Supplementary Material for: Therapy Response Prediction in Patients with Metastatic Soft Tissue Sarcomas Using CT based Delta Radiomics

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Frederik Hartmann [1], Christianne Jansma [2,3],
Manon Verburg[2], David Hanff [1], Wiro J. Niessen[4],
Geert J.L.H. van Leenders[5], Cornelis Verhoef[2], Enrico Martin [3],
Stefan Klein [1], Dirk J. Grünhagen[2], Martijn P.A. Starmans [1,5], Douwe J. Spaanderman [1]

[1]Department of Radiology and Nuclear Medicine, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands.
[2]Department of Surgical Oncology and Gastrointestinal Surgery, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands.
[3]Department of Plastic and Reconstructive Surgery, University Medical Center Utrecht, Utrecht, the Netherlands.
[4]Faculty of Medical Sciences, University of Groningen, Groningen, the Netherlands.
[5]Department of Pathology and Clinical Bioinformatics, Erasmus MC Cancer Institute, University Medical Center Rotterdam, Rotterdam, the Netherlands.

Corresponding authors: f.hartmann@erasmusmc.nl; m.starmans@erasmusmc.nl;

Supplement 1: Delta Radiomics Computation

This section formalizes the computation of delta-radiomics at the subject level.

Metastasis-wise aggregation (with correspondence). For a given subject, let $x_i^t \in \mathbb{R}$ denote the value of a scalar radiomic feature measured on metastasis i at time $t \in \{0, 1\}$, where $t = 0$ is pre-treatment (baseline) and $t = 1$ is follow-up. If a metastasis-to-metastasis correspondence between time points is available, let $\mathcal{I}$ be the index set of matched metastases, with $n = |\mathcal{I}|$ denoting the number of matched metastases.

For each $i \in \mathcal{I}$ the additive (absolute) change d_i can be defined as

$$d_i \overset{\text{def}}{=} x_i^1 - x_i^0, \tag{1}$$

and, when $x_i^0 \neq 0$, the relative change $d_{i,\text{rel}}$ can be defined as

$$d_{i,\text{rel}} \overset{\text{def}}{=} \frac{x_i^1 - x_i^0}{x_i^0}. \tag{2}$$

To obtain a single per-subject delta-radiomic value Δx, we apply an aggregation function f

$$f : \mathbb{R}^n \to \mathbb{R}, \qquad (z_1, \ldots, z_n) \mapsto f(z_1, \ldots, z_n),$$

that is permutation-invariant (i.e., symmetric). Then

$$\Delta x \overset{\text{def}}{=} f\big((d_i)_{i \in \mathcal{I}}\big), \qquad \Delta x_{\text{rel}} \overset{\text{def}}{=} f\big((d_{i,\text{rel}})_{i \in \mathcal{I}}\big). \tag{3}$$

In the main analysis, f was chosen to be the sum,

$$\Delta x = \sum_{i \in \mathcal{I}} d_i, \qquad \Delta x_{\text{rel}} = \sum_{i \in \mathcal{I}} d_{i,\text{rel}}. \tag{4}$$

In the supplements, we additionally evaluated the arithmetic mean

$$\Delta x = \frac{1}{p} \sum_{i \in \mathcal{I}} d_i, \qquad \Delta x_{\text{rel}} = \frac{1}{p} \sum_{i \in \mathcal{I}} d_{i,\text{rel}}, \tag{5}$$

and the maximum

$$\Delta x = \max_{i \in \mathcal{I}} d_i, \qquad \Delta x_{\text{rel}} = \max_{i \in \mathcal{I}} d_{i,\text{rel}}. \tag{6}$$

Remarks. (i) Relative changes are undefined when $x_i^0 = 0$; such lesions must be handled with a pre-specified rule, here the replacement with 1 (e.g., corresponding to 100% growth) is chosen. (ii) The definitions above apply to scalar features; vector-valued features can be handled component-wise.

