Short Communication

iMedPub Journals
http://www.imedpub.com/

Biomarkers Journal

2016
Vol.2 No.1:12

Textural Analysis to Assess Heterogeneity in Breast Cancer

Alexis Moscoso[1], Pablo Aguiar[1-3], Juan Pardo Montero[1,5] and Alvaro Ruibal[1-4]

[1]Molecular Imaging Group, IDIS Research Institute, Santiago Compostela, Spain

[2]Departamento de Psiquiatría, Radioloxía e Saúde Pública, Universidade de Santiago de Compostela, Spain

[3]Servizo Medicina Nuclear, Complexo Hospitalario Universitario de Santiago de Compostela, Spain

[4]Fundación Tejerina, Madrid, Spain

[5]Servizo Radiofísica e Protección Radiolóxica, Complexo Hospitalario Universitario de Santiago de Compostela, Spain

Corresponding author: Pablo Aguiar, Molecular Imaging Group, Psiquiatry, Radiology and Public Health Department of Faculty of Medicine, University of Santiago de Compostela, Galicia, Spain, Email: pablo.aguiar@usc.es; pablo.aguiar.fernandez@sergas.es

Received date: January 21, 2016; **Accepted date:** March 10, 2016; **Published date:** March 17, 2016

Short Communication

Tumor heterogeneity is defined as the coexistence of different types of cells within a particular tumor. These cells may show significantly different phenotypic and morphological features such as variations in metabolic activity or gene expression, as well as differences in malignant potential [1]. Therefore, the understanding and characterization of tumor heterogeneity can help to decide an effective treatment plan.

Several studies using imaging techniques, most of them Magnetic Resonance (MR) and ultrasonography, have investigated the way of quantifying this heterogeneity and results were used, for instance, as biomarkers for tumor characterization, tumor response or tumor vascularization [2-4]. Positron Emission Tomography (PET) is expected to give more valuable information about heterogeneity since it reflects the biology of the tumor. However, most of the predictions based on PET images only used parameters that have no direct relation with heterogeneity, namely, metabolically active tumor volume (MATV), standardized uptake values (SUVmax, SUVmean) and combinations of the previous two, called total lesion glycolysis (TLG) [5]. Although heterogeneity quantification with PET is a novel research, there are already investigations [6] pointing that it is possible to use heterogeneity-related parameters as biomarkers or predictors of patient outcome.

Various methods have been used to measure heterogeneity but the two most common in PET are the so-called first order statistics (FOS) and higher order statistics. FOS is based on the analysis of the histogram generated by the uptake value of each voxel within the tumor. It does not take into account any spatial information. On the other hand, higher order statistics take into account spatial correlations between voxel values at different distances [7]. Dozens of textural features describing heterogeneity can be obtained from these approaches. However, only a few have shown to be really valuable. Firstly, not always visual heterogeneity corresponds with parameters describing heterogeneity. In [8], visual heterogeneity scored higher for tumors with high Homogeneity index, revealing the necessity of testing whether a particular feature is really measuring heterogeneity in its most intuitive form or if, on the contrary, we are measuring a less intuitive, and probably useless, form of heterogeneity. Secondly, most of these features correlate with each other and with SUVs and MATV so it is crucial to check that our textural features are not surrogates of already studied parameters [9]. And, finally, features must reflect only the underlying biological structure so their values cannot be significantly affected by technical characteristics of the scanner such as the spatial resolution or the number of iterations during reconstruction [10]. Robustness under different tumor delineations is also important due to the great number of delineation methods and their inherent imprecision.

Statistical analysis of features data has recently become a matter of discussion. Two extensive investigations reviewed published results on heterogeneity measurements and their statistical analysis [11, 12], finding that several published articles suffer from low statistical significance. The use of many parameters to describe a small dataset is known as over fitting and is common not only in PET, but also in all of the imaging modalities [11], resulting in a great power to reproduce the current analyzed dataset but in poor predictive performance when new data is studied. This is because the great number of parameters is able to describe the statistical fluctuations of the measured data instead of the underlying relationship, exaggerating minor fluctuations when new data is tested by that model. Another issue with PET statistical analyses is inflation of type-I error [12]. As previously mentioned, it is possible to obtain dozens of textural indices from a PET image. Consider, for instance, that our hypothesis is that two types of tumors can be identified by the values of some textural index. If we compute a high number of indexes compared with the size of our dataset, it is likely to find an index that separates the two types of tumors just by random chance instead of identifying the biological universal pattern showed by that type of tumor. As a result, our model fails when evaluating new data. These two major problems can be quantified if cross-validation datasets and multiple hypothesis corrections are used; however, this is not the most common procedure yet [11, 12].

