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Review:

Towards precision medicine: from quantitative imaging to radiomics

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Abstract: Radiology (imaging) and imaging-guided interventions, which provide multi-parametric morphologic and functional information, are playing an increasingly significant role in precision medicine. Radiologists are trained to understand the imaging phenotypes, transcribe those observations (phenotypes) to correlate with underlying diseases and to characterize the images. However, in order to understand and characterize the molecular phenotype (to obtain genomic information) of solid heterogeneous tumours, the advanced sequencing of those tissues using biopsy is required. Thus, radiologists image the tissues from various views and angles in order to have the complete image phenotypes, thereby acquiring a huge amount of data. Deriving meaningful details from all these radiological data becomes challenging and raises the big data issues. Therefore, interest in the application of radiomics has been growing in recent years as it has the potential to provide significant interpretive and predictive information for decision support. Radiomics is a combination of conventional computer-aided diagnosis, deep learning methods, and human skills, and thus can be used for quantitative characterization of tumour phenotypes. This paper discusses the overview of radiomics workflow, the results of various radiomics-based studies conducted using various radiological images such as computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET), the challenges we are facing, and the potential contribution of radiomics towards precision medicine.

Key words: Radiological imaging; Personalised medicine; Precision medicine; Quantitative imaging; Radiogenomics; Radiomics
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1 Introduction

Precision medicine is gaining popularity for providing customised or personalised healthcare (Chen and Snyder, 2013). It employs diagnostic testing for the selection of appropriate and optimal therapies (treatments) based on the patient's genetic context (Chen and Snyder, 2013). Thus, by practising precision medicine in healthcare, medical decisions and treatments can be tailored to suit every individual patient's need. Diagnostic radiology and image-guided intervention are playing an increasingly significant role in precision medicine. For decades, radiology has been dealing with diagnosis and has provided anatomical abnormality information. With the advent of digital technology, quantitative imaging has been contributing to improved diagnosis and in addition, radiological imaging has become a recognised technology in the clinical assessment and confirmation of a disease (Cook et al., 2014; WHO, 2017). One of the significant contributions of radiology is in oncology, as cancer has become the number one source of mortality in recent years and there is an increasing proliferation of cancer cases in developing countries

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(Hawkins et al., 2014). Different radiological imaging modalities have the capability to detect different information that is present on the various types of tissue. However, extracting informative data from all radiological images is difficult in this era of 'big data'. The latest progress in computational power and the exploitation of genomics have given rise to a recently developed field of research coined 'Radiomics'.

Radiomics is a promising field of medical research that employs state-of-the-art machine learning techniques to extract imaging features from various modalities such as computed tomography (CT), magnetic resonance imaging (MRI), and positron-emission tomography (PET) to objectively and computably characterise tumour phenotypes. Radiomics was first formally introduced by Lambin et al. in 2012 (Lambin et al., 2012; Scrivener et al., 2016). It is the extraction and study of huge quantities of features from radiological images and these data are used to predict or decode concealed genetic and molecular traits for decision support (Kumar et al., 2012; Cook et al., 2014; Court et al., 2016; Gillies et al., 2016; Narang et al., 2016; Yip and Aerts, 2016; Sala et al., 2017). Radiomics features contain useful spatial and textural information on the greyscale patterns and the correlation between image pixels. Further, these features can be modelled into computer-aided systems that can supplement as an adjunct instrument for individualised diagnosis and treatment guidance (Parekh and Jacobs, 2016). Hence, information obtained from these radiological images can also be combined with additional 'omics' (genomics, proteomics, metabolomics, and transcriptomics) data for further analysis.

Radiomics has been extensively studied in oncology with a substantial contribution from the Quantitative Imaging Network (QIN) and National Cancer Institute (NCI) (Gillies et al., 2016). It has been researched and reported, notably in, breast cancer (Wu et al., 2016), glioblastoma (Narang et al., 2016), head and neck cancer (Wong et al., 2016), lung cancer (Scrivener et al., 2016), oesophageal cancer (van Rossum et al., 2016), prostate cancer (Stoyanova et al., 2016), and rectal cancer (Dinapoli et al., 2016). Furthermore, radiomics has been adopted in dermatology (Cho et al., 2015).

2 Workflow of radiomics

Fig. 1 shows a typical workflow of radiomics that consists of four main stages.

