Oncologic Imaging REVIEW

An Introduction to Radiomics: Capturing Tumour Biology in Space and Time

Nickolas Papanikolaou, Joao Santinha
Computational Clinical Imaging Group, Champalimaud Foundation, Centre for the Unknown, Lisbon, Portugal

SUBMISSION: 8/1/2018 | ACCEPTANCE: 16/3/2018

ABSTRACT

Currently, there is a shift from visual interpretation of medical images, which is highly variable, to the extraction of high-dimensional meaningful data the so called Radiomic signatures that can be used in conjunction with machine learning algorithms to predict clinical outcomes. Quantification of imaging biomarkers can be used to make predictions on whether a specific treatment will work for a specific patient, and can aid in differential diagnosis problems or may offer prognostic capabilities related to disease recurrence or relapse. Modern algorithms based on machine learning techniques can be used to provide automatic or semi-automatic segmentation with minimal human interaction. Feature extraction is the calculation of texture and shape imaging features that can be used along with clinical biomarkers. Feature selection is important to avoid overfitting and exclude redundant features improving the quality of data, by reducing their dimensionality. Following to that, multiple machine learning algorithms can be recruited in order to find the optimal that can provide with the best performance. Algorithms like Bays, linear regression, Support Vector Machines, Random Forests and others are currently used.

KEY WORDS | radiomics; machine learning; models; imaging biomarkers; oncology

Introduction

Molecular profiling by means of genome, proteome and metabolome is at the core of precision medicine. In current clinical practice, tumours are monitored by invasive biopsy and molecular profiling, but their spatial and temporal pathologic heterogeneity limits the ability of invasive biopsy techniques to capture their state fully [1-4]. Furthermore, the necessity of repeated, invasive

CORRESPONDING AUTHOR, GUARANTOR

Nickolas Papanikolaou
Principal Investigator in Oncologic Imaging, Head of Computational Clinical Imaging Group, Champalimaud Foundation, Centre for the Unknown, Av. Brasília, Doca de Pedrouços, 1400-038 Lisbon, Portugal, Email: nickolas.papanikolaou@research.fchampalimaud.org

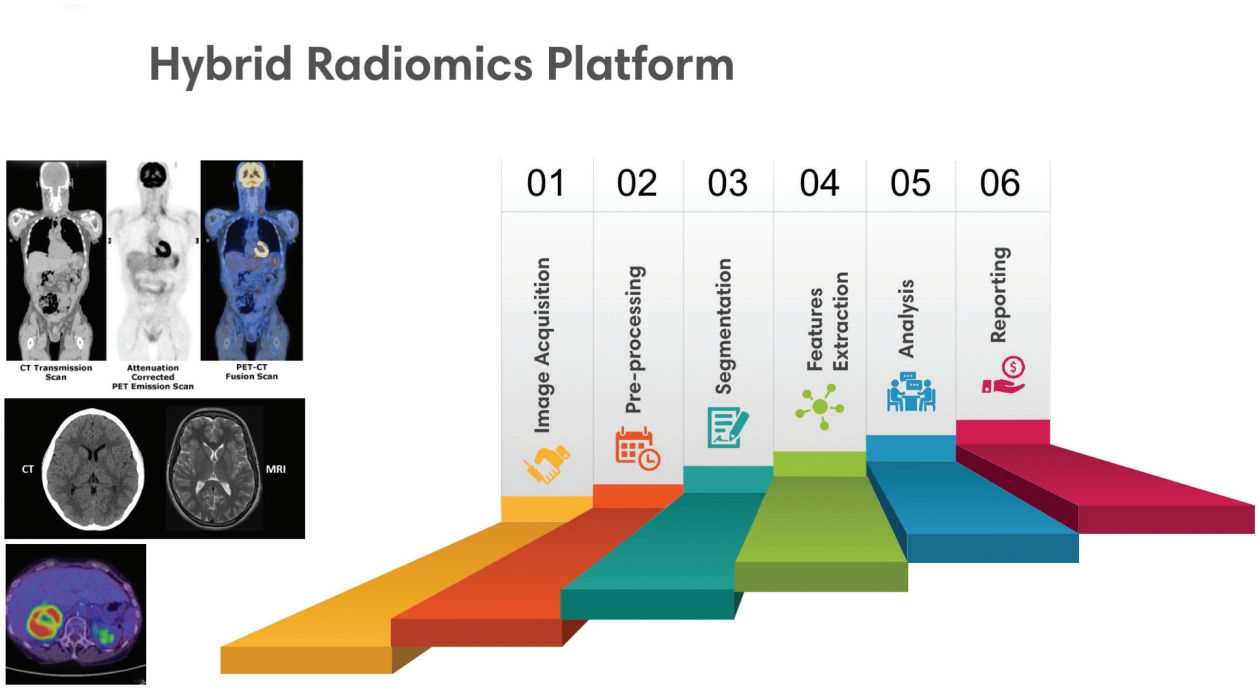

Fig. 1. *Radiomics Platform developed by the Computational Clinical Imaging Group at the Centre for the Unknown, Champalimaud Foundation. The platform can be used to process multi-modality data, including plain CT, MRI, PET-CT, as well as parametric functional maps like ADC, Ktrans, SUV etc.*

sampling may be burdensome to the patient, is expensive, and limits the practical number of opportunities to monitor disease progression and treatment response.

