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A Feature-Pooling and Signature-Pooling Method for Feature Selection for Quantitative Image Analysis: Application to a Radiomics Model for Survival in Glioma

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Abstract. We proposed a pooling-based radiomics feature selection method and showed how it would be applied to the clinical question of predicting one-year survival in 130 patients treated for glioma by radiotherapy. The method combines filter, wrapper and embedded selection in a comprehensive process to identify useful features and build them into a potentially predictive signature. The results showed that non-invasive CT radiomics were able to moderately predict overall survival and predict WHO tumour grade. This study reveals an associative inter-relationship between WHO tumour grade, CT-based radiomics and survival, that could be clinically relevant.

Keywords: Quantitative imaging feature · Feature selection · Glioma

1 Introduction

With ever-increasing utilization of radiological imaging in the diagnosis and treatment workflow for deadly cancers such as glioblastoma, there is intense interest in use of quantitative image analysis to extract as much clinically relevant information as possible for research and routine care. Despite the growing repertoire of drug agents and radiotherapy tools available to oncologists for treating non-resectable brain tumours, survival among glioblastoma patients remains

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depressingly low, with median survival time just over 14 months and as little as 10% of patients still alive after 5 years.

Radiomics [1,4] is an emerging field of translational clinical research aiming to convert vast amounts of routine clinical imaging data into a mineable "big data" resource to promote research into better treatments and to derive actionable insights to guide medical decision-making. Image-derived metric, i.e. radiomics features, are though to encode information about cancer and its phenotype, using subtle characteristics of pictures that are not easily quantifiable by an unaided human eye. Among imaging modalities, computed tomography (CT) radiomics is widely used, due to the relatively universal coverage of CT scanners in oncology centres [13]. However, reproducibility of radiomics studies across multiple independent institutions remains a significant translational research challenge, though good reproducibility is generally reported for CT [13] and rapid progress is being made in the magnetic resonance imaging (MRI) [9] and positron emission imaging (PET) radiomics domain [12].

Generally, radiomics analysis relies heavily on supervised machine learning, and the process can be divided into a number of essential parts: (i) image acquisition (ii) identification of the tumour region of interest (iii) radiomics feature extraction, (iv) selection of potentially predictive features from a vast set of computed features, and finally (v) model development and validation [6].

Among these steps, robust and comprehensive methods for feature selection plays a major role in regards to reducing risk of over-fitting and developing a compact, parsimonious final model that only contains the essential predictive variables. Feature selection in machine learning generally comes in three distinct flavours of method, each with their own advantages and disadvantages – filter methods (e.g. chi-squared test), wrapper methods (e.g. stepwise feature inclusion/elimination) and embedded methods (e.g. regularization) [10].

Previous work in this area have compared combinations of feature selection approaches and machine classifiers. Hawkins et al. compared four different feature selection and classification methods for CT-based survival prediction of lung cancer [5]. Parmar et al. first evaluated 14 feature selection methods and 12 classification methods to predict overall survival of lung cancer patients [7], then chose 13 feature selection methods and 11 classification methods to predict overall survival of head and neck cancer patients [8]. Zhang et al. compared 54 cross-combinations of six feature selection methods and nine classification methods for prediction of local and distant failure in advanced nasopharyngeal carcinoma [16]. Wu et al. compared 24 feature selection and three classification methods for the prediction of lung cancer histology [15].

It is clear that inappropriate feature selection method can adversely affect the performance of a radiomics signature. However, there is no known a prior method for selecting the most predictive features from the beginning. The motivations for developing a good feature selection procedure are clear to obtain an unbiased and generalizable model. We need feature selection to deal with the two-fold problem that is common in many clinical transnational radiomics studies – a limited patient sample size (that is, a small number of outcome events) relative

to the feature dimensional space which could be one or more orders of magnitude larger than the patient sample size.

In this manuscript, we propose a comprehensive feature selection procedure combining several advantages of different filter, wrapper, and embedded approaches. The intention was to develop a feature selection method that could work with different combinations of feature selection and classifier training approaches. The proposed method uses feature pooling to make transparent which individual features are frequently selected, and allows a set of competing candidate signatures to be assessed in the training set. As proof of concept, we used this method to select a CT radiomics-based signature for overall survival in glioma/glioblastoma patients. We evaluated the predictive performance of this model on a single-institution dataset, and further considered the relationships between the selected signature, tumour aggressiveness grade and overall survival at one year post-radiotherapy.