2.1 Images

The radiological images are acquired from different non-invasive imaging modalities such as CT, MRI, and PET (Castellino, 2005; Lambin et al., 2012; Aerts, 2016; Court et al., 2016; Yip and Aerts, 2016). These images are pre-processed to ensure that they are consistent and uniformity is maintained. Then, all images are progressively pooled together to form a large database. In addition, the image contrast is enhanced using a technique known as Contrast Limited Adaptive Histogram Equalization (CLAHE) and the noise and artefacts are removed in this pre-processing step (Pizer et al., 1987; Wang et al., 2005).

2.2 Segmentation

Segmentation is an essential step as highly distinctive features are obtained from the segmented area of the images and these features are used in the development of a model for automated screening of radiological images. The aim of segmentation is to simplify or to modify the image for more meaningful analyses (Aerts, 2016).

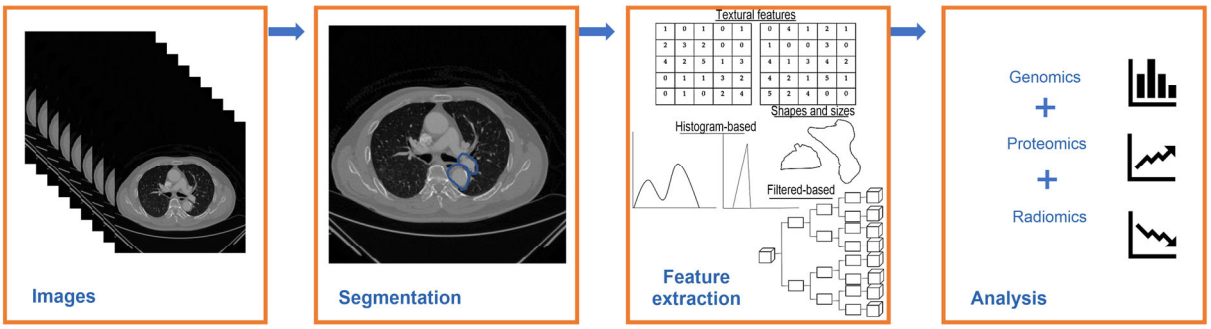

Fig. 1 A typical workflow of radiomics

Once the images are pre-processed, segmentation of a region of interest (ROI) is performed. Initially, an ROI is selected as a part of an image that is of interest and where some machine learning algorithms have to be applied (https://www.mathworks.com/help/images/roi-processing-in-image-processing-toolbox.html). Segmentation of an ROI can be carried out manually, semi-automated, or fully automated. Comparative studies have been reported to increase the performance of fully automated, manual, or semi-automated segmentation of these images (Egger et al., 2013; Velazquez et al., 2013, 2015; Kumar et al., 2016; Narang et al., 2016). The 3D-Slicer is a free open source segmentation software for biomedical research that is widely adopted in the medical field (Velazquez et al., 2013).

Manual segmentation of the tumour volume is a normal clinical procedure in the planning process before patients receive radiotherapy (Eminowicz and McCormack, 2015). Manual delineation is easy but it is highly subjective and labour-intensive. In addition, manual segmentation is not recommended for radiomics evaluation as it requires a large amount of data and would be very time-consuming. Semi-automated segmentation and fully automated segmentation can be performed on radiological images with the help of software and segmentation algorithms. Furthermore, the present consensus is to implement computer-aided edge detection followed by manual adjustment (Gillies et al., 2016).

The various segmentation techniques namely active contour, level-set, region-based and graph-based methods have been used. The active contour model relies on knowledge of size, position, and structure of the ROI. Based on prior knowledge, the active contour can outline the ROI for segmentation (Kass et al., 1988). The level-set model retrieves the shapes and contours from medical images to two or three dimensions (Malladi et al., 1995). It is also a sort of active contour modelling (Malladi et al., 1995). The region-based technique, on the other hand, is a method based on grey level features. This technique relies on the principle of homogeneity where the ROI is determined by examining its neighbouring pixels relative to the initial seed point (Sonka et al., 2007). The graph-based approach is based on the selection of edges from the graph where every single pixel in the image corresponds to a node in the graph (Felzenszwalb and Huttenlocher, 2004). The segmentation criterion is then adjusted according to the variability of the pixels in the neighbourhood (Felzenszwalb and Huttenlocher, 2004). These segmentation techniques are commonly used in a computer-aided detection system.

Recently, deep learning-based approaches such as the convolutional neural network (CNN) have been used for medical image segmentation and demonstrated promising results (Ma et al., 2017a, 2017b).

2.3 Feature extraction

Feature extraction is the next step after an ROI is identified and segmented. Feature extraction is the selection of useful information to assist in the characterization of normal and abnormal radiological images. These features are comprised of intensity, shape, size, and texture of an ROI identified on the images.

