY_1 = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} P(i,j) \ln(p_x(i)p_y(j))$,

$HXY_2 = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p_x(i)p_y(j) \ln(p_x(i)p_y(j))$.

35. Average ($\mu$) 

\[
\text{average} \ (\mu) = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i + j)P(i,j)}{2}
\]

Note that for a symmetrical GLCM, $\mu = \mu_x = \mu_y$.

36. Autocorrelation 

\[
\text{autocorrelation} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} ijP(i,j)
\]
37. **Cluster Prominence**

\[
\text{cluster prominence} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} [i + j - \mu_x - \mu_y]^2 P(i,j)
\]

38. **Cluster Shade**

\[
\text{cluster shade} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} [i + j - \mu_x - \mu_y]^3 P(i,j)
\]

39. **Cluster Tendency**

\[
\text{cluster tendency} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} [i + j - \mu_x - \mu_y]^2 P(i,j)
\]

40. **Contrast [12]**

\[
\text{contrast} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} |i - j|^p P(i,j) = \sum_{k=0}^{N_g-1} k^2 p_{x-y}(k)
\]

41. **Correlation**

\[
\text{correlation} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} ij P(i,j) - \mu_x \mu_y}{\sigma_x \sigma_y}
\]

42. **Difference Average (\(\mu_{x-y}\))**

\[
\text{difference average (\(\mu_{x-y}\))} = \sum_{k=0}^{N_g-1} kp_{x-y}
\]

43. **Difference Entropy**

\[
\text{difference entropy} = -\sum_{l=0}^{N_g-1} P_{x-y}(i) \log_2 [P_{x-y}(i)]
\]

44. **Difference Variance**

\[
\text{difference variance} = \sum_{l=0}^{N_g-1} (i - \mu_{x-y})^2 P_{x-y}(i)
\]
45. **Dissimilarity**

\[
dissimilarity = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} |i - j| P(i,j)
\]

46. **Energy [13]**

\[
ergy = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} [P(i,j)]^2
\]

This feature is also called Angular Second Moment (ASM) and Uniformity [12].

47. **Entropy (H)**

\[
entropy (H) = -\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} P(i,j) \log_2 [P(i,j)]
\]

48. **Homogeneity 1**

\[
\text{homogeneity 1} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{P(i,j)}{1 + |i - j|}
\]

This feature is also called Inverse Difference [12].

49. **Homogeneity 2 [13]**

\[
\text{homogeneity 2} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{P(i,j)}{1 + |i - j|^2}
\]

This feature is also called Inverse Difference Moment [12].

50. **Informational measure of correlation 1 (IMC1)**

\[
IMC1 = \frac{H - HXY_1}{\max\{HX, HY\}}
\]

Where \(H\) is the entropy (47).

51. **Informational measure of correlation 2 (IMC2)**

\[
IMC2 = \sqrt{1 - e^{-2(HXY_2 - H)}}
\]

Where \(H\) is the entropy (47).
52. **Inverse Difference Moment Normalized (IDMN)**

\[
IDMN = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{P(i,j)}{ \left( i - j \right)^2 + \frac{N_g^2}{N_g} }
\]

53. **Inverse Difference Normalized (IDN)**

\[
IDN = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{P(i,j)}{ \left( i - j \right)^2 + \frac{N_g^2}{N_g} }
\]

54. **Inverse variance**

\[
inverse \ variance = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} \frac{P(i,j)}{ \left( i - j \right)^2 }, i \neq j
\]

55. **Maximal Correlation Coefficient**

\[
maximal \ correlation \ coefficient = \sqrt{\text{second largest eigenvalue of } Q}
\]

\[
Q = \sum_{k=1}^{N_g} \frac{P(i,k)P(j,k)}{p_x(i)p_y(k)}
\]

56. **Maximum Probability**

\[
maximal \ probability = \max\{P(i,j)\}
\]

57. **Sum average (SA)**

\[
sum \ average \ (SA) = \sum_{i=2}^{2N_g} iP_{x+y}(i)
\]

58. **Sum entropy**

\[
sum \ entropy = -\sum_{i=2}^{2N_g} P_{x+y}(i) \log_2[P_{x+y}(i)]
\]

59. **Sum variance**

\[
sum \ variance = \sum_{i=2}^{2N_g} (i - SA)^2 P_{x+y}(i)
\]
60. **Variance (sum of squares)**

\[
\text{variance} = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} (i - \mu)^2 P(i, j)
\]
Gray-Level Run-Length matrix based features

Gray-level run-length matrix (GLRLM) based features, as described by Galloway et al. [4]. Run length metrics quantify gray level runs in an image. A gray level run is defined as the length in number of pixels, of consecutive pixels that have the same gray level value. In a gray level run length matrix \( p(i,j|\theta) \), the \((i,j)\)th element describes the number of times \( j \) a gray level \( i \) appears consecutively in the direction specified by \( \theta \). Let:

- \( p(i,j) \) be the \((i,j)\)th entry in the given run-length matrix \( p \), generalized for any direction \( \theta \),
- \( N_g \) the number of discrete intensity values in the image,
- \( N_r \) the maximum run length,
- \( N_s \) the total number of runs, where \( N_s = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p(i,j) \),
- \( p_r \) the sum distribution of the number of runs with run length \( j \), where \( p_r(j) = \sum_{i=1}^{N_g} p(i,j) \),
- \( p_g \) the sum distribution of the number of runs with gray level \( i \), where \( p_g(i) = \sum_{j=1}^{N_r} p(i,j) \),
- \( N_p \) the number of voxels in the image, where \( N_p = \sum_{j=1}^{N_r} j p_r \),
- \( p_n(i,j) \) the normalized run-length matrix, where \( p_n(i,j) = \frac{p(i,j)}{N_s} \),
- \( \mu_r \) the mean run length, where \( \mu_r = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} j p_n(i,j) \),
- \( \mu_g \) the mean gray level, where \( \mu_g = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} i p_n(i,j) \).

