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PET Radiomic Features Variability: A Phantom Study on the Influence of Reconstruction and Discretization Method

Variabilidade de Atributos Radiômicos em PET: Um Estudo com Simuladores sobre a Influência dos Métodos de Reconstrução e Discretização

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Abstract

We aimed to explore the variability of PET radiomic features for varying reconstruction methods and quantification settings. The IQ-NEMA phantom was scanned five times with a sphere to background F-18 concentration ratio of 10:1. The activity and the scan duration were matched to result in typical counting statistics for 18F-FDG oncologic examinations. The images were reconstructed with OSEM and PSF reconstructions, then 99 radiomic features were extracted using two discretization methods: fixed bin number (FBN = 16, 32 and 64 gray levels) and fixed bin width (FBW=0.25). This scheme resulted in a total of 1,188 features, classified as having low (<5.0%), intermediate (5-29.9%) or high (≥30%) variability. In general, FBW discretization yielded more stable features. A total of 499, 558 and 131 features had low, intermediate and high variability, respectively. First-order features such as energy and entropy and textural features such as entropy (GLCM), long run emphasis and short run emphasis (GLRLM) were more likely to present low variability, regardless the reconstruction and discretization method. Other textural features such as large area emphasis (GLSZM), zone percentage (GLSZM) and complexity (NGTDM) had more frequently intermediate or high variability.These findings could facilitate features' selection for further PET radiomic applications.

Keywords: PET radiomic features; variability; quantification; standardization.

Resumo

O objetivo deste estudo é explorar a variabilidade de atributos radiômicos do PET para diferentes métodos de reconstrução e parâmetros de quantificação. Foram realizadas cinco imagens do simulador IQ-NEMA com uma razão de concentração esfera-fundo de F-18 de 10:1. A atividade radiativa e o tempo de aquisição das imagens foram combinados para alcançar uma estatística de contagens típica de exames oncológicos com 18F-FDG. As imagens foram reconstruídas com os métodos OSEM e PSF, obtendo-se em seguida a quantificação de 99 marcadores de imagens a partir de dois métodos de discretização: fixed bin number (FBN = 16, 32 e 64 níveis de cinza) e fixed bin width (FBW=0.25). Esta configuração resultou em 1.188 elementos de imagens (radiomic features), classificados quanto à variabilidade como baixa (<5.0%), intermediária (5-29.9%) ou alta (≥30%). Em geral, o método FBW resultou em atributos mais estáveis. Um total de 499, 558 e 131 atributos tiveram variabilidades classificadas como baixa, intermediária e alta, respectivamente. Atributos de primeira ordem como energia e entropia, e marcadores de textura como entropia (GLCM), long run emphasis e short run emphasis (GLRLM) foram classificados como baixa variabilidade independentemente dos métodos de reconstrução e quantização. Outros atributos de textura como large area emphasis (GLSZM), zone percentage (GLSZM) e complexity (NGTDM) foram classificados mais frequentemente como variabilidade intermediária ou alta. Estes achados podem facilitar a escolha e seleção de atributos de imagens em aplicações futuras com radiômica em PET.

Palavras-chave: *Características Radiômicas do PET; variabilidade; quantificação; padronização.*

1. Introduction

Positron emission tomography (PET) and computed tomography (CT) hybrid imaging (PET/CT) is widely used for clinical diagnosis, staging, prognosis and treatment response assessment (1,2). The ability to use imaging biomarkers such as the standardized uptake value (SUV) and metabolic tumor volume (MTV) emphasizes this type of PET role (3,4). It is a consensus today that the novel PET biomarkers based on texture, morphological and metabolic features (radiomics) provide substantially more information about the disease than the current imaging practices (5–11). In this regard, there is a growing interest to assess PET radiomics features stability and reproducibility (8,12,13).

