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PET radiomics-based lesions representation in Hodgkin lymphoma patients

Rappresentazione delle lesioni di pazienti affetti da linfoma di Hodgkin basata su radiomica PET

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Abstract As medical image analysis has been proven to entail tumor-specific information, the so-called radiomics paradigm holds the promise to characterize the disease and infer long term outcomes of chemotherapy. In this work, we propose an insightful framework for disease characterization in Hodgkin lymphoma which could inform future research. Particularly, an intra-patient similarity index (ISI) was built to represent the homogeneity of the patients' disease, while a radiomics-based fingerprint was create for local lesion description. Through descriptive statistics and classification algorithms, ISI-weighted fingerprint has been showed to be discriminatory between responders and relapsing patients.

Abstract *Recentemente, l'informazione derivante da immagini mediche è stata introdotta in maniera massiva nell'analisi quantitativa delle lesioni, volta alla creazione di modelli diagnostici e prognostici. Questo paradigma, in particolare ma non limitatamente al contesto oncologico, prende il nome di radiomica. Nel presente lavoro, proponiamo un metodo di profilazione dei pazienti affetti da linfoma di Hodgkin in termini di omogeneità paziente-specifica della malattia (ISI) e descrizione locale dellle lesioni, basata su caratteristiche radiomiche. Attraverso statistiche descrittive e algoritmi di classificazione, tale metodo si è rivelato essere discriminante dei pazienti che hanno risposto e quelli refrattari alla prima linea di chemioterapia.*

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1 Introduction

Hodgkin's lymphoma (HL) is one out of a group of blood cancers that develop from lymphocytes. Although most of the cases end up with long term outcome [3], up to 30% of patients with early or advanced stage HL can become refractory or relapsing [1], bringing the first-line therapy into failure. For this reason, detecting cases at high risk of event recurrence at baseline would inform and significantly impact on HL patients therapy trial. However, at this stage, according to the gold standard of the International Prognostic Score, stratification and therapeutic strategies are based on clinical risk factors [1]. The staging system for patients with HL relies on the number of involved lesion sites, the severeness of lesions (i.e. bulky), the nodal or extra nodal nature of the disease, the presence of typical systemic symptoms (B symptoms) and lymph nodes stage (on one or both sides of the diaphragm). Early prognostic factors are often investigate the presence of a large mediastinal mass, an elevated sedimentation rate, the involvement of multiple nodal sites, including extra-nodal, age $\geq$ 50 years, or massive splenic disease [6].

Over the last years, research has moved forward to a more quantitative approach. Indeed, the value of image analysis applied to Positron Emission Tomography (PET)/Computer Tomography (CT) for response evaluation and treatment monitoring has been suggested and showed as a promising strategy [2]. Specifically, standardized texture feature extraction in PET/CT images, i.e. radiomics, quantifies the heterogeneity of tracer uptake within a metabolically active region of interest, i.e. tumor lesions. In combination with patients' information, such data are fed into statistical models developed for both research and clinical purposes, such as diagnosis or prognosis. Accordingly, radiomics-derived lesion description of refractory/relapsing HL has been supposed to differ from the one of long term responders [2]. Although straightforward, this workflow might suffer from several limitation and critical issues, such as the enormous amount of parameters that may be computed within image regions, the high co-linearity between features and the lack of biological interpretation which can be inferred from the analyses. The present study aimed at developing a methodological framework in HL for radiomics feature reduction and selection in order to locally describe lesions, different in size and nature, while combining their characterization at patient's level though an intra-patient similarity index. The ultimate perspective of such patient representation lies on further modeling responding/refractory phenotypes in first-line chemotherapy response assessment.

2 Materials and Methods

In accordance with the Declaration of Helsinki, this observational retrospective study was approved by the local ethics committee of all the three centers involved and the signature of a specific informed consent was waived.

Data have been collected from 85 patients with pathological diagnosis of HL undergoing a pre-treatment PET/CT scan. In particular, two categories of patients have been analyzed: non-relapsing/refractory (non-R/R), i.e. long term responders, and relapsing/refractory (R/R) subjected to more than one chemotherapy line and candidate to immunotherapy. Patients with extravasation at injection site, no clinical data availability or having only one tumor lesion have been excluded.

In order to assess imaging data, pre-treatment (baseline) [18F]FDG-PET/CT and the study before immunotherapy have been analyzed for non-R/R HL and R/R HL patients, respectively. PET/CT images have been acquired according to standard institution-specific procedure protocols and images have been retrieved and qualitatively evaluated with LIFEx package [4]. Specifically, HL [18F]FDG-avid lesions have been identified, semi-automatically segmented by clinical experts and labeled as lymph nodal or extra-nodal. Fifty-two radiomic features have been computed with respect to every region of interest from histograms of grey levels, geometric factors, co-occurrence and higher order zone-length and run-length matrices. After z-score normalization, a feature reduction has been performed as described by the framework below where the pairwise distances were calculated according to the Euclidean distance definition. An intra-patient similarity index (ISI) defined by the silhouette has been built and treated as a proxy of lesions' homogeneity within patients. Specifically, high values of silhouette implies high similarity within patient's lesions and, viceversa, low values were interpreted as high heterogeneity among patient's tumor sites.