61. **Short Run Emphasis (SRE)**

\[
SRE = \frac{1}{N_s} \sum_{j=1}^{N_r} \frac{p_r(j)}{j^2}
\]

62. **Long Run Emphasis (LRE)**

\[
LRE = \frac{1}{N_s} \sum_{j=1}^{N_r} j^2 p_r
\]

63. **Gray Leven Non-Uniformity (GLN)**

\[
GLN = \frac{1}{N_s} \sum_{i=1}^{N_g} \frac{p_g(i)}{i^2}
\]
64. **Gray Level Non-Uniformity Normalized (GLNN)**

\[
GLNN = \frac{1}{N_s^2} \sum_{i=1}^{N_g} p_g^2
\]

65. **Run Length Non-Uniformity (RLN)**

\[
RLN = \frac{1}{N_s} \sum_{j=1}^{N_r} p_r^2
\]

66. **Run Length Non-Uniformity Normalized (RLNN)**

\[
RLNN = \frac{1}{N_s^2} \sum_{j=1}^{N_r} p_r^2
\]

67. **Run Percentage (RP)**

\[
RP = \frac{N_s}{N_p}
\]

68. **Low Gray Level Run Emphasis (LGRE)**

\[
LGRE = \frac{1}{N_s} \sum_{i=1}^{N_g} \frac{p_g}{i^2}
\]

69. **High Gray Level Run Emphasis (HGRE)**

\[
HGRE = \frac{1}{N_s} \sum_{i=1}^{N_g} i^2 p_g
\]

70. **Short Run Low Gray Level Emphasis (SRLGE)**

\[
SRLGE = \frac{1}{N_s} \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{p(i,j)}{i^2 j^2}
\]

71. **Short Run High Gray Level Emphasis (SRHGE)**

\[
SRHGE = \frac{1}{N_s} \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{p(i,j) i^2}{j^2}
\]

72. **Long Run Low Gray Level Emphasis (LRLGE)**

\[
LRLGE = \frac{1}{N_s} \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} \frac{p(i,j) j^2}{i^2}
\]
73. **Long Run High Gray Level Emphasis (LRHGE)**

\[
LRHGE = \frac{1}{N_x} \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p(i,j)i^2j^2
\]

74. **Gray level variance (GLV)**

\[
GLV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} (i - \mu_g)^2 p_n(i,j)
\]

75. **Run length variance (RLV)**

\[
RLV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} (j - \mu_r)^2 p_n(i,j)
\]

76. **Run entropy (RE)** [14]

\[
RE = \sum_{i=1}^{N_g} \sum_{j=1}^{N_r} p_n(i,j|\theta) \log_2[p_n(i,j)]
\]
Gray-Level size-zone matrix based features

Gray-level size-zone matrix (GLSZM) based features, as described by Thibault et al. [15, 16]. A gray level size-zone matrix describes the amount of homogeneous connected areas within the volume, of a certain size and intensity. The \((i,j)\)th entry of the GLSZM \(p(i,j)\) is the number of connected areas of gray-level (i.e. intensity value) \(i\) and size \(j\). GLSZM features therefore describe homogeneous areas within the tumor volume, describing tumor heterogeneity at a regional scale [5]. Let:

\[ p(i,j) \] be the \((i,j)\)th entry in the given GLSZM \(p\),

\[ N_g \] the number of discrete intensity values in the image,

\[ N_z \] the size of the largest, homogeneous region in the volume of interest,

\[ N_s \] the total number of homogeneous regions (zones), where \(N_s = \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} p(i,j)\),

\( p_z \) the sum distribution of the number of zones with size \(j\), where \(p_z(j) = \sum_{i=1}^{N_g} p(i,j)\),

\( p_g \) the sum distribution of the number of zones with gray level \(i\), where \(p_g(i) = \sum_{j=1}^{N_z} p(i,j)\),

\[ N_p \] the number of voxels in the image, where \(N_p = \sum_{j=1}^{N_z} j p_z\),

\( p_n(i,j) \) the normalized size-zone matrix, where \( p_n(i,j) = \frac{p(i,j)}{N_s} \),

\[ \mu_z \] the mean zone size, where \( \mu_z = \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} j p_n(i,j) \theta \),

\[ \mu_g \] the mean gray level, where \( \mu_g = \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} i p_n(i,j) \theta \).