Radiomic features are affected by several factors, including image acquisition and reconstruction parameters, the feature calculation workflow as the image segmentation, discretization, feature mathematical design and calculation settings. However, the lack of standardisation in PET radiomic research is limiting its potential new applications (9),(14). Some authors have studied different robustness aspects to identify potential radiomic features or clusters (13,15,16). Nyflot et al (16) used realistic phantom simulations to evaluate the effects of noise and patient size on the feature variability (type II error) and image reconstruction on metrics bias (type I error). They used a fixed feature calculation setting of 256 gray level discretization and estimated the sample size that would be required for clinical trials to power for clinical effects of 30% and 15% due to only stochastic variability. They found a large and feature-dependent PET features sensitivity

to imaging parameters. Pfaehler et al [13] on the other hand, explored PET radiomic feature variability using IEC/NEMA and 3D printed phantoms. They used different image reconstruction, noise and segmentation methods on the composition of feature clusters and studied two discretization methods: fixed bin number (FBN) of 64 gray levels and fixed bin width (FBW) of 0.25 and 0.05. Their results confirmed the sensitivity of PET radiomic features to imaging parameters and suggested image acquisition and processing standardization.

Despite the increased use of radiomic for PET imaging, relatively little is known about the image reconstruction and quantification parameters impact on feature variability, limiting its standardization and clinical applications. Understanding the image biomarkers' quantitative aspects may simplify the features' selection, so this study uses IEC/NEMA phantom experiments to analyze PET radiomic features variability with respect to reconstruction methods and discretization parameters.

2. Materials and Methods

2.1. Scanner characteristics

PET/CT imaging was performed on a LSO-based PET Siemens Biograph TruePoint TrueV (Knoxville, TN, USA) combined with a 16-slice helical CT scanner (Emotion 16; Siemens). PET images were corrected for random coincidences, normalization, dead time losses, scatter and attenuation. The attenuation map was obtained by a spiral CT scan (100 kVp, automatic tube-current modulation), 3 mm slice thickness and a standard soft tissue reconstruction kernel (Siemens B30s).

2.2. Phantom preparation and imaging

We used an IEC/NEMA body phantom with 6 spheres (internal diameters of 10, 13, 17, 22, 28 and 37 mm) with a sphere to background F-18 concentration ratio of 10:1, according to the EANM guideline (17). To evaluate feature variability, five PET/CT images were sequentially acquired with two bed positions and the activity and the scan duration matched to result 416 MBq.s/kg (9.4 kg was the phantom weight considered in background concentration). This counting statistic represents typical whole-body oncologic examination (17).

2.3. Phantom image reconstruction

Images were reconstructed on a 168x168 matrix size (4.07 x 4.07 mm² voxels) with 3 mm slice thicknesses. Three reconstruction algorithms were used: (1) Ordered-Subsets Expectation-Maximization with 3 iterations, 21 subsets and 5 mm Gaussian filter (OSEM3D) (EARL-compliant); (2) Point Spread Function Ordinary Poisson with 3 iterations, 21 subsets and 7 mm Gaussian filter (PSF7) (EARL-compliant); and (3) Point Spread Function Ordinary Poisson with 2 iterations, 21 subsets and 2 mm Gaussian filter (PSF2). Both reconstructions PSF7 and OSEM3D are compliant with the EANM standards for quantification, being the PSF2 the option of choice for detectability purposes (18).

2.4. Radiomic feature extraction

Spheres were segmented with the Beth Israel PET/CT plugin for FIJI (ImageJ, Bethesda, MD, USA) [18] using the automatic segmentation with 41% threshold of maximum SUV (SUVmax). The segmented volumes of interest (VOIs) were analyzed with PyRadiomics, an open-source platform available at www.radiomics.io that enables a large panel of radiomic features extraction (21). We resampled the matrix grid to cubic voxels of 4x4x4 mm³ using B-Spline interpolation and the discretization within each VOI were scaled to FBN = 16, 32 and 64 grayscale levels and FBW = 0.25. The radiomic feature classes and corresponding features as defined by Griethuysen et al (21) are presented in the supplementary material. A total of 99 features were calculated, including 18 first order and 81 textural features: 16 gray level run length matrix (GLRLM), 16 gray level size zone matrix (GLSZM), 5 neighborhood gray-tone difference matrix (NGTDM) and 22 gray level co-occurrence matrix (GLCM). GLCM features were computed by 2 different methods: using 13 matrices, one calculated for each spatial direction separately, after which the mean of these values is returned (method A); and using only one matrix, weighted by factor 1 and summed, without the average step (method B) (22).