Medical imaging is a proven technology for the clinical assessment of cancer. It has served as a valuable clinical tool for several decades. Consequently, imaging is often viewed as an old technique, a misperception that, unfortunately, has limited its potential and perceived effect on precision medicine. It is well known that tumours exhibit strong phaenotypic differences in patients that can be visualised by imaging [5-8]. A significant advantage of medical imaging is its ability to noninvasively assess cancer's features, such as intra-tumoural heterogeneity, on a macroscopic level, at baseline and follow-up, from the primary tumour to potential metastasis.

Currently, a hypothesis-driven research is the mainstream methodology incorporating the selection of a single or multiple imaging biomarkers targeting the improvement of specificity, trying to provide with prognostic information regarding treatment response or to monitor and guide therapy. Apparently, this strategy suffers from selection bias, and therefore there is a shift in cancer imaging biomarkers to a more "holistic" approach by quantifying and extracting myriads of imaging patterns including texture and shape features on a pixel by pixel basis, otherwise invisible to the human eye. The latter methodology is summarised under the term Radiomics, and it's the process where an intelligent algorithm is undergoing training with labelled data, then validation and testing are performed to determine the clinical performance answering a specific clinical question [9-12]. Radiomics refers to the process of extracting mineable, high-dimensional data from the routine, standard of care computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) images, using automatic or semiautomatic extracted data-characterisation algorithms.

The Rise of Radiomics

Tumour histology classification is based on biopsy, that is invasive, destructive (reducing the number of monitoring opportunities) and suffers from poor cost efficiency. Biopsy sampling of a random spatial subregion of a tumour at a single time point may not be able to reflect the complex tumour state accurately [13]. Further-

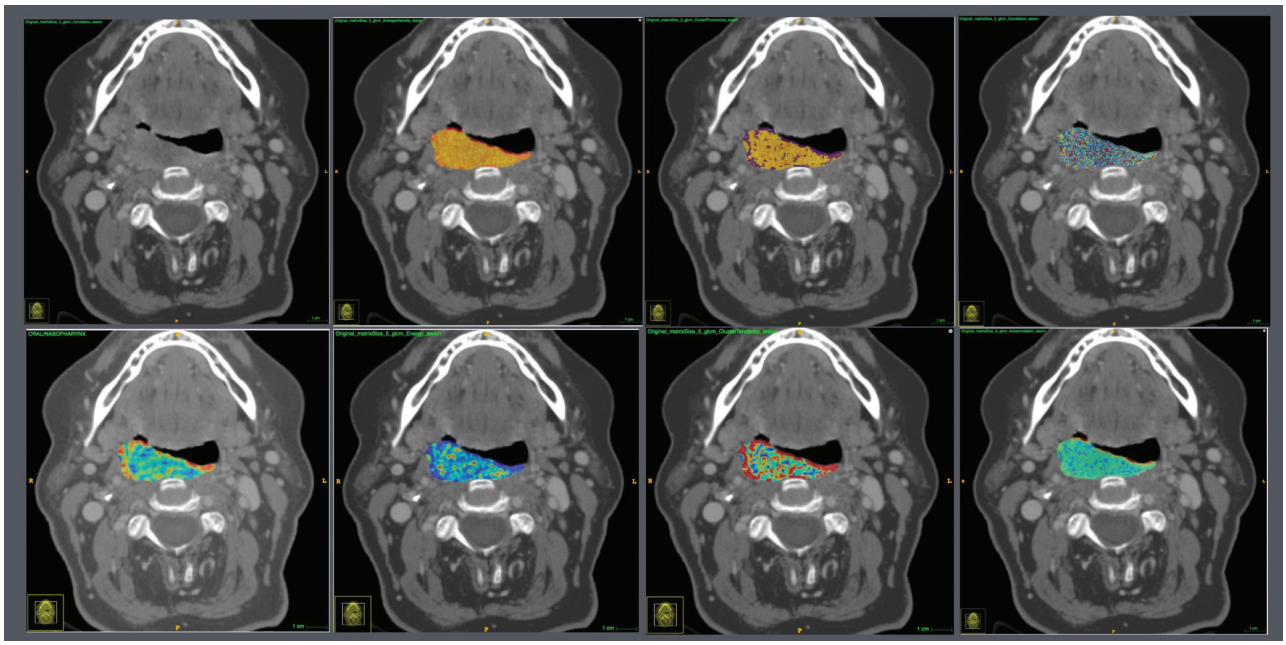

Fig 2. *Various texture maps obtained from post contrast CT images in a patient with HPV positive oropharyngeal carcinoma.*

more, it is well known that a hallmark of tumours is their spatial and temporal heterogeneity. On the other hand, imaging provides an opportunity to extract valuable information regarding tumour characteristics in a non-invasive way. It's not subjected to bias selection, since the entire tumour can be assessed multiple times during the course of the disease (before, during and after treatment). However, currently imaging evaluation is based on the subjective opinion of radiologists, is time consuming, varies significantly protocol-wise and therefore suffers from low reproducibility. These are the main driving forces for the development of Radiomics, where there is an effort to infer from macroscopic based imaging features, tumour histological subtypes and proteo-genomic patterns [14]. Machine learning methods are used to build, train and validate models that can aid in the prediction and early stratification of patients, a concept that represents the core of precision medicine [15, 16].