77. Small area Emphasis (SAE)

\[ SAE = \frac{1}{N_s} \sum_{j=1}^{N_z} \left( \frac{p_z(j)}{j^2} \right) \]

78. Large area Emphasis (LAE)

\[ LAE = \frac{1}{N_s} \sum_{j=1}^{N_z} j^2 p_z \]

79. Intensity Non-Uniformity (IN)

\[ IN = \frac{1}{N_s} \sum_{i=1}^{N_g} p^2_g \]
80. Intensity Non-Uniformity Normalized (INN)

\[ INN = \frac{1}{N_s^2} \sum_{i=1}^{N_g} p_g^2 \]

81. Size-zone Non-Uniformity (SZN)

\[ SZN = \frac{1}{N_s} \sum_{j=1}^{N_z} p_z^2 \]

82. Size-zone Non-Uniformity Normalized (SZNN)

\[ SZNN = \frac{1}{N_s^2} \sum_{j=1}^{N_z} p_z^2 \]

83. Zone Percentage (ZP)

\[ ZP = \frac{N_s}{N_p} \]

84. Low intensity Emphasis (LIE)

\[ LIE = \frac{1}{N_s} \sum_{i=1}^{N_g} \frac{p_g}{i^2} \]

85. High intensity Emphasis (HIE)

\[ HIE = \frac{1}{N_z} \sum_{i=1}^{N_g} i^2 p_g \]

86. Low intensity small area Emphasis (LISAE)

\[ LISAE = \frac{1}{N_s} \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} \frac{p(i,j)}{i^2 j^2} \]

87. High intensity small area Emphasis (HISAE)

\[ HISAE = \frac{1}{N_z} \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} \frac{p(i,j) i^2}{j^2} \]

88. Low intensity large area Emphasis (LILAE)

\[ LILAE = \frac{1}{N_s} \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} \frac{p(i,j) j^2}{i^2} \]
89. **High intensity large area Emphasis (HILAE)**

\[ HILAE = \frac{1}{N_s} \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} p(i,j) i^2 j^2 \]

90. **Intensity variance (IV)**

\[ IV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} (i - \mu_g)^2 p_n(i,j) \]

91. **Size-zone variance (SZV)**

\[ SZV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} (j - \mu_z)^2 p_n(i,j) \]

92. **Zone entropy (ZE)**

\[ ZE = \sum_{i=1}^{N_g} \sum_{j=1}^{N_z} p_n(i,j) \log \left[ p_n(i,j) \right] \]
Gray-Level distance-zone matrix based features

Gray-level distance-zone matrix (GLDZM) based features, as described by Thibault et al. [6]. A gray level distance-zone matrix describes the amount of homogeneous connected areas within the volume, of a certain intensity and distance to the shape border. The shape border is defined by 6-connectedness in 3D (i.e. a voxel is on the border, if at least one face is exposed). In contrast to the original definition by Thibault et al. [6], the minimum distance to the border is 1, instead of 0 (i.e. voxels on the border have a distance of 1), to allow for correct feature calculations. The $(i,j)$th entry of the GLDZM $p(i,j)$ is the number of connected areas of gray-level (i.e. intensity value) $i$ and minimum distance $j$ to the shape border. GLSZM features therefore describe the radial distribution of homogeneous areas within the tumor volume. Let:

$p(i,j)$ be the $(i,j)$th entry in the given GLDZM $p$,

$N_g$, the number of discrete intensity values in the image,

$N_d$ the largest distance of a homogeneous region in the volume of interest to the shape border,

$N_s$ the total number of homogeneous regions (zones), where $N_s = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p(i,j)$,

$p_d$ the sum distribution of the number of zones with distance $j$, where $p_d(j) = \sum_{i=1}^{N_g} p(i,j)$,

$p_g$ the sum distribution of the number of zones with gray level $i$, where $p_g(i) = \sum_{j=1}^{N_s} p(i,j)$,

$N_p$ the number of voxels in the image, where $N_p = \sum_{j=1}^{N_d} p_d$,

$p_n(i,j)$ the normalized size-zone matrix, where $p_n(i,j) = \frac{p(i,j)}{N_s}$,

$\mu_d$ the mean distance, where $\mu_d = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} j p_n(i,j)$,

$\mu_g$ the mean gray level, where $\mu_g = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} i p_n(i,j)$.

**Small distance Emphasis (SDE)**

$$SDE = \frac{1}{N_s} \sum_{j=1}^{N_d} \frac{p_d}{j^2}$$
94. **Large distance Emphasis (LDE)**

\[ LDE = \frac{1}{N_S} \sum_{j=1}^{N_d} j^2 p_d \]

95. **Intensity Non-Uniformity (IN)**

\[ IN = \frac{1}{N_S} \sum_{i=1}^{N_g} p_g^2 \]

96. **Intensity Non-Uniformity Normalized (INN)**

\[ INN = \frac{1}{N_S^2} \sum_{i=1}^{N_g} p_g^2 \]

97. **Distance-zone Non-Uniformity (DZN)**

\[ DZN = \frac{1}{N_S} \sum_{j=1}^{N_d} p_d^2 \]

98. **Distance-zone Non-Uniformity Normalized (DZNN)**

\[ DZNN = \frac{1}{N_S^2} \sum_{j=1}^{N_d} p_d^2 \]

99. **Zone Percentage (ZP)**

\[ ZP = \frac{N_s}{N_p} \]