2.5. Variability estimation and analysis

Feature variability was estimated through a variation of the metric used for maximum Standard Uptake Value (SUVmax) (18) by calculating the average coefficient of variation for each reconstruction and discretization as follows:

$$Q_{var}\frac{\sum_{i=4}^{6}(\sigma_i/\mathrm{M})}{3} \quad (1)$$

Where σ_i is the standard deviation of the feature across realizations for sphere *i*, and *M* is the mean value of the feature. The 10 mm, 13 mm and 17 mm spheres were excluded from the analysis due to insufficient pixels for quantification of textural features. Only the three largest spheres were included (volumes: 5.6, 11.5 and 26.5 cm³).

Features were classified into three ranges of variability: low (<5.0%), intermediate (5-29.9%) and high (≥30.0%) and the total number of stable features was then used as a measure to investigate the influence of reconstruction and discretization on feature stability.

Low variability level was defined based on our previous efforts to study the variability of SUVmax (18), while the intermediate and high levels were defined based on the rationale presented by Galavis et al (15).

3. Results

A total of 499, 558 and 131 features quantifications were ranked as low, intermediate, and high, respectively (Table 1). PSF7 (FBN=32) was the reconstruction that yielded more features with low variability (n=59); and PSF7 (FBN=16) was those with

higher variability (n=55). PSF7 was, therefore, very sensitive to the number of bins. Concerning the discretization method, FBW=0.25 and FBN=32 presented the smallest number of features with high variability (n=14).

Table 1 - Number of features according to variability classification.

	FBW:0.25	*FBN:16*	*FBN:32*	*FBN:64*
Low				
OSEM	56	46	45	47
PSF2	37	32	37	34
PSF7	36	20	59	50
Intermediate				
OSEM	38	51	51	41
PSF2	57	61	53	56
PSF7	59	24	38	29
High				
OSEM	5	2	3	11
PSF2	5	6	9	9
PSF7	4	55	2	20

Variability: low (<5.0%), intermediate (5-29.9%) and high (≥30.0%). FBN: fixed bin number. FBW: fixed bin width.

Figure 1 presents the variability (Qvar) of 20 selected features for improved readability, where GLCM is presented for the setup using only one array considering all 13 directions simultaneously, without an average step. The features in Figure 1 were selected based on previous reports (10,13,15,16,22,23), the complete list of all 99 features is available in the supplementary material (Table S2). The feature named Dissimilarity reported in other studies (10,16) has been discontinued in Pyradiomics, as it is mathematically equal to Difference Average (GLCM) (21); and high intensity large area emphasis (HILAE - GLSZM) reported by Hatt et al [21] is mathematically equal to large area emphasis, the nomenclature used in Pyradiomics (Figure 1). Colour blue, yellow, and red highlights the features classified as low, intermediate, and high variability, respectively. Some quantifications were possibly negatively biased because outliers, since the standard deviation in equation 1 is sensitive to replications number and hence the Qvar. For example, the feature Large Area Emphasis (GLSZM) at OSEM reconstruction (FBN=64) achieved high variability (Qvar = 80.7%) while its quantification at FBW = 0.25 had an intermediate variability (Qvar = 14.2%). The higher variability is solely explained by one measurement three-fold higher in one of the spheres.

The presented variability in Table 1 and Table S2 support future radiomic studies by selecting the adequate reconstruction, radiomic features and discretization method. For example, for a given reconstruction algorithm (eg.: OSEM or PSF) and discretization method (eg.: FBN=64 or FBW=0.25), one may select a subset of features from Figure 1 (eg.: 10-20 features) to investigate their disease relationship.

4. Discussion

This study presents a pool of features that might be used to simplify future PET radiomic applications. We classified radiomic features according to their variability performance for different discretization methods and using reconstruction algorithms currently used in clinical practice (24–26). However, the variability analysis was performed through a simple metric and phantom preparation used to characterize the SUVmax variability with respect to image noise and reconstruction algorithm previously reported by Machado and colleagues (18). It was found a 1.5% < Qvar < 4.6% for SUVmax, a biomarker widely used in several oncologic PET studies.