Recent developments in the fields of machine and deep learning are offering opportunities in the area of robust algorithms that could be used to assess more objectively critical clinical questions in oncologic patients. Currently, research efforts are focused on developing such algorithms and optimising the workflows for an easy, user-friendly application in the clinical routine. A typical workflow of Radiomics comprises image acquisition, lesion segmentation, feature extraction, feature selection, development and validation of the predictive model (**Fig. 1**). In all phases, there are unsolved problems and challenges. In the image acquisition part, we need to make sure that the raw information as provided on our images adds value to answer the clinical question. In other words, we need to optimise our image acquisition protocols to contain as much as possible of valuable information and remove noise. Various image filters can be used to achieve the latter task, including exponential, Laplacian of the Gaussian (LoG) and others.

One of the bottlenecks in Radiology when it comes to quantification of imaging biomarkers is the lesion segmentation. Usually, the radiologist must trace the lesions in multiple images manually, which is time-consuming and results in low reproducibility. Modern algorithms based on machine learning techniques can be used to provide automatic or semi-automatic segmentation with minimal human interaction.

The following step is feature computation or extraction, where texture and shape features will be calculated along with clinical biomarkers. Feature selection will be made to avoid redundant features and improve the quality of data, by reducing their dimensionality. Following to that, multiple machine learning algorithms are evaluated to select the optimal one that can provide the best prognostic power. Algorithms like Naïve Bays, linear regression, Support Vector Machines, Random Forests and others are mostly used in Radiomics research.

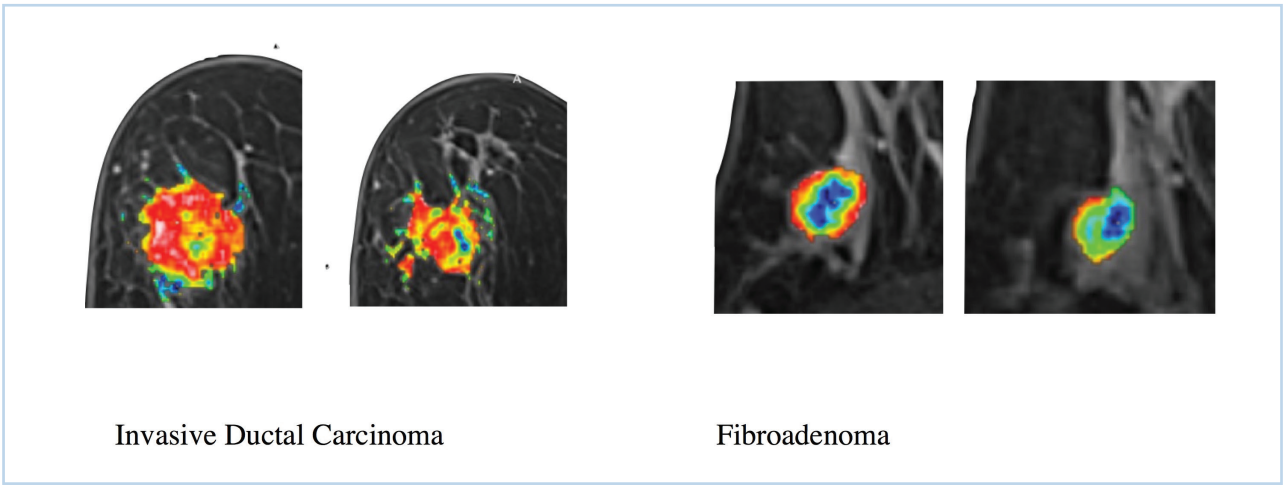

Fig. 3. *Texture entropy is a measure of randomness of the gray-level distribution. Malignant lesions present with significantly higher randomness versus benign, possibly reflecting the imaging heterogeneity as disclosed in contrast-enhanced T1-w MRI images. Red colours are compatible with high entropy values, green with moderate and blue with low entropy values.*

Non-imaging layers of information can be employed in the form of genomics, proteomics or metabolomics to explore correlations and interactions at a molecular level further. Apart from conventional anatomical imaging in the form of T1 and T2-weighted imaging, functional methods like DW MRI or DCE MRI can be used to assess specific components of the disease including angiogenesis, abnormal metabolism, hypoxia, and hypercellularity.