100. **Low intensity Emphasis (LIE)**

\[ LIE = \frac{1}{N_S} \sum_{i=1}^{N_g} \frac{p_g}{i^2} \]

101. **High intensity Emphasis (HIE)**

\[ HIE = \frac{1}{N_S} \sum_{i=1}^{N_g} \frac{i^2 p_g}{i^2} \]

102. **Low intensity small distance Emphasis (LISDE)**

\[ LISDE = \frac{1}{N_S} \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{p(i,j)}{i^2 j^2} \]
103. High intensity small distance Emphasis (HISDE)

\[ HISAE = \frac{1}{N_g \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{p(i,j)i^2}{j^2}} \]

104. Low intensity large distance Emphasis (LILDE)

\[ LILAE = \frac{1}{N_g \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{p(i,j)j^2}{i^2}} \]

105. High intensity large distance Emphasis (HILDE)

\[ HILAE = \frac{1}{N_g \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} \frac{p(i,j)i^2j^2}{i^2j^2}} \]

106. Intensity variance (IV)

\[ IV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} (i - \mu_g)^2 p_n(i,j) \]

107. Distance-zone variance (DZV)

\[ SZV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} (j - \mu_d)^2 p_n(i,j) \]

108. Distance-zone entropy (DZE)

\[ DZE = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p_n(i,j) \log_2[p_n(i,j)] \]
**Neighborhood gray tone difference matrix based features**

Neighborhood gray tone difference matrix (NGTDM) based features, as described by Amadasun and King [7]. The \( i \)th entry of the NGTDM \( s(i|d) \) is the sum of gray level differences of voxels with intensity \( i \) and the average intensity \( A_i \) of their neighboring voxels within a distance \( d \). In contrast to the original paper, a complete neighborhood is not required and \( A_i \) is determined over the valid voxels. Let:

- \( n_i \) be the number of voxels with gray level \( i \),
- \( N_v = \sum n_i \), the total number of voxels (defined as \( n^2 \) by Amadasun and King [7]),
- \( s(i) = \left\{ \begin{array}{ll} \sum_n |i - A_i| & \text{for } n_i > 0 \\ 0 & \text{otherwise} \end{array} \right. \), generalized for any distance \( d \),
- \( N_g \) be the maximum discrete intensity level in the image,
- \( p(i) = \frac{n_i}{N_v} \), the probability of gray level \( i \),
- \( N_p \), the total number of gray levels present in the image.

109. **Coarseness**

\[
\text{coarseness} = \frac{1}{\varepsilon + \sum_{i=1}^{N_g} p(i) s(i)}
\]

Where \( \varepsilon \) is a small number to prevent coarseness becoming infinite.

110. **Contrast**

\[
\text{contrast} = \left( \frac{1}{N_p(1 - N_p)} \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i)p(j)(i - j)^2 \right) \left( \frac{1}{N_v} \sum_{i=1}^{N_g} s(i) \right)
\]

111. **Busyness**

\[
\text{busyness} = \frac{\sum_{i=1}^{N_g} p(i)s(i)}{\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} |p(i) - p(j)|}, \quad p(i) \neq 0, \ p(j) \neq 0
\]

112. **Complexity**

\[
\text{complexity} = \frac{1}{N_v} \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} |i - j| \left\{ \frac{p(i)s(i) + p(j)s(j)}{p(i) + p(j)} \right\}, \quad p(i) \neq 0, \ p(j) \neq 0
\]

113. **Strength**

\[
\text{strength} = \frac{\sum_{i=1}^{N_g} \sum_{j=1}^{N_g} [p(i) + p(j)](i - j)^2}{\varepsilon + \sum_{i=1}^{N_g} s(i)}, \quad p(i) \neq 0, \ p(j) \neq 0
\]
Neighboring gray level dependence matrix based features

Neighboring gray level dependence matrix (NGLDM) based features, as described by Sun and Wee [8]. NGLDM features are invariant under spatial rotation. The \((i,j)\)th entry of the NGLDM \(p(i,j|d,a)\) describes the number of neighborhoods with center voxel gray-level (i.e. intensity value) \(i\) and dependence (i.e. number of dependent voxels) \(k = j - 1\). A neighborhood are all voxels within a distance \(d\) from the center voxel. The center voxel and a neighboring voxel are dependent if their absolute gray value difference \(\leq a\), the dependency coarseness parameter. The features originally specified by Sun and Wee are analogous to the GLRLM and GLSZM features, and the feature set is extended accordingly. Let:

\(p(i,j)\) be the \((i,j)\)th entry in the given NGLDM \(p\), generalized for any \(d\) and \(a\),

\(N_g\), the number of discrete intensity values in the image,

\(N_d\), the maximum dependence value,

\(N_s\), the total number of neighborhoods, where \(N_s = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} p(i,j)\),

\(p_d\), the sum distribution of the number of neighborhoods with dependence \(j = k + 1\), where \(p_d(j) = \sum_{i=1}^{N_g} p(i,j)\),

\(p_g\), the sum distribution of the number of neighborhoods with center voxel gray level \(i\), where \(p_g(i) = \sum_{j=1}^{N_d} p(i,j)\),

\(p_n(i,j)\) the normalized NGLDM, where \(p_n(i,j) = \frac{p(i,j)}{N_s}\),

\(\mu_d\), the mean dependence, where \(\mu_d = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} j p_n(i,j|\theta)\),

\(\mu_g\), the mean gray level, where \(\mu_g = \sum_{i=1}^{N_g} \sum_{j=1}^{N_g} i p_n(i,j|\theta)\).