Image-wise aggregation (without correspondence). As an alternative, when metastasis-level correspondences are not available, all feature values at each time point can be aggregated before computing the change to achieve image-wise aggregation.

For each subject s, the baseline feature values were collected into the vector

$$\mathbf{x}_s^0 = \left(x_j^0\right)_{j=1}^{n_0},$$

and the follow-up feature values into

$$\mathbf{x}_s^1 = \left(x_k^1\right)_{k=1}^{n_1},$$

where n_0 and n_1 denote the number of segmented metastases at baseline and follow-up, respectively. To obtain a single per-subject delta-radiomic value Δx, we apply an aggregation function f

$$f : \mathbb{R}^m \to \mathbb{R}$$

separately to $\mathbf{x}_s^0$ and $\mathbf{x}_s^1$. The absolute image-wise delta-radiomic value can now be computed as

$$\Delta x_{\text{img},s} = f\left(\mathbf{x}_s^1\right) - f\left(\mathbf{x}_s^0\right), \tag{7}$$

and the relative image-wise delta-radiomic value as

$$\Delta x_{\text{rel,img},s} = \begin{cases} \dfrac{f\left(\mathbf{x}_s^1\right) - f\left(\mathbf{x}_s^0\right)}{f\left(\mathbf{x}_s^0\right)}, & \text{if } f\left(\mathbf{x}_s^0\right) \neq 0, \\ 1, & \text{if } f\left(\mathbf{x}_s^0\right) = 0. \end{cases} \tag{8}$$

The functions f evaluated in the supplements are:

$$f_{\text{sum}}(\mathbf{x}) = \sum_{r=1}^{m} x_r, \tag{9}$$

$$f_{\text{mean}}(\mathbf{x}) = \frac{1}{m} \sum_{r=1}^{m} x_r, \tag{10}$$

$$f_{\text{max}}(\mathbf{x}) = \max_{1 \leq r \leq m} x_r. \tag{11}$$

Equations (7)–(8) are applied for each choice of f.

Supplement 2: PyRadiomics Features

The used features are shown in Table 1. All features are extracted with PyRadiomics using default settings (version 3.1.0).

Table 1 PyRadiomics features grouped by category

Category	**Features**
Shape	Elongation, Flatness, LeastAxisLength, MajorAxisLength, Maximum2DDiameterColumn, Maximum2DDiameterRow, Maximum2DDiameterSlice, Maximum3DDiameter, MeshVolume, MinorAxisLength, Sphericity, SurfaceArea, SurfaceVolumeRatio, VoxelVolume
First-order	10Percentile, 90Percentile, Energy, Entropy, InterquartileRange, Kurtosis, Maximum, MeanAbsoluteDeviation, Mean, Median, Minimum, Range, RobustMeanAbsoluteDeviation, RootMeanSquared, Skewness, TotalEnergy, Uniformity, Variance
GLCM	Autocorrelation, ClusterProminence, ClusterShade, ClusterTendency, Contrast, Correlation, DifferenceAverage, DifferenceEntropy, DifferenceVariance, Id, Idm, Idmn, Idn, Imc1, Imc2, InverseVariance, JointAverage, JointEnergy, JointEntropy, MCC, MaximumProbability, SumAverage, SumEntropy, SumSquares
GLDM	DependenceEntropy, DependenceNonUniformity, DependenceNonUniformityNormalized, DependenceVariance, GrayLevelNonUniformity, GrayLevelVariance, HighGrayLevelEmphasis, LargeDependenceEmphasis, LargeDependenceHighGrayLevelEmphasis, LargeDependenceLowGrayLevelEmphasis, LowGrayLevelEmphasis, SmallDependenceEmphasis, SmallDependenceHighGrayLevelEmphasis, SmallDependenceLowGrayLevelEmphasis
GLRLM	GrayLevelNonUniformity, GrayLevelNonUniformityNormalized, GrayLevelVariance, HighGrayLevelRunEmphasis, LongRunEmphasis, LongRunHighGrayLevelEmphasis, LongRunLowGrayLevelEmphasis, LowGrayLevelRunEmphasis, RunEntropy, RunLengthNonUniformity, RunLengthNonUniformityNormalized, RunPercentage, RunVariance, ShortRunEmphasis, ShortRunHighGrayLevelEmphasis, ShortRunLowGrayLevelEmphasis
GLSZM	GrayLevelNonUniformity, GrayLevelNonUniformityNormalized, GrayLevelVariance, HighGrayLevelZoneEmphasis, LargeAreaEmphasis, LargeAreaHighGrayLevelEmphasis, LargeAreaLowGrayLevelEmphasis, LowGrayLevelZoneEmphasis, SizeZoneNonUniformity, SizeZoneNonUniformityNormalized, SmallAreaEmphasis, SmallAreaHighGrayLevelEmphasis, SmallAreaLowGrayLevelEmphasis, ZoneEntropy, ZonePercentage, ZoneVariance
NGTDM	Busyness, Coarseness, Complexity, Contrast, Strength