Setting up the models

A critical phase in a Radiomics project is the precise identification of the clinical question. The latter can be prognosis regarding treatment response, accurate subtype classification in a histopathological or molecular level, patient stratification regarding: i) toxicity of specific treatments (i.e., radiation therapy), ii) tumour aggressiveness, iii) tumour resistance to treatment, and iv) metastatic propensity. The choice of the clinical question should be based on the clinical importance and the amount of available patient data. Although it is relatively easy to train a machine learning algorithm with homogeneous data (laboratory conditions), the challenging and exciting part is to validate your model using heterogeneous data from multiple institutions to introduce variability (real-life conditions). Only if such requirements are satisfied the model could make robust, accurate predictions on unknown cases. Therefore, Radiomics can be significantly strengthened by multi-institutional studies. Regarding the number of cases that are needed for training and validating a model, it depends on the amount of information that can be found on the imaging features. As a rule of thumb, 10-15 cases are needed for each feature that will contribute the final Radiomic signature [17]. So, for a 15-feature model we need at least 150 cases to train, and validate the model, in case of the use of k-fold cross-validation. Additional cases, not used on the development of the model, are required to test the model, which will provide an unbiased evaluation of the model.

Development of Radiomics Signatures

Different phases that should be considered before developing the final model are the following.

1. Identification of a patient cohort

Even in this era of big data, right patient datasets are surprisingly difficult to build. Identifying a patient cohort is a critical part of any Radiomics project. Below we have outlined strategies for making good datasets.

1.1 Patient cohort homogeneity

Some heterogeneity in the patient cohort may be necessary to achieve sufficient patient numbers, but too much heterogeneity not only can dilute the potential impact of the findings but also can introduce too much variability into the dataset. An example of weakening the effect could be including patients whose overall staging varies widely because staging may already be a prognostic factor. An example of too much variability in the data-

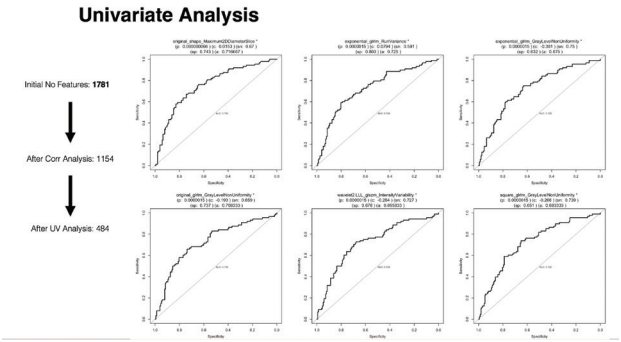

Fig 4a. *Univariate analysis can be used to perform feature reduction, by identifying the relevant features. In this example, the initial number of features evaluated was 1781, and after correlation analysis to identify and remove redundant features, they were reduced to 1154, from which only 484 (6 of them are shown) presented with statistically significant differences between the two classes that were HPV (+) or HPV (-) oropharyngeal cancers.*

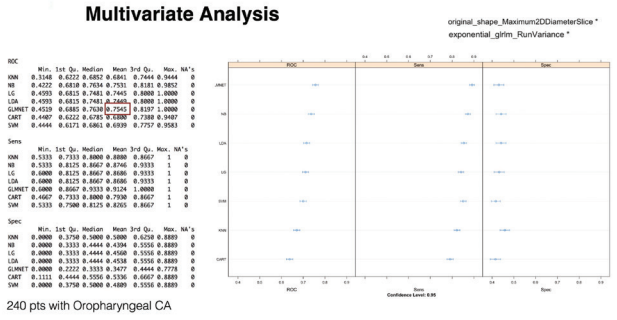

Fig 4b. *Following to the application of feature reduction techniques, only 2 features extracted from post-contrast CT images (original_shape_Max2DDiameterSlice and exponential_glrlm_RunVariance) survived and provided a Radiomic signature that was capable to differentiate HPV(+) from HPV(-) oropharyngeal cancers. The accuracy of various machine learning algorithms is shown, with generalised linear model via penalised maximum likelihood (GLMNET) providing the highest Area Under Receiver Operating Characteristsic (AUROC) of 0.7545.*

set could be involving patients whose treatments vary significantly (i.e., widely different regimens comprising different surgery, chemotherapy and radiotherapy approaches).

1.2 Sample size

Small sample sizes increase both the type-I (incorrectly detecting a difference) and type-II (not detecting an actual difference) error rates. Radiomics studies have been published with as few as 15 patients, but there is much risk of overfitting the data, and researchers should aim for much larger datasets.

2. Optimisation of Acquisition Protocols

One of the significant issues in quantitative imaging studies is the ample variability regarding acquisition protocols and lack of standardisation. Imaging parameters vary depending on the vendor, the type of hardware and software available on the imager, the radiologist, and radiographer who are conducting the examination. So, comparing results across different institutions can be challenging.

Therefore, it is vital to develop and follow standardised acquisition protocols that can guarantee accurate, reproducible, repeatable results for further analysis.

3. Tumour Segmentation

After acquiring an imaging dataset (CT, MRI or PET), the next step in the Radiomics workflow is the segmentation of the region of interest (ROI). Manual tracing of ROIs might have high inter-user variability, especially for modalities like MRI, which may affect the Radiomics image features. One of the main reasons of active research in the field of segmentation is to reduce inter-user variability by the use of semi- or fully automated segmentation tools, however even if those algorithms are successful the final result should always be verified by a board-certified radiologist.

A more recent approach is the delineation of the different physiologically distinct regions (e.g. blood flow, cell density, necrosis and oedema) within the tumour, also known as habitats [11]. The Radiomic features can then be extracted for each of these habitats.