Feature reduction and similarity computation framework:

Step 1 Selection of all the lesions meeting the inclusion criteria of the current analysis, grouped by patients;

Step 2 Volume-based grouping of radiomics variables: whether covariates show significant correlation (p-value of the chi-squared test > 0.8) or uncorrelation (p-value of the chi-squared test < 0.0001) with respect to lesion volume, they are grouped into two set of features, representing volume-related (*VOL_set*) and heterogeneity-related (*NOVOL_set*) information respectively;

Step 3 Application of principal component analysis on both *VOL_set* and *NOVOL_set* of covariates, resulting in two new set of features describing 95% of the total variability;

Step 4 Juxtaposition of *VOL_set* and *NOVOL_set* of covariates to form a representative fingerprint of each lesion in the cohort;

Step 5 Computation of the silhouette (equation 1) within each patient as the comparison between cohesion (equation 2) and separation (equation 3) of his/her lesions:

$$s(P_i) = \frac{b(P_i) - a(P_i)}{maxa(P_i), b(P_i)} \tag{1}$$

where

$$a(P_i) = \frac{1}{|P_i| - 1} \sum_{i,j \in P_i, i \neq j} d(i,j) \tag{2}$$

$$b(P_i) = \min_{k \neq i} \frac{1}{|P_k|} \sum_{i \in P_i, k \in P_k} d(i,k) \tag{3}$$

Step 6 Evaluation of similarity indexes in different groups.

3 Results

First, ISI values have been computed and analyzed within each group, non-R/R and R/R, independently. Specifically, homogeneity across subjects has been assessed including only nodal and both nodal and extra nodal lesions. While accounting for nodal lesions of the two groups, probability density functions were compared; on contrary, when extra nodal lesions were added upon the nodal ones, overall-ISI results have been evaluated in terms of variation with respect to nodal-ISI: increments of values suggest an increasing in the homogeneity of lesions coming from different sites, while decrements are a proxy of heterogeneity in lesions of diverse nature. The analysis shows the different profiles of distributions of non-R/R (0.11 ± 0.42 - 18/26 positive) and R/R (0.24 ± 0.45 - 38/49 positive). Overall, the comparison between distributions suggest a higher intra-patients lesions similarity in the R/R dataset than in the non-R/R one. In the non-R/R dataset, distribution of ISI built upon nodal lesions is centered in -0.01 ± 0.46, increasing up to 0.12 ± 0.61 after adding extra-nodal lesions: positive ISI increases from 4/8 to 6/8. Similarly, the distribution of ISI in R/R dataset evolves from from 0.13 ± 0.46 to 0.42 ± 0.43 as extra-nodal lesions are included beside the nodal ones: positive ISI rise from 12/19 to 17/19. Overall, these results support a higher intra-patients lesions similarity in the R/R dataset than in the non-R/R.

In order to test ISI discrimination power between the two groups, a Logistic Regression (LR) model has been built upon the only ISI value per patient, resulting in a significant odds ratio of 1.85. Basing on this evidence, a classification model has been performed on the ISI-weighted fingerprint covariates: indeed, each lesion's vector of covariates enclosed both radiomic fingerprint - as described above - and its patient's ISI value. ISI thus represents a grouping/weighting factor, suitable for

mantaining the hierarchical inherent nature of data. Specifically, from the original dataset comprising 85 patients and 543 observations, 115 non-R/R and 255 R/R lesions have been randomly sampled to form the training set, while the test set included 57 non-R/R and 116 R/R lesions. Since class imbalance represents a diriment issue to be addressed in medical applications, a Random Undersamplig Boosting of Tree Ensemble (RUBTE) was used for classification purposes [5]. The RUBTE performance has been evaluated in terms of accuracy (82%), sensitivity (70%) and specificity (88%). Furthermore, results at lesion level were aggregated at patient's level through majority voting. Accordingly, true positive rate rose to 89%, although accuracy slightly fell to 73% and recall dropped to 38%.

4 Discussion and conclusion

The present work underlines the different radiomics information entailed on non-R/R and R/R lesions. R/R patients showed higher intra-patients lesion similarity with respect to non-R/R ones, behavior further confirmed while introducing extra-nodal lesions to nodal ones. Indeed, in the non-R/R group, the addition of extra-nodal lesions ones had a minor effect on similarity. Physicians speculated that non-R/R group, naïve from any treatment, including either long term responders, and primary refractory patients is keen on being the most heterogeneous one. Conversely, R/R patients would be biologically more homogeneous, since repeated treatments might result in resistant clones selection.

Despite the current approach suffer from several limitations due to the retrospective design of the study and the reduced sample size, the goal of defining a methodological feature reduction framework to demonstrate the potential predictive value of radiomics in HL has been achieved. Further efforts will be focused on testing our ISI-weighted fingerprint as representative for any kind of lesion at baseline.

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