The shape and size of the tumours are regularly used to define lesions which can be easily identified without computer assistance. On the other hand, the texture of a radiological image is defined by the way the grey levels are apportioned over the pixels in an image (van Rossum et al., 2016). These texture features are mathematically extracted using first-order, or second-order, and/or higher-order statistical methods (Davnall et al., 2012; Mitra and Shankar, 2015; van Rossum et al., 2016).

First-order statistics are characterised based on the distribution of values of individual voxels without concern for spatial relationships. They are generally histogram-based techniques which reduce an ROI to single value representation for entropy, kurtosis, maximum, mean, median, minimum, skewness, and uniformity of the intensities on the radiological image (Gillies et al., 2016). Second-order statistics are universally defined as textural features. They define statistical correlations between voxels with alike or unlike contrast value (Gillies et al., 2016). Grey level co-occurrence matrix (GLCM), grey level run-length matrix, and size-zone matrix are typically extracted from the images. Higher-order statistics set filter grids to obtain patterns on these images. Fractal analysis, Gabor transform, Laplacian transforms of Gaussian bandpass filters, laws kernel, and wavelets are commonly performed to extract textural information from the images (Yip and Aerts, 2016). Various textural features extracted from radiological images are summarised in Table 1.

Table 1 Summaries of selected radiomics studies

Author (year)	Objective of study	Radiomics features	Techniques used	Performance
Computed tomography				
Hunter et al. (2013)	Identify radiomics features that are consistent across multiple diagnostic tools	Geometry, intensity histogram, absolute gradient image, textural features	Hierarchical clustering, dice similarity coefficient, Jaccard index, CCC	Feature reproducibility is depended on the machine and images
Velazquez et al. (2013)	Evaluate the clinical applicability of a semiautomatic segmentation method		3D-Slicer algorithm	It is noted that 3D-Slicer illustrated high agreement, smaller uncertainty areas, and lower volume differences as compared to manual slice delineation
Aerts et al. (2014)	Assess the correlation of radiomics features with clinical data and the predictive capability of radiomics features	Intensity histogram, shape, textural features, wavelet features	Friedman test, Wilcoxon test, Kaplan-Meier analysis	It is concluded that radiomics features possess prognostic capability
Balagurunathan et al. (2014b)	Assess the reproducibility of quantitative imaging features	Intensity histogram, textural features, Laws' kernels features	Test-retest CCC, Kaplan-Meier plot	Texture features are statistically significant
Balagurunathan et al. (2014a)	Assess the reproducibility of image features	Morphological features, first-order features, wavelets feature	CCC, dynamic range, redundancy reduction, weighted Kappa index, optical threshold linear discriminant analysis, ROC curve	It is concluded that most features show high reproducibility with semi-automated segmentation
Fried et al. (2014)	Investigate if pre-treatment textural features can enhance the predictive capability in stage III non-small cell lung cancer	Intensity histogram, textural features	Kaplan-Meier curves, leave-one-out cross-validation, CCC	Pre-treatment textural features have better predictive values
Parmar et al. (2014)	Evaluate the performance of using 3D-Slicer		Intra-class correlation coefficient	Radiomics features obtained from 3D-Slicer had notably higher reproducibility than those from manual delineation
Hawkins et al. (2014)	Propose an automated prognostic model	Intensity histogram, textural features, geometric features	Decision tree, leave-one-out cross-validation	Accuracy=77.50%
Coroller et al. (2015)	Prognostic capability to identify distant metastasis for lung adenocarcinoma patients	Intensity histogram, shape and texture features	Laplacian of Gaussian filter, wavelet filter, minimum redundancy maximum relevance feature selection	Radiomics features possess strong prognostic capability
Parmar et al. (2015a)	Compare radiomics features across different cancer types	Intensity histogram, shape, textural and wavelet features	Consensus clustering, ROC analysis, concordance index, logistic regression, Jaccard index	Radiomics features possess clustering and prognostic characteristics
Parmar et al. (2015b)	Assess the different feature selection and classification methods in terms of their performance and prognostic capability	Intensity histogram, textural features	Various feature selection and classification techniques implemented	It is concluded that conditional infomax feature extraction, minimum redundancy maximum relevance, and mutual information feature selection produced the highest stability and predictive capability