4. Feature Extraction

The primary objective of Radiomics is to provide a comprehensive assessment of the imaging phaenotype using automated data extraction algorithms. The latter can be served by calculating a large number of computational, quantitative features that capture a wide variety of phaenotypic traits. Radiomic features can be classified into agnostic and

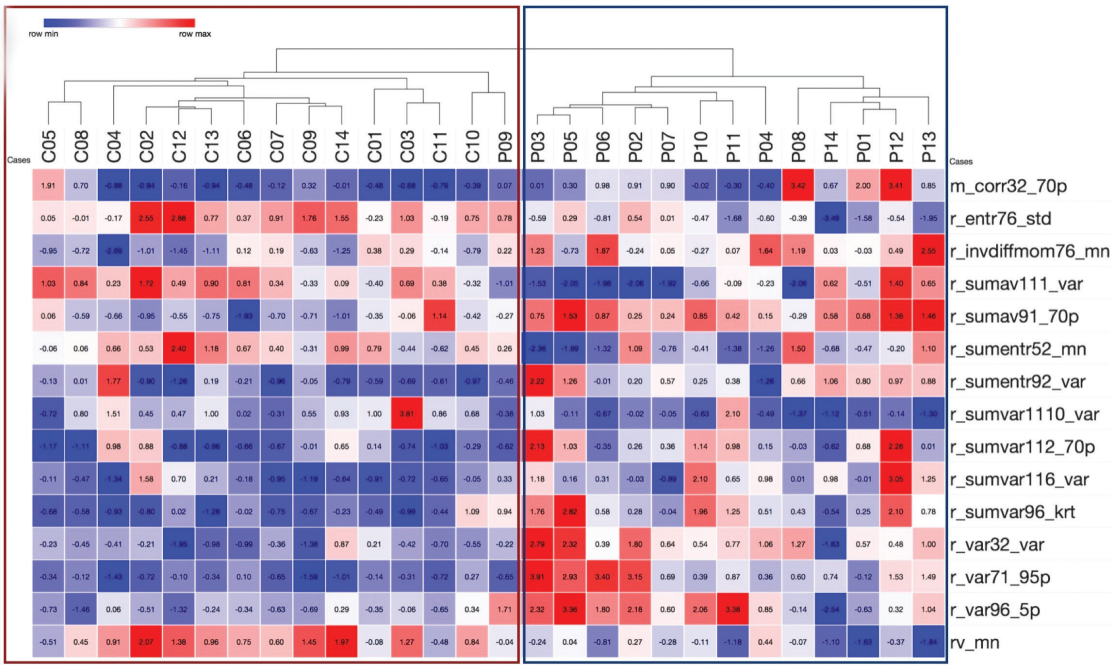

Fig 5. *Hierarchical cluster analysis was done using 15 texture features extracted from b1000 diffusion images obtained on patients with pancreatic cancer and normal controls. The Radiomic Signature comprised these 15 texture features provided with very high discrimination accuracy between Controls and Patients (only one patient P09 was misclassified).*

semantic. Semantic features are commonly used by radiologists to describe lesions like diameter, volume, morphology, while agnostic features are mathematically extracted quantitative descriptors, which are not part of the radiologists' lexicon. These features are identified by algorithms that capture patterns in the imaging data, such as first-, second-, and higher-order statistical determinants, shape-based features and fractal features. First-order statistics can be used to describe voxel values without concern for spatial relationships. These measures can be used to quantify phaenotypic traits, such as overall tumour intensity or density (mean and median of the voxels), or variations (range or entropy of the voxels). There is also shape- and location-specific features that capture 3-dimensional shape characteristics of the tumour. Second-order statistical features can take spatial relationships of contrast between voxels into account. They are also referred to as texture features. Texture is defined as "a regular repetition of an element or pattern on a surface with the characteristics of brightness, colour, size and shape".

Examples of texture features include the gray-level co-occurrence matrix, gray-level dependence matrix, gray-level run-length matrix, and gray-level size zone matrix (**Fig. 2**). These matrices describe textural differences based on grey tone spatial dependencies. Advanced methods, such as wavelet and Laplacian of Gaussian filters, can be applied to enhance complex patterns in the data that are difficult to quantify by eye (**Fig. 3**).

5. Feature Selection

Since a large number of features is extracted, it is advised to utilise feature selection methodologies to identify non-redundant, stable and relevant features that are more likely to result in models with better performance (**Fig. 4a**). Stability can be assessed in terms of consistency of the features in a test-retest setting or in terms of robustness of features to variations in tumour segmentation [10]. A basic approach to remove redundant features is the correlation-based feature elimination [13]. Many other feature selection methods are available to reduce the dimensionality. These methods can be divided into three categories, namely filter, wrapper and embedded methods. Filter methods perform feature ranking and selection based on statistical measures and they are characterised by their computational efficiency, generalisation and robustness to overfitting. Filter meth-

Fig 6. *The most common categories of algorithms used in Machine Learning.*

ods can either rank features independently (univariate methods), by ignoring the relationship between features, or take into account the dependency between features (multivariate methods). Univariate filter methods are usually used as a pre-processing step since redundancy is not analysed. In wrapper methods, searches to identify subsets of relevant and non-redundant features are performed and each subset is evaluated based on the performance of the model generated with the candidate subset. These methods are susceptible to overfitting and are computationally expensive. The embedded methods perform feature selection and classification simultaneously, taking advantage of their own feature selection methods and learning which features create a more accurate model. In comparison with wrapper methods, embedded methods are computationally efficient [15].