We found also that the textural features presented worst variability more frequently than first-order features. Pfaehler and colleagues (13) used 10 replications of the IEC/NEMA and 3D printed phantoms to demonstrate the impact of contrast (sphere to background concentration ratio), image reconstruction, noise, discretization and segmentation methods on the repeatability of PET radiomic features through intraclass correlation coefficients (ICC) and cluster analysis. Here, we evaluated additional discretization parameters and assessed variability through a simpler method. Despite the agreement of variability levels of several features (for matched reconstruction and discretization), the direct comparison with our results is challenging because of differences in metrics used (Qvar versus ICC - data shown for EARL-compliant reconstruction (13)) and the number of features (here, 99 features versus 246 features in their work, we did

Features	OSEM				PSF2				PSF7			
	FBN=64	FBN=32	FBN=16	FBW=0.25	FBN=64	FBN=32	FBN=16	FBW=0.25	FBN=64	FBN=32	FBN=16	FBW=0.25
first order_Energy	3,0%	3,0%	3,0%	2,8%	3,1%	3,1%	3,1%	2,6%	2,1%	2,1%	2,1%	2,0%
first order_Entropy	1,3%	1,3%	1,7%	1,3%	2,2%	2,6%	3,0%	1,5%	1,0%	0,9%	17,2%	2,0%
first order_Kurtosis	4,0%	4,0%	4,0%	3,0%	4,5%	4,5%	4,5%	6,2%	2,2%	2,2%	2,2%	2,3%
first order_Skewness	48,0%	48,0%	48,0%	20,0%	80,0%	80,0%	80,0%	20,0%	22,0%	22,0%	22,0%	7,0%
glcm_ClusterProminence	13,7%	14,0%	13,3%	9,1%	30,9%	31,0%	31,8%	15,8%	10,8%	10,5%	219,2%	24,1%
glcm_Correlation	7,0%	7,0%	6,8%	4,6%	23,4%	23,3%	22,7%	12,0%	6,3%	6,1%	6,1%	8,8%
glcm_DifferenceAverage	3,3%	3,3%	3,3%	2,4%	6,5%	6,5%	7,0%	3,9%	1,6%	1,6%	83,5%	3,7%
glcm_JointEntropy	1,0%	1,2%	1,5%	1,3%	1,2%	1,5%	2,3%	1,1%	0,9%	0,9%	6,8%	1,0%
glrlm_HighGrayLevelRunEmphasis	7,1%	6,7%	8,8%	6,8%	15,3%	13,7%	14,0%	12,5%	2,9%	3,2%	162,4%	13,3%
glrlm_LongRunEmphasis	0,8%	1,7%	3,0%	1,9%	1,1%	1,6%	2,8%	1,7%	1,0%	1,2%	7,9%	1,3%
glrlm_LongRunHighGrayLevelEmphasis	6,7%	5,8%	7,4%	6,3%	15,1%	13,3%	13,4%	12,9%	4,3%	5,1%	148,9%	13,1%
glrlm_ShortRunEmphasis	0,2%	0,5%	0,8%	0,5%	0,3%	0,5%	0,7%	0,5%	0,3%	0,3%	2,2%	0,4%
glszm_HighGrayLevelZoneEmphasis	81,2%	10,6%	11,2%	11,0%	15,2%	13,7%	11,7%	13,2%	3,3%	4,5%	171,3%	14,2%
glszm_LargeAreaEmphasis	80,7%	20,0%	15,5%	14,2%	14,6%	90,4%	23,4%	25,8%	153,0%	14,2%	46,4%	13,7%
glszm_SmallAreaEmphasis	1,9%	3,6%	6,6%	5,4%	2,3%	1,9%	4,8%	3,9%	2,0%	3,2%	15,3%	5,1%
glszm_ZonePercentage	2,9%	77,2%	6,7%	6,4%	76,9%	78,6%	81,0%	6,9%	3,5%	77,7%	30,3%	4,7%
ngtdm_Busyness	14,0%	11,4%	14,6%	7,5%	14,1%	11,9%	12,9%	13,2%	7,4%	9,2%	48,6%	18,4%
ngtdm_Coarseness	10,1%	9,2%	9,5%	5,2%	6,7%	7,1%	5,3%	4,8%	6,5%	7,1%	13,6%	6,6%
ngtdm_Complexity	8,1%	8,6%	10,8%	7,3%	18,9%	15,1%	15,6%	11,6%	4,2%	4,6%	202,3%	16,2%
ngtdm_Contrast	10,4%	8,9%	9,3%	8,9%	11,1%	15,0%	19,0%	13,2%	8,3%	8,8%	111,7%	7,5%

Figure 1 - Quantification variability of 20 selected features. Variability: low (<5.0%), intermediate (5-29.9%) and high (≥30.0%) are highlighted in colours blue, yellow and red, respectively.

not include in this work morphological features and 2D measures of textural features) included in the analysis. Nevertheless, our results are also in concordance with Pfaehler et al (13) that FBW=0.25 yields more stable features (Qvar low and intermediate) than FBN=64, but we found that FBN=32 were equivalent to FBW=0.25 respective to stable features number. In addition, resampling with FBN lower to 32 gray levels (eg.: FBN = 16) should be considered with caution due to the high correlation among features (10). Indeed, each feature shall be analyzed individually before choosing predictors of clinical outcomes. Figure 1 shows that some features are highly stable regardless the reconstruction and/or discretization method.