2 Materials and Methods

This was an internal ethics board-approved retrospective study comprising 160 patients with pathologically-confirmed glioma treated at a single radiotherapy institution between January 2004 and December 2014. Of these, 130 DICOM-RT studies with the requisite radiotherapy dose planning CT scans were extracted from a research picture archival system (PACS). The case mix examined here consists of 93 glioblastoma (GBM) and 37 non-GBM astrocytomas of various subtypes. All patients received only biopsy prior to high-dose radiotherapy with temozolomide or radiotherapy only. Follow-up consisted of quarterly clinical consultations including MRI examination, until death from any cause. MRI and CT images were co-registered and a gross tumour volume (GTV) was manually drawn by an experienced radiation oncologist. Radiotherapy dose and radiomics features were calculated on helical CT (Siemens, Erlangen, Germany) with 0.98 mm by 0.98 mm pixels, 1 mm reconstructed slice thickness and 120 kVp tube potential.

2.1 Feature Extraction

Image features were extracted from hand-drawn GTVs using an open-source package O-RAW [11] that is an extension wrapper for the freely available radiomics software PyRadiomics [14]. Each CT slices was uniformly resampled to isotropic voxels of 1 mm by using linear interpolation. A total of 1105 radiomic features, consisting of first-order statistics, shape descriptors, texture features, and filter-based features by Wavelet and Laplacian of Gaussian (LoG), were extracted from each 3D GTV. Documentation of pyradiomics features can be found (https://pyradiomics.readthedocs.io).

2.2 Feature Selection

We proposed an integrated feature selection procedure to minimize the risk of over-fitting the radiomics model on the available patient outcome data, and this is shown schematically in Fig. 1. The principal idea is based on pooling the features and signatures over numerous bootstrap sampling iterations. The feature pooling part was used to individually rank potentially predictive radiomics features by its cumulative selection frequency. The signature pooling part reveals the set of potentially predictive signatures built using these frequently selected individual features, rather than just one signature. For this proof of concept, we used 500 bootstrap iterations as example, and we then selected the first signature from its pool to assess the area under a receiver-operator curve (AUC) and classification accuracy. We elaborate the process in detail below.

First, the available patient cohort was randomly split into a training (75%) subset for feature selection and model development, and a validation subset (25%) for model assessment only. By counting outcome labels only, we confirmed that the ratio of surviving to deceased subjects in each subset was the same. Secondly, dimensionality reduction was performed in the training set only by testing (i) feature Pearson correlation coefficient [2] against volume (ii) pair-wise feature Pearson correlation coefficient to each other, and (iii) Kolmogorov-Smirnov (KS) non-parametric similarity of features among the surviving and deceased outcome labels. For this study, we selected a p-value of 0.05 as the elimination threshold. Thirdly, the least absolute shrinkage and selection operator (LASSO) was used as an embedded regularization and feature selection method. Within the LASSO operation, we applied the Synthetic Minority Oversampling Technique (SMOTE) [3] 500 times to ameliorate the effects of the unbalanced alive to dead ratio in the training subset.

With individual feature pooling, we kept count of the number of times each radiomic feature was retained after the previous LASSO step. We then ordered these retained features from most-frequent to least-frequent and kept only those individual features which occurred more often than the mean frequency. These relatively frequently-retained features were then subjected to 5-fold, 500-repetition recursive feature elimination (RFE) with a logistic regression classifier to compile a set of candidate radiomics signatures. Each signature thus consists of a maximally compact set of individual frequently-appearing features from the feature pool that collectively contributes to the outcome prediction. However, the RFE step above often selects the same subset of individual features. Again, we tracked the number of times signature with the same combination of features was selected at the end of RFE. We ordered these candidate signatures from most-frequently to least-frequently appearing. For this study, we arbitrarily retained the top 5 most-commonly occurring signatures for inspection. We computed the AUC of all top 5 signatures on all the subjects in the training subset only, and then chose one signature with the highest AUC for testing in the validation subset. Throughout the feature selection with LASSO and signature development with RFE, we used a multi-variable logistic regression statistical model for the binary surviving vs dead outcome prediction.