Note: By definition, the number of voxels in the image \((N_p)\) equals the total number of neighborhoods \((N_s)\), since in our implementation every voxel is considered to have a neighborhood.

Feature “dependence percentage” \(\left(\frac{N_s}{N_p}\right)\), which is the equivalent to run-length feature “run percentage” (RP; 67), is therefore omitted, because it will always evaluate to 1.
114. **Small Dependence Emphasis (SDE)**

\[
SDE = \frac{1}{N_s} \sum_{j=1}^{N_d} \frac{p_d}{j^2}
\]

This feature is also called Small Number Emphasis [8].

115. **Large Dependence Emphasis (LDE)**

\[
LDE = \frac{1}{N_s} \sum_{j=1}^{N_d} j^2 p_d
\]

This feature is also called Large Number Emphasis [8].

116. **Gray-level Non-Uniformity (GLN)**

\[
GLN = \frac{1}{N_s} \sum_{i=1}^{N_g} p^2_g
\]

117. **Gray-level Non-Uniformity Normalized (GLNN)**

\[
GLNN = \frac{1}{N_s^2} \sum_{i=1}^{N_g} p^2_g
\]

118. **Dependence Non-Uniformity (DN)**

\[
DN = \frac{1}{N_s} \sum_{j=1}^{N_d} p^2_d
\]

This feature is also called Number Nonuniformity [8].

119. **Dependence Non-Uniformity Normalized (DNN)**

\[
DNN = \frac{1}{N_s^2} \sum_{j=1}^{N_d} p^2_d
\]

120. **Low Gray-level Emphasis (LGE)**

\[
LGE = \frac{1}{N_s} \sum_{i=1}^{N_g} \frac{p_g}{i^2}
\]
121. **High Gray-level Emphasis (HGE)**

\[
HGE = \frac{1}{N_g} \sum_{i=1}^{N_g} i^2 p_g
\]

122. **Low Gray-level small Dependence Emphasis (LGSDE)**

\[
LGSDE = \frac{1}{N_g} \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p(i,j) \frac{i^2}{j^2}
\]

123. **High Gray-level small Dependence Emphasis (HGSDE)**

\[
HGSDE = \frac{1}{N_g} \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p(i,j) i^2
\]

124. **Low Gray-level large Dependence Emphasis (LGLDE)**

\[
LGLDE = \frac{1}{N_g} \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p(i,j) j^2 \frac{i}{j^2}
\]

125. **High Gray-level large Dependence Emphasis (HGLDE)**

\[
HGLDE = \frac{1}{N_g} \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p(i,j) i^2 j^2
\]

126. **Gray-level variance (GLV)**

\[
GLV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} (i - \mu_g)^2 p_n(i,j)
\]

127. **Dependence variance (DV)**

\[
DV = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} (j - \mu_d)^2 p_n(i,j)
\]

128. **Dependence entropy (DE), also called Entropy [8]**

\[
DE = \sum_{i=1}^{N_g} \sum_{j=1}^{N_d} p_n(i,j) \log_2[ p_n(i,j) ]
\]

Note: the definition of entropy by Sun and Wee [8] uses the dependence counts \( p \) instead of the dependence propabilities \( p_n \).
129. **Second moment (SM) [8]**

\[
SM = \frac{\sum_{i=1}^{N_B} \sum_{j=1}^{N_D} p(i,j)^2}{N_S}
\]

Note: for this feature, defined by Sun and Wee [8], there is no gray-level run-length equivalent.
Machine learning

Machine learning has provided self-driving cars, practical speech recognition, effective web search, a vastly improved understanding of the human genome, and can be leveraged in radiomics analysis. Given below are resources for two of the most effective software packages (caret and scikit-learn) to perform machine learning through the prevalent coding languages R and Python. These resources will enable the reader to gain knowledge implementing appropriate machine learning techniques though practical know-how, leading to quick, powerful, and appropriate application of machine learning techniques to new problems.

- **caret**
  

  [https://cran.r-project.org/web/packages/caret/caret.pdf](https://cran.r-project.org/web/packages/caret/caret.pdf)

- **scikit-learn**
  

Example PET/CT and MR imaging protocols for Radiomics

One of the major challenges of radiomics is standardization, which is especially important for multicenter studies. A recent phantom study demonstrated that inter-scanner differences in radiomics features can be substantial and should not be neglected. Therefore, replication and validation of a developed radiomic model is only possible if a complete set of protocols is available (e.g., patient indication and preparation, image acquisition, reconstruction, processing, contouring, feature extraction, radiomic analysis, reporting, data collection, storage and mining). Ideally, all of the acquired data is obtained in accordance with an internationally agreed protocol. Nevertheless, the complete protocol should be reported extensively enabling external review and validation. We provide example protocols for PET/CT and MR imaging.