Focusing on breast cancer, the four existing studies [6, 13-15] have not reached agreement on the predictive

performance of textural features. Three of them [6, 13, 14] claimed that the observed heterogeneity is a valuable biomarker and predictor of patient outcome. None of these studies reported use of cross-validation datasets or corrections for multiple hypothesis testing. In [13], the heterogeneity measure dV / dT showed a strong linear correlation with MATV, probably motivated by the fact that dV / dT has volume dimensions. Not surprisingly, they found that dV / dT correlated with survival, a good known result for MATV. In [6], non-corrected p - values are presented for different features classifying types of tumors. Just in one type of tumor (triple negative), the discriminative power of the heterogeneity feature was tested by means of ROC curves, showing no significant improvement with respect to the performance of SUVmax. In [14], just non corrected p-values are computed, making impossible to evaluate the predictive power of the tested features. On the other hand, [15] has not found strong correlations between PET-derived indices and histological or clinical features. Multiple hypothesis corrections and ROC curves were used to evaluate the predictive power of textural features, showing low discriminative performance and worse than results obtained from SUV's. No cross-validation dataset was used, although in this case is less important since the results are negative, not supporting the hypothesis of heterogeneity as a predictor. All in all, assessment of tumor heterogeneity as a valuable indicator, especially in breast cancer, is still under debate. It is clear that a more standardized and rigorous statistical protocol is needed to prevent false discoveries. That protocol should check whether all the desirable characteristics of a textural feature (robustness, uncorrelated with SUV's or MATV, etc.) are fulfilled in order to really disentangle the heterogeneity contribution from already known biological features. Tumor delineation might be another point to improve. Many thresholding methods, like the one in [6], use a quantity derived from the maximum uptake value within the tumor to compute the tumor threshold. Although these methods do not take into account absolute values, this construction can introduce some hidden correlation of textural features with SUVmax. The correct implementation of statistical protocols and investigation on the controversial methodological aspects is crucial to elucidate the usefulness of textural features in PET for improving tumor characterization.

Acknowledgement

This work was supported by the project PI14 / 02001 (ISCIII and FEDER).

References

1. Lleonart ME, Martin - Duque P, Prieto RS, Moreno A, Ram´on y Cajal S (2000) Tumor heterogeneity: morphological, molecular and clinical implications. Histol Histopathol 15: 881-898.
2. Aerts HJ, Velazquez ER, Leijenaar RT, Parmar C, Grossmann P, et al. (2014) Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. Nat Commun 5: 1-8.
3. Aerts HJ, Bussink J, Oyen WJ, Elmpt WV, Folgering AM, et al. (2012) Identification of residual metabolicactive areas within NSCLC tumours using a pre - radiotherapy FDG-PET-CT scan: a prospective validation. Lung Cancer 75: 73-76.
4. Hayes C, Padhani AR, Leach MO (2002) Assessing changes in tumour vascular function using dynamic contrastenhanced magnetic resonance imaging. NMR Biomed 15: 154-163.
5. Van de Wiele C, Kruse K, Smeets P, Sathekge M, Maes A (2013) Predictive and prognostic value of metabolic tumour volume and total lesion glycolysis in solid tumours. Eur J Nucl Med Mol Imaging 40: 290-301.
6. Soussan M, Orlhac F, Boubaya M, Zelek L, Ziol M, et al. (2014) Relationship between tumor heterogeneity measured on fdg - pet / ct and pathological prognostic factors in invasive. Breast Cancer PLoS One 9: e94017.
7. Kassner, Thornhill RE (2010) Texture analysis: a review of neurologic mr imaging applications. AJNR Am J Neuroradiol 31: 809-816.
8. Tixier F , Groves AM, Goh V, Hatt M, Ingrand P, et al. (2014) Correlation of intra - tumor 18f - fdg uptake heterogeneity indices with perfusion ct derived parameters in colorectal cancer. PLoS One 6: e99567.
9. Orlhac F, Soussan M, Maisonobe J, Garcia CA, Vanderlinden B et al. (2014) Tumor texture analysis in 18F - FDG PET: relationships between texture parameters, histogram indices, standardized uptake values, metabolic volumes, and total lesion glycolysis. J Nucl Med 55: 414- 422.
10. Yan J, Shern JL, Loi HY, Khor LK, Sinha AK, et al. (2015) Impact of image reconstruction settings on texture features in 18f - fdg pet. J Nucl Med 56: 1667-1673.
11. Alic L, Niessen WJ, Veenland JF (2014) Quantification of heterogeneity as a biomarker in tumor imaging: a systematic review. PLoS One 10: e110300.
12. Chalkidou, Odoherty MJ, Marsden PK (2015) False Discovery Rates in PET and CT Studies with Texture Features: A Systematic Review. PLoS One 5: e0124165.
13. Son SH, Kim D, Hong CM, Kim C, Jeong SY, et al. (2014) Prognostic implication of intratumoral metabolic heterogeneity in invasive ductal carcinoma of the breast. BMC Cancer 14: 585.
14. Yoon H, Kim Y, Kim BS (2015) Intratumoral metabolic heterogeneity predicts invasive components in breast ductal carcinoma in situ. European Radiology 12: 3648-3658.
15. Yoon H, Kim Y, Kim BS (2015) Do clinical, histological or immunohistochemical primary tumour characteristics translate into different 18F - FDG PET / CT volumetric and heterogeneity features in stage II / III breast cancer?. European Journal of Nuclear Medicine and Molecular Imaging 11: 1682-1691.