6. Model Development

After feature selection, a set of non-redundant, stable and relevant features can be used to develop a model that will try to answer the selected clinical question, the so-called ground truth variable (**Fig. 4b**). Depending on whether the result of the clinical question is a continuous or a discrete variable, different methods should be used. When working with continuous variables, regression methods, such as, Linear, Cox (Proportional Hazards), Regression Trees, Lasso, Ridge, ElasticNet or others can be used (**Fig. 5**). As for discrete variables, we can use classification methods such as Naïve Bays, Support Vector Machines, Decision Trees, Random Forests, KNN, Generalised Linear Models, Bagging and others (**Fig. 6**) [16]. To evaluate the obtained model, the cohort should be divided into two different subsets, the training, used to developed the model, and the testing, used only for validation and evaluation of the model developed. In the case of shortage of data, one way to deal with this problem is to utilise a cross-validation approach that comprises the separation of the cohort into training and testing sets [15]. In k-fold cross-validation, the original sample is randomly partitioned into k equal sized subsamples. Of the k subsamples, a single subsample is retained as the validation data for testing the model, and the remaining k–1 subsamples are used as training data. The cross-validation process is then repeated k times (the folds), with each of the k subsamples

used exactly once as the validation data. The k results from the folds can then be averaged to produce a single estimation.

Clinical Applications of Radiomics in Oncology

When considering potential clinical applications of Radiomics, several questions need to be addressed, including: Can imaging features inform about essential genomics features? Can integration of imaging and genomics features lead to higher power in prediction? Is it possible to decide about targeted therapy based on imaging-genomics association results? Can imaging serve as a virtual biopsy since it is non-invasive, covers the complete tumour, and is highly repeatable? The first publication trying to address the latter questions was published by Segal E, et al. [18], posed the question whether imaging features could predict gene expressions and managed to show that 28 image features could reconstruct 78% of a liver cancer gene expression profile. Additionally, it has been demonstrated that features such as the tumour image heterogeneity are associated with genomic heterogeneity and are correlated with increased treatment resistance and metastatic probability [19-21].

Tissue Characterisation

Wibmer, et al. [21] showed that texture features could discriminate cancerous from noncancerous prostate tissue on both T2-weighted MR images and ADC maps in a cohort of 147 men with biopsy-proven prostate cancer. Radiomic features extracted from plain CT images have been used to classify a pulmonary nodule as benign or malignant [22-25]. Kido, et al. [23] showed that the fractal dimensions for bronchogenic carcinomas were significantly smaller than pneumonias and tuberculomas ($p<0.0001$). Petkovska, et al. [24] showed that Gray Level Co-OcurrenceMatrix (GLCM) textures extracted from contrast-enhanced CT can accurately identify malignant from benign nodules, while visual inspection by three experienced radiologists performed worse in malignant-benign nodule differentiation. Combining shape-, size, and histogram-based features has been shown to improve the differentiation between malignant and benign nodules [25]. In another study [26], it was shown that texture analysis can perform preoperative stratification of thyroid nodules with high sensitivity and specificity on multi-institutional Diffusion Weighted Imaging datasets. The developed model comprised of texture features correctly classified 89% of the nodules from 18 patients in an independent validation dataset (AUC: 0.97, Sensitivity: 92% and Specificity: 96%).

Disease Prognosis

CT texture and histogram analysis allowed independent prediction of overall survival in patients treated with induction chemotherapy in locally advanced squamous cell carcinoma of the head and neck. The authors identified 2 texture and histogram features namely, primary mass entropy and histogram skewness to be independent predictors of overall survival [27]. Several studies [28-30] have reported correlations between Radiomic signatures extracted from CT images and disease-free survival (DFS). Parmar, et al. discovered a Radiomic signature comprising of size, intensity, shape, texture and wavelet features to have an association with lung cancer prognosis, stage and histology [31], and Coroller, et al. developed and validated a signature that correlated with presence of distant metastasis [32]. Using tumour habitats segmentation approach, Zhou et al. were able to distinguish different survival groups (<400 days or >400 days) [33], while Gevaert et al. were able to find Radiomic features that significantly correlated with survival and molecular subgroups [34].

Tumour Staging

It has been shown by various studies that Radiomic features are able to differentiate between various tumour stages. Radiomic features extracted from PET images were able to differentiate stage I and II from stage III and IV in 42 patients with cervical cancer [33]. In particular, Run Length Matrix (RLM) percentage texture was found to be most associated with cervical tumour stage. Early identification of tumour stage using imaging phaenotypes may improve patient stratification into different subgroups, subsequently optimising treatment outcomes. Towards this extent, texture features extracted from Laplacian of Gaussian (LoG) filtered plain CT images were found to predict high stage lung tumours (>stage II) [34]. In another study [35], comprised 40 patients with oesophageal cancer who underwent PET examination, Standarised Uptake Value (SUVmax), GLCM-entropy, and GLCM-energy were found to be significantly correlated with T and N stage. In particular, a GLCM-entropy value >4.70 could accurately identify tumours with stages above stage IIb [35].