In the future, protocols should be agreed upon and developed by the community to achieve standardization for all modalities, scanner manufacturers, disease sites, and radiomics workflow techniques (e.g., patient indication and preparation, image acquisition, reconstruction, processing, contouring, feature extraction, radiomic analysis, reporting, data collection, storage and mining).

The take home message is that researchers should make every effort to provide as much detail and information as possible/practical when publishing a radiomics study.

NB: These protocols are not recommendations for optimal radiomics studies! They are merely intended to illustrate the desired level of detail to be supplied as supplementary material when reporting findings in future radiomics publication.
Radiomics PET/CT imaging protocol

Background

The goal of the Radiomics project is to link the phenotype through imaging to the genotype in tumors. One of the activities is to extract existing and new features are from PET and CT imaging. This protocol is meant to minimize known sources of variations in the PET and CT imaging. It is a condensed version of the so-called Netherlands protocol [17, 18] and the EANM procedure guideline for tumour PET imaging version 2.0 [19].

General considerations

- Date of last cycle of chemotherapy, administration of growth factors (G-CSF, GM-CSF) or other treatments must be reported.
- The interval between end of last (chemo-)therapy cycle and FDG-PET must be at least 14 days.

Patient instruction/preparation before the administration of FDG

- Patients should fast for at least 6h before the administration of FDG.
- Patients should take in 1l of water during 2h prior to the administration of FDG. In case of venous hydration, no glucose may be present in the infusate.
- Patients should not exercise 6h prior to the administration of FDG
- Blood glucose level must be measured before the administration of FDG using calibrated and medically approved devices.
- If blood glucose level is greater than 11 mmol/L (about 200 mg/dL), the patient must be rescheduled.
Waiting conditions, preparation room and room temperature must be comfortable to allow optimal resting conditions during and after FDG administration in order to minimize muscle and brown-fat uptake. Blankets must be provided to the patient when needed/requested.

- A urinary catheter may be used upon indication preferably placed before administration of FDG.
- Patient weight and height must be measured using calibrated and medically approved devices.

**In case of type I and insulin-dependent type II diabetes:**
- It is preferred to reach normal blood glucose levels in mutual agreement with patient and referring physician
- Study will be scheduled preferably at the end of morning
- Patient will have a normal breakfast at 7:00 A.M. and uses a regular dose of insulin, followed by fasting as described above.

**In case of type II diabetes:**
- Study will be scheduled preferably at the end of morning
- Patients will need to be fasted for at least 6 h. Intake of water is recommended as is for non-diabetics.
- Oral anti diabetic drugs should be continued.

**FDG administration and dosage**

- FDG should be administered through a three-way valve system attached to a venous canula.
- After injection, the entire administration system should be flushed with at least 10 cc saline to avoid remaining activity in the system.
- A dosage should be administered in accordance with the European Association of Nuclear Medicine recommendations for FDG administered activity [19].
- Administered dose should be measured with an error of ±3%

**Patient instruction/preparation after administration of FDG**

- Patients should drink 0.5 l water before the PET examination. When necessary, 0.5 l water or saline can be given intravenously.
- Patients should be instructed to relax, avoid motion and unnecessary talking,
- Patients are allowed to visit the rest room and are asked to void the bladder shortly (5 to 10 min) before the PET examination.

**PET-CT acquisition**

- The patient shall be scanned supine, head-first, with hands above the head. A knee rest should be provided. If the patient is to be treated with radiation therapy an immobilization device such as a wing board and T-bar may be used.
- Blankets must be provided to the patient when needed/requested.
- A photograph should be made for all patients positioned in a non-standard manner on the scanner to improve reproducibility for these patients.
- Patients receiving radiotherapy should be scanned in the radiotherapy treatment position.
• Correct isotope and decay times should be set or entered in the acquisition computer.
• FDG activity, activity calibration time, patient weight must be correctly set when required or possible by the acquisition software.
• The (low dose) CT attenuation scan shall be made first, followed by the PET scan. For GE scanners the 4D CT should be acquired at the beginning of the scanning session and with the Siemens PET/CT at the end of the scanning session.
• The (low dose) CT attenuation scan shall be a free-breathing scan.
• The CT and PET scan shall cover at least the whole thorax.
• 3D PET acquisition shall be used.
• The PET acquisition should start at 55 to 75 min after FDG administration.
• 5 min emission scans shall be acquired per bed position.
• The scan should start at the most inferior bed position

**PET scan and reconstruction parameters**

• The following correction methods shall be applied
  o Decay correction
  o Dead time correction
  o Detector efficiencies correction (normalization)
  o Random correction
  o Attenuation correction
  o Scatter correction

• PET images shall be reconstructed with and without attenuation correction. Besides locally preferred reconstruction settings for visual interpretation, EARL compliant reconstruction setting should be used in order to allow for harmonized interpretation and analysis of images collected across various centers.
**CT scan and reconstruction parameters**

The following scan acquisition protocols shall be used for the CT

<table>
<thead>
<tr>
<th>Item</th>
<th>Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acquisition type</strong></td>
<td>Helical</td>
</tr>
<tr>
<td><strong>Tube</strong></td>
<td>120kVp / 300MAs or higher for large patients (for low dose CT: users should use the vendor specified setting settings)</td>
</tr>
<tr>
<td><strong>Auto mA</strong></td>
<td>No</td>
</tr>
<tr>
<td><strong>Orientation</strong></td>
<td>Caudo-cranial</td>
</tr>
</tbody>
</table>

