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Early prediction of radiotherapy-induced parotid shrinkage and toxicity based on CT radiomics and fuzzy classification

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ABSTRACT

Motivation: Patients under radiotherapy for head-and-neck cancer often suffer of long-term xerostomia, and/or consistent shrinkage of parotid glands. In order to avoid these drawbacks, adaptive therapy can be planned for patients at risk, if the prediction is obtained timely, before or during the early phase of treatment. Artificial intelligence can address the problem, by learning from examples and building classification models. In particular, fuzzy logic has shown its suitability for medical applications, in order to manage uncertain data, and to build transparent rule-based classifiers.

In previous works, clinical, dosimetric and image-based features were considered separately, to find different possible predictors of parotid shrinkage. On the other hand, a few works reported possible image-based predictors of xerostomia, while the combination of different types of features has been little addressed.

Objective: This paper proposes the application of a novel machine learning approach, based on both statistics and fuzzy logic, aimed at the classification of patients at risk of *i)* parotid gland shrinkage and *ii)* 12-months xerostomia. Both problems are addressed with the aim of individuating predictors and models to classify respective outcomes.

Methods: Knowledge is extracted from a real dataset of radiotherapy patients, by means of a recently developed method named Likelihood-Fuzzy Analysis, based on the representation of statistical information by fuzzy rule-based models. This method enables to manage heterogeneous variables and missing data, and to obtain interpretable fuzzy models presenting good generalization power (thus high performance), and to measure classification confidence.

Numerous features are extracted to characterize patients, coming from different sources, i.e. clinical features, dosimetric parameters, and radiomics-based measures obtained by texture analysis of Computed Tomography images. A learning approach based on the composition of simple models in a more complicated one allows to consider the features separately, in order to identify predictors and models to use when only some data source is available, and obtaining more accurate results when more information can be combined.

Results: Regarding parotid shrinkage, a number of good predictors is detected, some already known and confirmed here, and some others found here, in particular among radiomics-based features. A number of models are also designed, some using single features and others involving models composition to improve classification accuracy. In particular, the best model to be used at the initial treatment stage, and another one applicable at the half treatment stage are identified.

Regarding 12-months toxicity, some possible predictors are detected, in particular among radiomics-based features. Moreover, the relation between final parotid shrinkage rate and 12-months xerostomia is evaluated.

The method is compared to the naïve Bayes classifier, which reveals similar results in terms of classification accuracy and best predictors.

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The interpretable fuzzy rule-based models are explicitly presented, and the dependence between predictors and outcome is explained, thus furnishing in some cases helpful insights about the considered problems.
Conclusion: Thanks to the performance and interpretability of the fuzzy classification method employed, predictors of both parotid shrinkage and xerostomia are detected, and their influence on each outcome is revealed. Moreover, models for predicting parotid shrinkage at initial and half radiotherapy stages are found.

1. Introduction

The risk of toxicity is the most common drawback of radiotherapy (RT) treatment. In particular, patients under RT for cancer in the head-and-neck zone (HNC) suffer very often of reduced saliva production and xerostomia [1]. These toxicity symptoms are associated with structural changes of parotid glands (PGs), responsible of salivary functionality, which, on the other hand, show particularly consistent volume shrinkage [2,3] during RT.

It is known that when parotids shrink, they also shift toward the head midline, which is typically the high dose region, thus a higher irradiation is received by the glands with respect to the planned dose [4]. The timely prediction of this volume change is thus relevant, since it allows a personalized re-planning strategy which can consider these anatomical variations, sparing the healthy parotid tissue from the highest dose region [5]. Adaptive Radiotherapy (ART) is currently of high interest in the clinical practice; in fact, as ultimate goal, it should reduce the risk of developing toxicity, as xerostomia, and thus preserving parotid functionality, by avoiding a high irradiation to them, due to the gland shrinkage and shift.