Supplement 3

Table 2 shows the results of the method presented in the main texts of the paper as well as the additionally performed experiments outlined in Supplements 1.

Table 2 Results from the presented main experiment (metastasis-wise,sum,relative) and supplementary approaches. For each metric, the arithmetic mean and 95% confidence intervals are reported. The highest mean value across all approaches is shown in bold, while the highest mean values within each input type (Full Radiomics, Diameter-only, and Volume-only) are underlined. In case of identical means, the value with the narrower 95% confidence interval is highlighted.

			Full radiomics (imaging) input		Diameter-only		Volume-Only	
Merging	Aggregation	Abs or Rel	c-index	cAUC	c-index	cAUC	c-index	cAUC
metastasis-wise	sum	relative	**0.68 [0.60; 0.76]**	**0.75 [0.55; 0.95]**	0.61 [0.51; 0.70]	0.60 [0.35; 0.85]	0.65 [0.53; 0.76]	0.63 [0.38; 0.88]
metastasis-wise	sum	absolute	0.55 [0.44; 0.66]	0.52 [0.33; 0.71]	0.63 [0.53; 0.72]	0.60 [0.35; 0.84]	0.61 [0.52; 0.71]	0.59 [0.35; 0.82]
metastasis-wise	mean	relative	0.66 [0.58; 0.75]	0.72 [0.56; 0.87]	0.61 [0.51; 0.72]	0.57 [0.33; 0.82]	0.63 [0.53; 0.72]	0.60 [0.35; 0.85]
metastasis-wise	mean	absolute	0.55 [0.46; 0.65]	0.48 [0.23; 0.73]	0.65 [0.56; 0.74]	0.57 [0.32; 0.82]	0.60 [0.50; 0.69]	0.56 [0.32; 0.79]
metastasis-wise	max	relative	0.62 [0.52; 0.73]	0.67 [0.44; 0.90]	0.63 [0.52; 0.73]	0.60 [0.35; 0.86]	0.63 [0.53; 0.73]	0.60 [0.37; 0.83]
metastasis-wise	max	absolute	0.61 [0.51; 0.70]	0.63 [0.38; 0.86]	0.66 [0.58; 0.74]	0.68 [0.48; 0.87]	0.61 [0.51; 0.71]	0.57 [0.35; 0.79]
image-wise	sum	relative	0.51 [0.43; 0.61]	0.47 [0.28; 0.67]	0.58 [0.48; 0.68]	0.49 [0.23; 0.75]	0.56 [0.47; 0.64]	0.48 [0.26; 0.70]
image-wise	sum	absolute	0.45 [0.34; 0.55]	0.48 [0.28; 0.68]	0.42 [0.31; 0.53]	0.40 [0.22; 0.59]	0.48 [0.40; 0.57]	0.48 [0.27; 0.68]
image-wise	mean	relative	0.51 [0.40; 0.62]	0.49 [0.30; 0.67]	0.57 [0.45; 0.68]	0.50 [0.23; 0.76]	0.55 [0.45; 0.64]	0.51 [0.28; 0.73]
image-wise	mean	absolute	0.52 [0.41; 0.64]	0.60 [0.40; 0.80]	0.50 [0.41; 0.59]	0.53 [0.34; 0.73]	0.44 [0.36; 0.52]	0.45 [0.29; 0.61]
image-wise	max	relative	0.52 [0.41; 0.62]	0.52 [0.29; 0.75]	0.60 [0.49; 0.72]	0.56 [0.33; 0.78]	0.57 [0.47; 0.67]	0.50 [0.28; 0.72]
image-wise	max	absolute	0.47 [0.38; 0.56]	0.55 [0.37; 0.73]	0.53 [0.43; 0.63]	0.58 [0.35; 0.81]	0.52 [0.40; 0.63]	0.51 [0.29; 0.74]