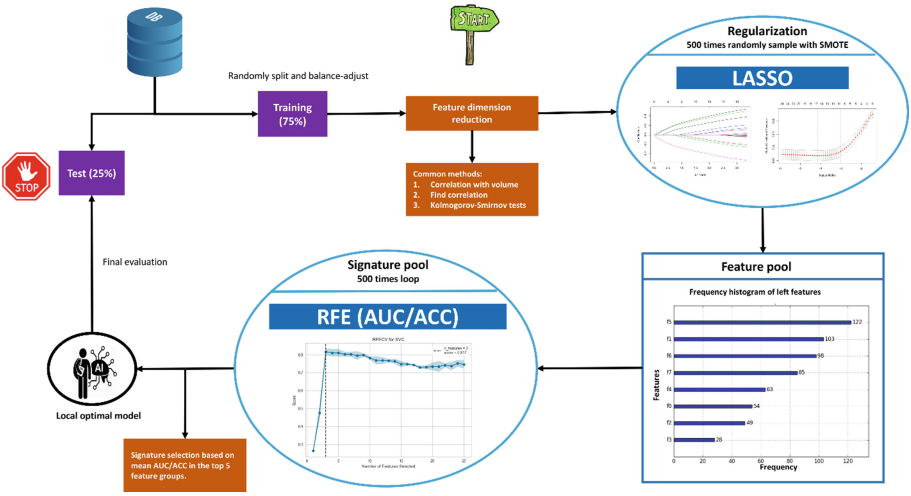

Fig. 1. The processing workflow of the proposed feature-pooling and signature-pooling method for feature selection for quantitative image analysis. The details are explained in the text.

2.3 Statistical Analysis

The above methodology was implemented in its entirety in R (version 3.30, https://www.r-project.org). 95% confidence intervals around the mean AUC and mean classification accuracy were estimated using 2000 stratified bootstrap replications. To assess goodness of fit, we assessed the slope and intercept of the final model calibration curve on the validation subset, accompanied by a Hosmer-Lemeshow test statistic.

2.4 Model Development

A prognostic model of overall survival at one year following radiotherapy treatment of glioma, using radiomics features only, was developed using the above-mentioned method. For comparison, we evaluated the AUC and accuracy of one-year survival prediction using only the World Health Organization (WHO) tumour aggressiveness grades at diagnostic baseline and at the start of radiotherapy. For comprehensiveness of our understanding of the role of radiomics, we also investigated the prediction of WHO tumour grade using radiomics features alone, following the same radiomics signature as we developed for survival.

3 Results

At one year following radiotherapy, there was similar proportion of surviving to deceased patients on the training and validation subsets (training: 64 deceased,

33 alive; training: 20 deceased, 13 alive), see Supplementary Fig. 1. After executing our feature selection process for survival prediction, we arrived at the individual radiomics features at the top of the feature pool, as shown in Supplementary Fig. 2. From the AUC metrics of the top 5 most-frequently appearing signatures in the signature pool, we selected the top AUC signature to test against the validation subset. We gave this tentative signature the label "shi:2019a-gbm" for reference.

The "shi:2019a-gbm" signature validated well, achieving an AUC of 0.82 (95% CI: 0.67–0.97) and accuracy of 0.70 (95% CI: 0.51–0.84) in the validation subset. For comparison, the same signature achieved an AUC of 0.77 (95% CI: 0.66–0.87) and accuracy of 0.73 (95% CI: 0.63–0.82) in the training subset. The difference in AUCs and classification accuracies between the training and validation subsets were not statistically significant, as can be expected from the highly-overlapping confidence interval estimates.

Figure 2 gives the AUC plots of "shi:2019a-gbm" in the training subset (black line) and in the validation subset (red line). The calibration plots of the signature in both training and validation subsets with the Hosmer-Lemeshow test are shown in Supplementary Fig. 3. The Hosmer-Lemeshow test of the one-year survival prediction model yielded non-significant statistics ($p = 0.3$ and $p = 0.12$), indicating that deviation of model prediction from observed outcome was not statistically significant. The logistic regression coefficients of the "shi:2019a-gbm" signature is shown in Fig. 3.

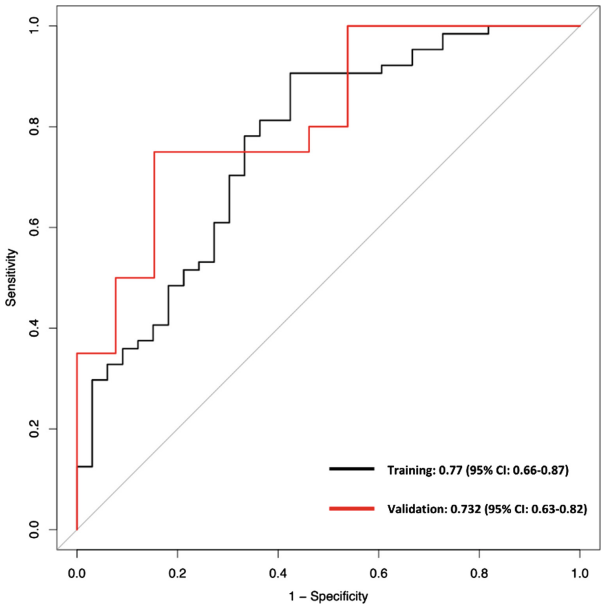

Fig. 2. Receiver-operating characteristic curves of the developed CT radiomics signature shi:2019a-gbm in the training and validation datasets. (Color figure online)