Pfaehler et al (13) also demonstrated that lower uptake regions are more sensitive to the segmentation method. Our study only used 41% threshold of SUVmax and used spheres with radiopharmaceutical concentrations 10:1 with respect to the background. In such case the radiopharmaceutical concentration is considerably higher than background, thus allowing for more consistently contouring the sphere, regardless the segmentation method. For this reason, our results may be extrapolated only to evaluations where lesions have radiopharmaceutical uptake concentration of 10:1 or higher, otherwise segmentation constraints shall be observed.

This study also evaluated two different methods for computation of GLCM features. A markedly improvement in variability was observed in PSF7 FBN=64 when method A was applied. In general, the features Cluster Prominence and Cluster Shade performed better in method B for PSF2 and FBN=16, 32 and 64; the feature Maximum Probability performed better in method A for all quantization settings; and the feature Joint Average significantly worsen in method B, PSF2, FBN=64.

Nyflot et al simulated 50 statistically independent IQ NEMA images from a GE D670 PET/CT scanner with PSF reconstruction (5 mm Gaussian filter) and performed quantifications with FBN = 256 (16). They also found complex trends in the coefficient of variation (variability) as a function of features, sphere, patient sizes and reconstruction parameters (by changing the iterations number from 2 to 6 in the reconstruction process).

It is important to stress that feature's choice also depends on the disease (22). For example, a given feature with intermediate variability may be clinically better than other with lower; since feature variation is sufficiently large to detect a difference in disease presentation. Because several features are highly correlated and redundant, a maximum number of around ten features is usually used at the reduced space preserving the information that explains a biological or clinical phenomena (10,22,23,27–29).

A heuristic comparison among our findings with those found in Pfaehler (13) and Nyflot et al (16), identified common features with reasonable variability, for example: 1) energy and entropy from first order statistics metrics, 2) difference average and entropy from GLCM, 3) long run emphasis and short run emphasis from GLRLM, 4) zone percentage and large area emphasis from GLSZM, and 5) complexity and coarseness from NGTDM. Therefore, we recommend that these features are included in further PET radiomic studies to simplify the study design.

A limitation of this study is the use of only high uptake and homogenous spheres, not mimicking a real clinical condition. However, we presented a starting point where features, reconstruction method and quantification setup might be mined for further radiomic research. An additional drawback in radiomic studies are variations in nomenclature and formulas among studies and quantification software (9), which have recently been subjected to standardization along with other reporting standards (30). Here, we highlighted the features HILAE and Difference Average, which have been reported to yield clinical significance and presented low to intermediate variability in most reconstruction and quantization setups.

In clinical practice, the use of PSF reconstruction is preferable because it allows for improved lesion detectability and reduced image noise (18,25,31). Our results present several radiomic feature variability measures using two PSF reconstruction settings. In addition, the ability of PSF reconstructions to improve the system spatial resolution is also expected to detect smaller differences in textural features. This study did not assess type I error, wich informs the feature variation between different scanners. Thus, one must be careful when selecting radiomic features for multicenter studies and harmonization techniques shall be considered (32).

The radiomic features extraction provides a powerful method to assess differences in tumor biology by identifying predictors that may have a functional role in specific phenotypes. Our results contribute to overcoming standardization challenges that need to be addressed before radiomics can safely be implemented in the clinic.

5. Conclusions

Our data show the PET radiomic features' sensitivity regarding the reconstruction and discretization method, allowing researchers to assess a starting point for feature selection, reconstruction and discretization's choice in further PET radiomic studies. Some often reported features were likely low variability, regardless of the reconstruction and discretization method, while others (mostly textural features) were likely intermediate or high variability depending on the reconstruction and/ or discretization setup.

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