Supplement 4

Figure 1 shows how often features were selected in the outer training folds of the main experiment (metastasis-wise merging of relative delta radiomics using the sum).

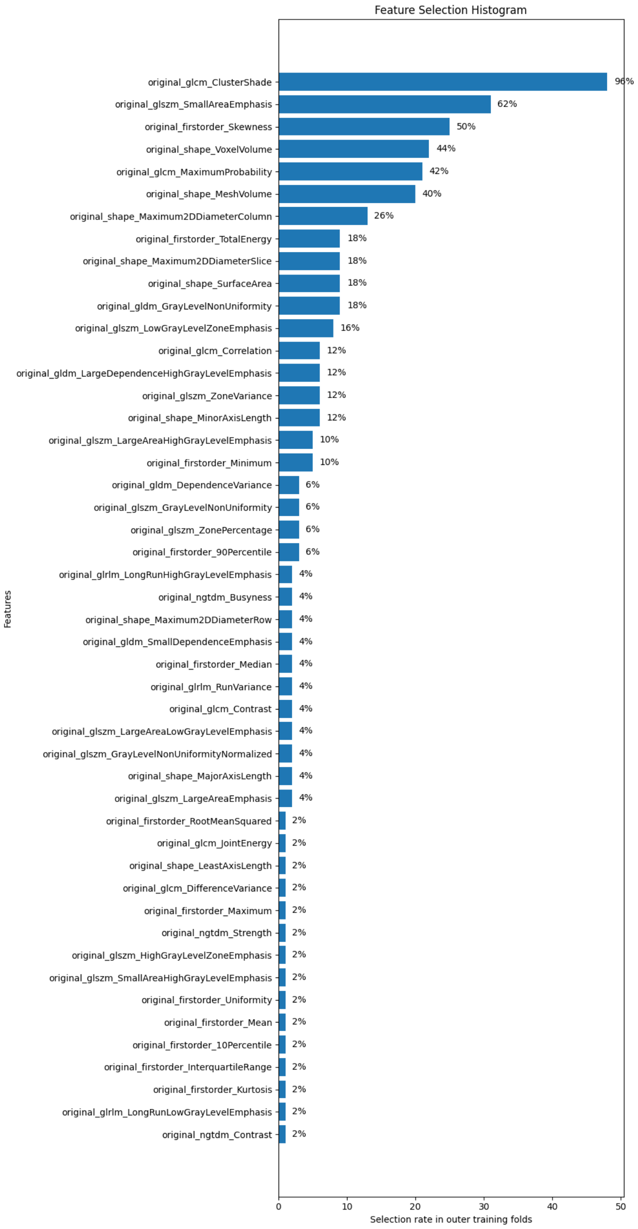

Figure 1 Histogram of selected features. Percentage calculations are relative to the fifty outer folds. E.g., a selection rate of 4% corresponds to a selection of that feature in two of the fifty outer folds.