Feature name	Coefficients	Intercept = -1.784
original_glcm_Correlation	4.959	
wavelet.LHH_glszm_LowGrayLevelZoneEmphasis	-1.484	
wavelet.LHH_glrlm_LongRunHighGrayLevelEmphasis	$-8.703\ e^{-4}$	
wavelet.LLH_gldm_SmallDependenceHighGrayLevelEmphasis	$5.545\ e^{-3}$	
wavelet.HLL_glcm_ClusterProminence	0.65	

Fig. 3. The logistic regression coefficient of each radiomic feature in the shi:2019a-gbm sinecure with intercept.

To set a comparative baseline for the prediction performance of signature "shi:2019a-gbm", we examined the survival prediction by WHO tumour grades at diagnostic baseline and at the start of radiotherapy using the same patient data, respectively. The tumour grades yielded similar results to the radiomics signature with accuracy of 0.79 (95% CI: 0.61–0.91) and 0.70 (95% CI: 0.51–0.84) in the validation subset, respectively. When we re-calculated regression coefficients in "shi:2019a-gbm" (i.e. the same set of potentially predictive radiomics features), we found this subset of radiomic features also performs well for predicting WHO tumour grades with AUCs of 0.80 (95% CI: 0.64–0.95) and 0.73 (95% CI: 0.64–0.93) for the tumour grades at diagnostic baseline and at the start of radiotherapy.

4 Discussion

We proposed a comprehensive feature selection method applicable generally to quantitative imaging analysis using derived features, using a new combination of filter, wrapper and embedded selection steps. We outlined the method in detail, and then used this to develop a binary outcome model for one-year overall survival after radiotherapy of glioma. We thus showed that a carefully selected radiomics signature could be developed as a prognostic model, with equivalent performance in validation and training subsets. We further probed the interrelationship between the radiomics signature, WHO tumour aggressiveness grade and overall survival.

We elected to use retrospective CT images in this study, because CT is a relatively routine and ubiquitous clinical imaging modality, and reproducibility between many different CT scanners could be reasonably achieved. Our notable finding is that CT images contain information, in form of radiomic features, that could (with further investigation) provide an entirely non-invasive means of stratifying patients for survival outcome. While it is thought that only MR imaging of the brain provides information, we have shown that routine CT imaging that would otherwise be single-use (for example, radiotherapy dose planning only) can be easily re-used to extract clinically relevant information.

The inter-relationship of radiomics with WHO tumour grade is interesting, quite apart and separately from survival prediction. With only re-calibration of the coefficients, we achieved promising results in predicting WHO tumour grade re-using the same radiomic features in the signature ("shi:2019a-gbm") as we used to predict survival. This suggests a hypothesis, that the signature we selected happens to associate closely with WHO tumour grade, therefore either the tumour grade or the radiomics signature provides an similar pathway towards predicting survival at one year, at least with a large overlap. It is highly likely, if we optimized the feature selection to predict WHO tumour grade from the very beginning (instead of survival) we would be able to additionally improve the prediction of tumour grade from a fully non-invasive radiomics signature alone. However, this was not the specific objective of this paper.

Before we can suggest clinical applicability and wider generalizability of the above model, we need to perform external validation across multiple clinical centres, and further examine the inter-relationship between radiomics signatures with clinical prognostic factors. In terms of tumour volume-confounding of radiomics features, we confirmed that the individual features incorporated into the signature "shi:2019a-gbm" had effectively zero Pearson correlation (median 0.02, range: −0.27–0.18) with GTV volume.

Even though a full explanation of radiomic features for survival of glioma patients is difficult, we have tried to show the definition and biological meaning of the selected features below. These features may different from the previously studies. However, as many radiomic features are correlated with each other, we may have similar findings to others. To verify this hypothesis, further studies are still needed.