Assessment of Treatment Outcomes

One of the most promising applications of Radiomics is related to the capability of Radiomic signatures to predict response to various types of treatment, including chemotherapy. Two independent studies have described a potential role for Radiomics in predicting pathological response to neoadjuvant chemotherapy prior to surgery, based on pre-treatment CT images of Non-Small Cell Lung Cancer [36, 37]. Through a systematic analysis of multi-parametric MRI features, Nie, et al. [38] were able to build models with improved predictive value over conventional imaging metrics. In 48 patients with rectal cancer that underwent chemoradiation treatment, Radiomic signatures were developed based on features extracted from plain T2 TSE images, diffusion weighted images and dynamic contrast enhanced images obtained prior to the initiation of treatment. Each subcategory images could generate moderate power in predicting the response, while if combining all information together, the Area Under the Curve (AUC) could be further improved to 0.84 for complete response and 0.89 for good response prediction, respectively [39].

Conclusions

Recent advances in imaging have opened new avenues for clinical research. There is a significant increase in the utilisation of quantitative techniques in Radiology, trying to make imaging more objective. The wealth of potentially useful information hidden in the clinical images that are not accessible through the naked eye is the main reason for the application of data mining techniques and the development of models that can aid optimal treatment strategies. Radiomics have enormous potential to facilitate further advances in oncologic research and clinical practice by accurately informing clinical decision-making, but thorough validation and adoption of proper methodological best practices should guarantee the achievement of the latter goal. **R**

Conflict of interest

The authors declared no conflicts of interest.

References

1. Marusyk A, Almendro V, Polyak K. Intra-tumour heterogeneity: A looking glass for cancer? *Nat Rev Cancer* 2012; 12: 323-334.
2. Fisher R, Pusztai L, Swanton C. Cancer heterogeneity: implications for targeted therapeutics. *Br J Cancer* 2013; 108: 479-485.
3. Chicklore S, Goh V, Siddique M, et al. Quantifying tumour heterogeneity in 18F-FDG PET/CT imaging by texture analysis. *Eur J Nucl Med Mol Imaging* 2013; 40: 133-140.
4. Maley CC, Galipeau PC, Finley JC, et al. Genetic clonal diversity predicts progression to esophageal adenocarcinoma. *Nat Genet* 2006; 38: 468-473.
5. Diehn M, Nardini C, Wang DS, et al. Identification of noninvasive imaging surrogates for brain tumour gene-expression modules. *Proc Natl Acad Sci* USA 2008; 105: 5213-5218.
6. Henriksson E, Kjellen E, Wahlberg P, et al. 2-Deoxy-2-[18F] fluoro-D-glucose Uptake and Correlation to Intratumoural Heterogeneity. *Anticancer Res* 2007; 27: 2155-2159.
7. Basu S, Kwee T, Gatenby R, et al. Evolving role of molecular imaging with PET in detecting and characterizing heterogeneity of cancer tissue at the primary and metastatic sites, a plausible explanation for failed attempts to cure malignant disorders. *Eur J Nucl Med Mol Imaging* 2011; 38: 987-991.
8. Yang X, Knopp M. Quantifying tumour vascular heterogeneity with dynamic contrast-enhanced magnetic resonance imaging: A review. *J Biomed Biotechnol* 2011; 2011: 12.
9. Lambin P, Rios-Velazquez E, Leijenaar R, et al. Radiomics: Extracting more information from medical images using advanced feature analysis. *Eur J Cancer* 2012; 48: 441-446.
10. Aerts HJWL, Velazquez ER, Leijenaar RTH, et al. Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach. *Nat Commun* 2014; 5: 4006.
11. Gillies RJ, Kinahan PE, Hricak H. Radiomics: Images are more than pictures, they are data. *Radiology* 2016; 278(2): 563-577.