The following scan reconstruction protocols shall be used for the CT

<table>
<thead>
<tr>
<th>Item</th>
<th>Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Slice thickness</strong></td>
<td>3mm</td>
</tr>
<tr>
<td><strong>Reconstruction interval</strong></td>
<td>1mm</td>
</tr>
<tr>
<td><strong>Window/Level</strong></td>
<td>Lung</td>
</tr>
<tr>
<td><strong>Pixels</strong></td>
<td>512x512</td>
</tr>
<tr>
<td><strong>Kernel</strong></td>
<td>B30f med smooth or B30f ultra sharp</td>
</tr>
</tbody>
</table>

The following guidelines apply to contrast CT

<table>
<thead>
<tr>
<th>Item</th>
<th>Norm</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preparation</strong></td>
<td>Clear liquid 4hr prior to scan</td>
</tr>
<tr>
<td><strong>Injection rate</strong></td>
<td>3-4 ml/s</td>
</tr>
<tr>
<td><strong>Contrast volume &amp; type</strong></td>
<td>150ml Optiray 320, Xenetix 300 or equivalent</td>
</tr>
<tr>
<td><strong>Scan delay</strong></td>
<td>Auto-monitoring</td>
</tr>
</tbody>
</table>
**Data transfer and post-processing**

- Both the uncorrected and attenuated corrected PET scan and CT data shall be transferred and stored using the DICOM standard.
- SUV shall be calculated using the following equation
  
  \[ \text{SUV} = \frac{\text{ACvoi} \text{(kBq/ml)}}{\text{FDGdose} \text{(MBq)/BW(kg)}} \]

  With ACvoi: activity in the volume of interest; FDGdose: administered FDG activity; BW: bodyweight.

- SUV corrected for blood glucose shall be calculated using the following equation
  
  \[ \text{SUV}_{\text{glu}} = \frac{\text{ACvoi} \text{(kBq/ml)}}{\text{FDGdose} \text{(MBq)/BW(kg)}} \times \frac{\text{Pglu} \text{(mmol/l)}}{5.0} \]

  With Pglu the blood glucose level.

**Quality Control and Scanner Calibration**

- PET/CT systems should be EARL accredited for multicenter PET/CT studies.
- Daily QC and or daily setup/tuning measurements should be performed according to the manufacturer’s specification.
- The PET scanner should be calibrated using the SOP described in Appendix 1, and QC results should meet the requirements indicated in the EANM guideline version 2.0.
- A PET image quality and volume recovery procedure should be done using the SOP described in Appendix 2, and QC results should meet the requirements indicated in the EANM guideline version 2.0.
- Monthly or more frequent QC on the CT via a scan of a uniform water phantom and the evaluation of CT numbers.
- Quarterly or more frequent couch linearity check
- Quarterly or more frequent CAT phantom check to assess image quality
- Quarterly or more frequent density/CT number check
Appendix 1: SOP/CRF “Calibration PET”

Accreditation
PET/CT systems should be EARL accredited for multicenter PET/CT studies.

Site / other information
Site Name =
Scanner type and model =
Volume of calibration phantom = (ml)
Scan date = (dd:mm:yyyy)
Scan time = (hh:mm:ss)

Materials
• About 70 MBq 18F-FDG (yet exact amount in syringe must be known)
• Cylindrical calibration phantom with exactly known volume (preferably 20cm diameter, 20 to 30 cm long phantom)
• PET or PET/CT scanner
• Dose calibrator

Preparation
• Prepare a 5 to 10 cc syringe with about 70 MBq F18-FDG
• Activity = .........................(MBq) specified or calibrated at .................(hh:mm:ss)
• Fill calibration phantom completely (with water) and then remove 10 cc water from the phantom
• Put the FDG in the phantom and flush the syringe a few times. Make sure that all activity is in the phantom. When possible absence of residual activity may be measured.
• Extensively shake the phantom to homogenize activity throughout the phantom

PET or PET CT scan acquisition
• Put phantom in the PET or PET/CT scanner
• Acquire a PET or PET/CT scan consisting of at least 2 PET bed positions of at least 5 min each.
• PET and PET/CT scans should be performed identically to patient studies as prescribed in the clinical protocol and must include a CT for attenuation correction purposes (CT-AC).
• Start of PET acquisition time (read from console) = ......................... (hh:mm:ss)
• PET scan acquisition date = ......................... (dd:mm:yyyy)

Reconstructions
• Reconstructions should be performed with attenuation, scatter, normalization, decay, dead time corrections.
• Follow the instructions given in the study protocol for reconstruction of the clinical studies.

Archiving
• All relevant data (SOP/CRF and reconstructed images) should be stored.
• Reconstructed images must be stored in DICOM format.
• DICOM files must fulfill the ‘DICOM conformance statement’ of the PET or PET/CT scanner manufacturer (Siemens, Philips of GE).