1. Original_glcm_Correlation feature is with the value between 0 (uncorrelated) and 1 (perfectly correlated) showing the linear dependency of gray level values to their respective voxels in the GLCM. Therefore, it may reflect the density and homogeneity of the tumour.
2. Wavelet.LHH_glszm_LowGrayLevelZoneEmphasis measures the distribution of lower gray-level size zones, with a higher value indicating a greater proportion of lower gray-level values and size zones in the image. Therefore, it may reflect the homogeneity of the tumour.
3. Wavelet.LHH_glrlm_LongRunHighGrayLevelEmphasis measures the joint distribution of long run lengths with higher gray-level values. Therefore, it may reflect the homogeneity of the tumour as well.
4. Wavelet.LLH_gldm_SmallDependenceHighGrayLevelEmphasis measures the joint distribution of small dependence with higher gray-level values. Unfortunately, we do not come up with the biological meaning to the tumour.
5. Wavelet.HHL_glcm_ClusterProminence is a measure of the skewness and asymmetry of the GLCM. A higher values implies more asymmetry about the mean while a lower value indicates a peak near the mean value and less variation about the mean. It may reflect the asymmetry and homogeneity of the tumour.

To increase the chances of clinical applicability and wider generalizability of radiomics, appropriate methods for feature selection and signature compilation are much needed in the field. Previous workers [5,7,8,15,16] have investigated the consequences of feature selection on radiomics model performance. We have tried to overcome some limitation of previous studies using our proposed approach. First, restricting oneself to a simple feature selection step might not be able to locate relevant signals associated with the outcome. Secondly, being overly profligate with feature dimensionality might lead to over-fitting, which will be observed when testing a signature in hold-out or external validation data. Thirdly, our feature-pooling and signature-pooling steps allow information derived from each bootstrap sample to be used to rank the most promising features. Pooling makes it transparent to the investigator that certain combinations of features are more likely to be encountered than others. This makes the feature selection method relatively independent of "lucky" happenstances in the way the cohort data is randomly divided.

It is possible that different learning algorithms may work better with certain feature selection methods. For example, selecting feature by a regularized linear regression approach may not be appropriate if one is ultimately intending to develop a non-linear classifier. Therefore, some consistency may be required between the feature selection steps and the model learning steps. Additionally, there are potential limitations when using penalty functions in regularization methods with high-dimensionality on data with limited number of outcomes. For instance, when the dimension P of radiomics is much larger than N the number of patients, a LASSO method can choose at most N features before it saturates. In this study, totally 1105 radiomic features were extracted, but only 97 patients were in the training dataset. Hence, the feature dimension reduction step was extremely necessary, which made LASSO work correctly. Furthermore, if there is a group of highly correlated features, then the LASSO method tends to select one feature from a group and ignore the others. To overcome this, we tracked the cumulative frequency of retention of individual features first, rather than using LASSO to select the final feature set for us.

In our knowledge, there is no a baseline approach for radiomic feature selection, as the feature selection procedure is highly dependent on radiomics feature dimension (e.g., hundreds to thousands), sample size and different categories of radiomics. This study described a new feature selection framework, especially proposing feature pooling and signature pooling approaches. These two steps are reasonable and feasible to select robust radiomic features so that avoiding overfitting. For the algorithms in the framework, such as KS test, LASSO, and REF, were suitable and worked well in our study. We showed them as enlightenment to new users, which could help them to start to use the proposed framework. Certainly, users could replace them with other relevant algorithms according to their specific cases.

The key limitation of this study is the lack of a fully independent external cohort from another radiotherapy institution. To test the methodology, we have only used hold-out validation on the single-institution cohort. For future work,

we are preparing additional validation cohorts from other institutions in order to externally validate and challenge our hypotheses. Testing of this method on other diseases and alternative clinical endpoints was outside the scope of the present study, however we are preparing lung cancer and oropharyngeal cancer data for several hundred subjects that we will share publicly. This feature selection method can be tested on those datasets in the near future.

A detailed comparison of different classifiers matched to different options for feature selection was outside the scope of this paper. Furthermore, combination of the radiomics signature with clinical variables (e.g., WHO tumour grade) still needs to be considered for future work. However, the method we have proposed here is modular in the sense that feature selection steps and model training steps can be changed without affecting the overall process. Thus, the pooling functionality can then be used to transparently document whether alternative choices of feature selection might produce different signatures.

5 Conclusion

We have proposed a pooling-based radiomics feature selection method, and show how it would be applied to the clinical question of predicting 1-year survival in patients treated for glioma by radiotherapy. The method combines filter, wrapper and embedded selection in a comprehensive process to identify useful features and build them into a potentially predictive signature. Non-invasive CT radiomics features were able to moderately predict overall survival and predict WHO tumour grade. Subject to further validation in future, this study reveals an associative inter-relationship between WHO tumour grade, CT-based radiomics and survival, that could be clinically relevant.

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