12. Kurland BF, Gerstner ER, Mountz JM, et al. Promise and pitfalls of quantitative imaging in oncology clinical trials. *Magn Reson Imaging* 2012; 30(9): 1301-1312.
13. Wu W, Parmar C, Grossmann P, et al. Exploratory Study to Identify Radiomics Classifiers for Lung Cancer Histology. *Front Oncol* 2016; 6: 71.
14. Aerts HJWL. The potential of radiomic-based phenotyping in precisionmedicine a review. *JAMA Oncol* 2016; 2(12): 1636-1642.
15. Parmar C, Grossmann P, Bussink J, et al. Machine Learning methods for Quantitative Radiomic Biomarkers. *Sci Rep* 2015; 5: 13087.
16. Parmar C, Grossmann P, Rietveld D, et al. Radiomic Machine-Learning Classifiers for Prognostic Biomarkers of Head and Neck Cancer. *Front Oncol* 2015; 5: 272.
17. Chalkidou A, O'Doherty MJ, Marsden PK. False discovery rates in PET and CT studies with texture features: A systematic review. *PLoS ONE* 2015; 10: e0124165.
18. Segal E, Sirlin CB, Ooi C, et al. Decoding global gene expression programs in liver cancer by non-invasive imaging. *Nat Biotechnol* 2007; 25(6): 675-680.
19. Vignati A, Mazzetti S, Giannini V, et al. Texture features on T2-weighted magnetic resonance imaging: New potential biomarkers for prostate cancer aggressiveness. *Phys Med Biol* 2015; 60(7): 2685-2701.
20. Chee CG, Kim YH, Lee KH, et al. CT texture analysis in patients with locally advanced rectal cancer treated with neoadjuvant chemoradiotherapy: A potential imaging biomarker for treatment response and prognosis. *PLoS One* 2017; 12(8): 1-12.
21. Wibmer A, Hricak H, Gondo T, et al. Haralick texture analysis of prostate MRI: Utility for differentiating non-cancerous prostate from prostate cancer and differentiating prostate cancers with different Gleason scores. *Eur Radiol* 2015; 25(10): 2840-2850.
22. McNitt-Gray MF, Hart EM, Wyckoff N, et al. A pattern classification approach to characterizing solitary pulmonary nodules imaged on high resolution CT: Preliminary results. *Med Phys* 1999; 26: 880-888.
23. Kido S, Kuriyama K, Higashiyama M, et al. Fractal analysis of small peripheral pulmonary nodules in thin-section CT: Evaluation of the lung-nodule interfaces. *J Comput Assist Tomogr* 2002; 26(4): 573-578.
24. Petkovska I, Shah SK, McNitt-Gray MF, et al. Pulmonary nodule characterization: A comparison of conventional with quantitative and visual semi-quantitative analyses using contrast enhancement maps. *Eur J Radiol* 2006; 59: 244–252.
25. Way TW, Hadjiiski LM, Sahiner B, et al. Computer-aided diagnosis of pulmonary nodules on CT scans: Segmentation and classification using 3D active contours. *Med Phys* 2006; 33: 2323-2337.
26. Brown AM, Nagala S, McLean MA, et al. Multi-institutional validation of a novel textural analysis tool for preoperative stratification of suspected thyroid tumours on diffusion-weighted MRI. *Magn Reson Med* 2016; 75(4): 1708-1716.
27. Zhang H, Graham CM, Elci O, et al. Locally advanced squamous cell carcinoma of the head and neck: CT texture and histogram analysis allow independent prediction of overall survival in patients treated with induction chemotherapy. *Radiology* 2013; 269(3): 801-809.
28. Huang Y, Liu Z, He L, et al. Radiomics signature: A potential biomarker for the prediction of disease-free survival in early-stage (I or II) non-small cell lung cancer. *Radiology* 2016; 281(3): 947-957.
29. Raghunath S, Maldonado F, Rajagopalan S, et al. Noninvasive risk stratification of lung adenocarcinoma using quantitative computed tomography. J *Thorac Oncol* 2014; 9(11): 1698-1703.
30. Depeursinge A, Yanagawa M, Leung AN, et al. Predicting adenocarcinoma recurrence using computational texture models of nodule components in lung CT. *Med Phys* 2015; 42: 2054-2063.
31. Parmar C, Leijenaar RTH, Grossmann P, et al. Radiomic feature clusters and prognostic signatures specific for lung and head & neck cancer. *Sci Rep* 2015; 5: 11044.
32. Coroller TP, Agrawal V, Narayan V, et al. CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. *Radiother Oncol* 2016; 119(3): 480-486.
33. Zhou M, Hall L, Goldgof D, et al. Radiologically defined ecological dynamics and clinical outcomes in glioblastoma multiforme: Preliminary results. *Transl Oncol* 2014; 7(1): 5-13.
34. Gevaert O, Mitchell L, Achrol AS, et al. Glioblastoma multiforme: Exploratory radiogenomic analysis by using quantitative image features. *Radiology* 2014; 273(1): 168-714. Erratum in: *Radiology* 2015; 276(1): 313.

35. Mu W, Chen Z, Liang Y, et al. Staging of cervical cancer based on tumor heterogeneity characterized by texture features on 18 F-FDG PET images. *Phys Med Biol* 2015; 60: 5123.
36. Ganeshan B, Abaleke S, Young RCD, et al. Texture analysis of non-small cell lung cancer on unenhanced computed tomography: Initial evidence for a relationship with tumour glucose metabolism and stage. *Cancer Imaging* 2010; 10: 137-143.
37. Ganeshan B, Skogen K, Pressney I, et al. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: Preliminary evidence of an association with tumour metabolism, stage, and survival. *Clin Radiol* 2012; 67: 157-164.
38. Nie K, Shi L, Chen Q, et al. Rectal cancer: Assessment of neoadjuvant chemoradiation outcome based on Radiomics of multiparametric MRI. *Clin Cancer Res* 2016 1; 22(21): 5256-5264.
39. Coroller TP, Agrawal V, Narayan V, et al. Radiomic phenotype features predict pathological response in non-small cell lung cancer. *Radiother Oncol* 2016; 119(3): 480-486.

READY - MADE CITATION

Papanikolaou N, Santinha J. An Introduction to Radiomics: Capturing Tumour Biology in Space and Time. *Hell J Radiol* 2018; 3(1): 49-59.