Pitfalls
• Make sure that all clocks (of dose calibrator and PET or PET/CT scanner) are synchronized.
• Remaining activity in the syringe will result in incorrect verification of PET scanner calibration.
Appendix 2: SOP/CRF “Image Quality & Volume Recovery”

Accreditation
PET/CT systems should be EARL accredited for multicenter PET/CT studies.

Site / other information
Site Name = 
Scanner type and model = 
Scan date = (dd:mm:yyyy)

Materials
- Various 18F activities in 2-5 ml syringes, two syringe with 20 MBq specified at expected phantom acquisition time.
- Bottle of (exactly) 1000 cc
- Dose calibrator with known time difference between PET and calibrator
- NEMA NU2-2001 (section 7) Image Quality phantom

Preparation
Stock / solution for spheres
- Fill bottle with exactly 1000 cc water
- Add 20 MBq 18F-FDG
- Make sure all activity is removed from the syringe into the phantom.
- Activity = ........................................ MBq specified or calibrated at .................. (hh:mm:ss)
- Volume (of FDG in syringe) = ........................................... (ml)
- Homogenize solution (20 MBq FDG in 1000 cc)
- Fill all spheres of the NEMA NU2-2002 image quality phantom with this solution.

Filling of back ground compartment of image quality phantom:
- Fill back ground compartment completely with water
- Remove 30cc water from the back ground compartment of the phantom
- Add 20MBq FDG in the 9700 cc background compartment.
- Make sure all activity is removed from the syringe and entered into the phantom (i.e. flush the syringe a few times). When possible check for residual activity in the syringe.
- Dose = ............................................MBq specified at .................. (hh:mm:ss)
- Homogenize the solution in the background compartment by shaking the phantom extensively.

PET or PET/CT Scans
- Put phantom in the PET or PET/CT scanner
- Acquire a PET or PET/CT scan consisting of at least 2 PET bed positions of at least 5 min each.
- PET and PET/CT scans should be performed identically to patient studies as prescribed in the clinical protocol and must include a CT for attenuation correction purposes (CT-AC).
- Start of PET acquisition time (read from console) = .................. (hh:mm:ss)
- PET scan acquisition date = ................................. (dd:mm:yyyy)

Reconstructions
- Reconstructions should be performed with attenuation, scatter, normalization, decay, dead time corrections.
- Follow the instructions given in the study protocol for reconstruction of the clinical studies.

Archiving
- All relevant data (SOP/CRF and reconstructed images) should be stored.
- Reconstructed images must be stored in DICOM format. DICOM files must fulfill the ‘DICOM conformance statement’ of the PET or PET/CT scanner manufacturer (Siemens, Philips of GE).
## Radiomics MR imaging protocol

<table>
<thead>
<tr>
<th>Manufacturer / Scanner type</th>
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</thead>
<tbody>
<tr>
<td>Field strength (T)</td>
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<tr>
<td>Coil</td>
</tr>
<tr>
<td>Structure</td>
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<tr>
<td>Sequence name</td>
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</table>

<table>
<thead>
<tr>
<th>Patient position =</th>
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<tbody>
<tr>
<td>Scan technique =</td>
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<tr>
<td>Dimension =</td>
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<tr>
<td>Orientation =</td>
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<tr>
<td>Phase encoding direction=</td>
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<tr>
<td>echoes =</td>
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<tr>
<td>partial echo =</td>
</tr>
<tr>
<td>Acquisition mode =</td>
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<tr>
<td>TE (ms) =</td>
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<tr>
<td>Act. TE (ms) =</td>
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<tr>
<td>TR =</td>
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<tr>
<td>Act. TR (ms) =</td>
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<tr>
<td>Flip angle (deg) =</td>
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<tr>
<td>WFS (pix) / BW (Hz) =</td>
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<tr>
<td>Fast Imaging mode =</td>
</tr>
<tr>
<td>shot mode =</td>
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<tr>
<td>TSE factor =</td>
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<tr>
<td>TSE es / shot (ms) =</td>
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<tr>
<td>k-space filling method=</td>
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<td>NSA =</td>
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<td>slices per</td>
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<tr>
<td>slab=</td>
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<tr>
<td>slice gap (mm) =</td>
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<tr>
<td>slice orientation =</td>
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<tr>
<td>phase oversampling =</td>
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<tr>
<td>fat shift direction =</td>
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<td>slice thickness (mm) =</td>
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<tr>
<td>Packages =</td>
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<td>Scan percentage (%) =</td>
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<tr>
<td>FOV (mm$^3$) =</td>
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<td>Reconstructed voxel size (mm$^3$) =</td>
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<td>Reconstruction matrix (mm$^2$) =</td>
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<td>Reconstruction mode =</td>
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<tr>
<td>Half scan factor =</td>
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<td>Water-fat shift =</td>
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</table>
Parallell imaging (R factor) =  
Accelleration factor =  

Shim =
Total scan duration =

- mDIXON
- Fat suppression
- Water suppression

Please specify settings

- Geometry correction
- Flow compensation
- Cardiac synchronization

Please specify settings

- Motion smoothing
- Respiratory compensation
- Navigator respiratory compens.

- Magnetization Transfer Contrast
- Arterial Spin labeling

Please specify settings

- Diffusion mode
- Susceptibility mode

Please specify settings

- Dynamic study
- Spectroscopy study
References


