Abstract

Impact of parameters variation in texture feature extraction process on a prognostic model for survival of DLBCL patients enrolled in the Large Prospective Phase III GOYA trial using clinical and PET/CT-derived characteristics

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Purpose: Diffuse large B-cell lymphoma (DLBCL) is a group of lymphoid malignancies that originate from B-cells. Many patients have advanced disease at diagnosis and the survival depends on the age of the patient and on the prognostic scores[1].
In the last year radiomics raised the interest of investigators as a prognostic tool. However, the radiomic features extraction process is characterized by many parameters whose variability affects the final result. Up to now there is no gold standard for parameter setup.
The purpose of this work is to verify if varying the parameters used in the extraction of the radiomics feature from baseline PET images affects the prognostic value of a Cox model that uses clinical and radiomic variable to predict the outcome of untreated DLBCL patients enrolled in the GOYA trial.

Methods and materials: GOYA[2] was an open-label, multicenter, phase III study that proved the equivalency in efficacy and safety of two drugs in previously untreated patients with DLBCL. Despite the advances in treatment in last years, still one third of patients treated with combined chemo-immunotherapy will experience refractory disease or relapse. The ability of traditional prognostic factors to identify such high-risk patients remains poor. New prognostic tools are needed and radiomics have raised the interest of the scientific community in the last years.
Radiomics is a rapidly evolving research field and it is defined as the quantitative extraction, analysis and modelling of many medical image features in relation to prediction targets, such as clinical end points and genomic features.
The scope is to build predictive models associating texture features to phenotypes, genetic and proteomic signatures, or treatment outcomes.
Innumerable quantitative image texture features (ITFs) can be calculated using high-throughput computing from medical images[3,4]. Subsequent mining of the data is then required for knowledge extraction and application. The typical workflow includes: image acquisition and reconstruction, volume segmentation, ITF extraction, data mining[5].
Many parameters are involved in the ITF extraction process, such as the VOIs segmentation method, the interpolation of the image to isotropic voxel size (both resampling size and interpolation method), the discretization of the voxel intensity values.
Variations in these parameters have a strong impact on the final metric values[6].
In this work we created a prognostic model for PFS based on radiomic ITFs extracted from the GOYA patient PET database along with SUV-related features and traditional prognostic indices. We evaluated the impact of the parameter variation on the final prognostic ability of the model.
The first step was the evaluation of the ITFs from the PET images under diverse configurations of the above mentioned parameters.

Then we applied a process of variable selection by means of random survival forest variable hunting (RSF-VH) algorithm[7], a supervised machine learning algorithm based on decision trees, which sorted the ITFs by importance for each configuration.
The first ten selected ITFs for each configuration have been used has risk factors in a proportional-hazard Cox model with the purpose to evaluate the respective hazard ratios and the hazard functions (HF).
The HF have been compared with the 48-months PFS using three statistical indices: Brier score, C-index and accuracy.
We then tested the ability of our model to identify those patients with higher risk of disease progression after treatment and the impact on the prognostic model of the image processing parameter variation during the ITF extraction.
The best cutoff method was then performed on HR and patients were divided into two prognostic subgroups of treatment-failure: High and Low-risk.
Kaplan-Meier (KM) non-parametric estimate is one of the most widely used methods in survival univariate analysis to analyze time-to-event data and to make comparison between two or more groups of participants[8].
KM curves have been used to represent the PFS for the two risk groups obtained starting from the diverse ITF extraction parameter configurations.

Results:
Baseline PET scans were available for radiomic analysis in 1263 patients and the median follow-up was 44.5 months.
The RSF-VH evaluated the importance of the variables for each parameter configuration. The most predictive variables resulted different for the diverse configurations. For each configuration, the ten most predictive variables have been used to evaluate the HF by means of Cox proportional-hazard model.
The comparison with the 48-months PFS showed weak agreement with the experimental data.
In particular, it was not possible to determine a parameter configuration leading to optimal values for Brier score, C-index and accuracy.
The univariate analysis of PFS shows that the model has indeed a prognostic value as the KM are significantly different.
We compared the KM curves for groups performing a log-rank test, with the null hypothesis that the groups do not differ in terms of PFS.
The obtained p-values are less than 0.05 for all the configurations, therefore the null hypothesis can be rejected within a confidence interval of 95%.

Conclusion:
The goal of radiomics is to develop a function or mathematical model to classify patients according to their predicted outcome by means of radiomic features. Predictive and prognostic models with high accuracy, reliability, and efficiency are vital factors driving the success of radiomics.
A huge amounts of texture features could be extracted by image data. These metrics are independent of tumor position, orientation, size, and brightness and take into account the local intensity-spatial distribution. Hence, the combination of these features can provide an intensity-spatially dependent map of the tumor metabolic uptake that can potentially be used as a signature to characterize the tumor phenotype and response to treatment.
It is important for textural feature values to be directly comparable, both between and within patients, in order to derive meaningful conclusions from radiomic analysis and allow their use in clinical routine.
Nonetheless, there are difficulties in generalization due to the variability in textural PET features among studies, related to the methodology used to carry on the diverse steps of the workflow from the image acquisition to the ITF extraction.

In this work we analyzed the impact of the parameter variation on the final prognostic value of a Cox regression model.
The image processing parameter variation during the ITF extraction proved not affect significantly the ability of our model to identify those patients for which the risk of disease progression after treatment is higher.
The identification of some radiomic risk factors resulted not to have effect on the prognostic power of the model and this is confirmed by the fact that the variation in the ITF extraction process has no measurable effect on the model.

References

1. Horvat, M. *et al.* Diffuse large B-cell lymphoma: 10 years' real-world clinical experience with rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisolone. *Oncol. Lett.* **15**, 3602–3609 (2018).
2. Vitolo, U. *et al.* Obinutuzumab or rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone in previously untreated diffuse large b-cell lymphoma. *J. Clin. Oncol.* **35**, 3529–3537 (2017).
3. Haralick, R. M., Shanmugam, K. & Dinstein, I. Textural Features for Image Classification. *IEEE Transactions on Systems, Man and Cybernetics* vol. SMC-3, No. 610–621 (1973).
4. Amadasun, M. & King, R. Textural features corresponding to textural properties. *IEEE Trans. Syst. Man. Cybern.* **19**, 1264–1274 (1989).
5. Lambin, P. *et al.* Radiomics: The bridge between medical imaging and personalized medicine. *Nat. Rev. Clin. Oncol.* **14**, 749–762 (2017).
6. Zwanenburg, A., Leger, S., Vallières, M., Löck, S. & Initiative, for the I. B. S. Image biomarker standardisation initiative. *arXiv* **preprint a**, (2018).
7. Ishwaran, H., Kogalur, U. B., Blackstone, E. H. & Lauer, M. S. Random survival forests. *Ann. Appl. Stat.* **2**, 841–860 (2008).
8. Etikan, I., Abubakar, S. & Alkassim, R. The Kaplan Meier Estimate in Survival Analysis. *Biometrics Biostat. Int. J.* **5**, 55–59 (2017).