Artificial intelligence can be very effective to address the problem of timely predicting parotid shrinkage or xerostomia, by learning from previous examples about the phenomena associated with PG structural changes and consequent toxicity. Indeed, if reliable knowledge is correctly extracted, patient and/or planned RT characteristics can be correlated with the appearance of severe symptoms, and a classification model can be built, which is able to identify patients at risk.

In some works, clinical and dosimetric features were considered to find different possible predictors of the shrinkage process and the xerostomia, like age, body mass index, tumour location, planned dose to PGs, initial PG volume and the overlap between PG and lymph node metastases [1,5–7]. However, the predicting power of models found by only considering these types of features could be surely improved.

More recently, increased interest has been found in quantitative image-based features extracted from tomographic images acquired before or during treatment. The analysis of these images allows the quantification of mineable high-dimensional data, which reflect information related to patho-physiological properties of the analysed tissue [8]. This process of converting images in quantitative data, now called radiomics, is based on different mathematical techniques, of which texture analysis is one of the most frequently employed. However, radiomics generally refers only to the analysis of tumoral region, while its use for the assessment of RT effects on Organs at Risk (OARs) is not yet consolidated.

A few works searched for predictors of parotid shrinkage among features extracted from Computed Tomography (CT) images, routinely acquired during RT, as parotid volume [9–11], Jacobian index [12], and parotid mean density [13–15], while others introduced texture analysis to evaluate higher order features [16]. On the other hand, a few works reported possible image-based predictors of xerostomia [2,3,17], while the combination of clinical, dosimetric and radiomics features to find a toxicity model has been little addressed.

Some difficulties are associated with the construction of a classification model comprising features that come from multiple sources, as often happens in medical field: *i)* the heterogeneity of data sources is reflected in the possible presence of heterogeneous features, represented by numerical, categorical, and/or binary variables; *ii)* the possibility exists that for some patients not all the data sources are available, therefore samples with missing data could be present during the training phase and the application of the classification model; *iii)* for the considered problem, it is preferable to obtain different models, the most accurate one comprising all the best predictors, even if measured when RT has already started, and another one comprising only features extracted from data sources available at the pre-treatment stage of the therapy, since a classifier able to express tentative predictions also at an early stage is particularly valuable. Therefore, a good classifier for the stated problem should address these difficulties.

At the same time, the method used to extract the model should ensure sufficient accuracy and robustness to data affected by uncertainty. Moreover, in medical ambit, the model should be semantically interpretable, in order to clearly show dependencies among features and outcomes, logically justify each prediction, and allow domain experts to validate it. Also, a confidence measure should be presented together with the classification results, in order to properly distinguish different cases. Finally, a model is the more reliable, the more numerous are the examples that were used to learn from.

In a preliminary work [18], a novel approach based on fuzzy logic was proposed to address these issues. The approach is not specific for the considered application, but can be applied to any classification problem. However, since it enables to address most of the above-mentioned issues, it results particularly useful in the medical ambit. It consists in firstly extracting the best model for each set of features, and then in building composite models by aggregating the simpler ones, thus considering different available data sources at the same time. This approach enables to: *i)* undertake possible missing values (present in the considered data); *ii)* individualise the best model comprising only some features (in this case, only pre-treatment features); *iii)* improve classification accuracy when more data sources are available. Each model was extracted using the Likelihood-Fuzzy Analysis (LFA) [19,20], which is based on both statistics and fuzzy logic, since: *i)* it enables to manage heterogeneous variables; *ii)* it ensures good performances, compared with state-of-the-art methods [18,21], and robustness to uncertain data; *iii)* the obtained models, made of linguistic variables and *if-then* rules, present high semantic interpretability; *iv)* a confidence measure of results can be calculated.

A preliminary attempt was presented in [18], using this approach for detecting possible predictors of PG shrinkage, among clinical features, dosimetric parameters, and the image-based Jacobian index at the same time.