To be continued

Table 1

Author (year)	Objective of study	Radiomics features	Techniques used	Performance
Cunliffe et al. (2015)	Investigate the correlation of radiation dose and radiomics features and the capability of radiomics features in the analysis of radiation pneumonitis	Textural features, fractal features	Laws' filters, linear regression model, ANOVA, ROC curve	Radiomics is a promising methodology that can diagnose patients with radiation pneumonitis
Mackin et al. (2015)	Study the variability between different CT scanners	Textural features	General Electric, Philips, Siemens, and Toshiba scanners, feature noise introduced	It is verified that the variability in features corresponded in the variability seen in the radiomics features obtained from the images
Mattonen et al. (2016)	Physician assessment versus radiomic assessment in the detection of local cancer recurrence for lung cancer	First-order statistics features, textural features	PRTools 5.0 (Delft Pattern Recognition Research, Delft) was utilised for feature selection and classification, leave-one-out cross-validation, SVM classifier	Radiomics can detect early changes associated with local recurrence
Mattonen et al. (2015)	Analysis of features for prognostic capability of lung cancer recurrence	Textural features	PRTools 5.0 (Delft Pattern Recognition Research, Delft) was utilised for classification, Wilcoxon signed rank test	High prognostic accuracy using GLCM
Wang et al. (2016)	Initiate and evaluate a normalised set of features obtained from CT images and their correlations with overall survival	Lexicon of BI-RADS, Fleischner Society as a guide to establish features	Weighted Kappa index, Kaplan-Meier analysis, CART classifier, PCA	It was reported that textural features are important in the characterisation of lung adenocarcinomas
Fave et al. (2015)	Validate the usefulness of predictive models using radiomics features extracted from CT images	Textural features	CCC analysis	Certain radiomics features are resistant to poor-quality CBCT images and noises
Huynh et al. (2016)	Analyse stereotactic body radiation therapy with lung cancer	Textural, shape, and statistical features	PCA, factor analysis, Wilcoxon rank-sum test	Radiomics features possess the potential to be predictive
Szigeti et al. (2016)	Propose an innovative technique to diagnose lung diseases	Nonlinear features	Radiomics-based fractal dimension analysis, Kruskal-Wallis test, Mann-Whitney post hoc test, Gaussian curves	It is reported that the proposed method is promising and can be implemented in clinical practices
Coroller et al. (2016)	Investigate if pre-treatment radiomics features have the prognostic capability in non-small cell lung cancer	Textural features	Wilcoxon-test, Kaplan-Meier analysis, logistic regression, ROC curve	Radiomics features are predictive
Zhao et al. (2016)	Investigate the reproducibility of radiomics features	Intensity histogram, morphological features, textural features	Gabor energy, wavelets, Laplacian of Gaussian, model-based feature of fractal dimension, CCC analysis	It is noted that radiomics features are reproducible over different algorithms
Yang et al. (2016)	Analyse quantitative imaging features in lung tumours	Intensity histogram, textural features, geometric shape	CCC analysis, Spearman's correlation, PCA, edge-preserving smoothing filter	Texture features could be utilised for predictive analysis in the future
Song et al. (2016)	Investigate if tumour heterogeneity of non-small cell lung cancer can be predicted with radiomics	Textural features	Statistical analysis	Radiomics has prognostic capability for clinical aided diagnosis

To be continued

Table 1

Author (year)	Objective of study	Radiomics features	Techniques used	Performance
Wu et al. (2016)	Identify the classifiers for radiomics in lung cancer histology	Intensity histogram, shape features, textural features	Twenty-four feature selection methods, random forest classifier, naïve Bayes classifier, K-NN classifier, ROC curve	Naïve Bayes classifier performed the best; the area under ROC curve: accuracy=0.72
Fave et al. (2016)	Evaluate how different image pre-processing techniques may impact the predictive outcome in univariate analysis	Intensity histogram, textural features	Harrell's concordance index (c-index), Benjamini-Hochberg procedure	Pre-processing of CT images has an impact on the volume dependence of a feature
He et al. (2016)	Examine the effects of contrast-enhancement, reconstruction slice thickness, and convolution kernel on the diagnosis performance of radiomics	Textural features	Laplacian of Gaussian spatial band-pass filter, statistical analysis, Mann-Whitney *U* test	It is noted that contrast-enhancement, reconstruction slice thickness, and convolution kernel affect the performance of radiomics
Emaminejad et al. (2016)	Develop a new quantitative image feature analysis scheme and examine the correlation of genomics and radiomics features	Textural features	Naïve Bayesian network-based classifier, leave-one-case-out cross-validation, synthetic minority oversampling technique	Accuracy=80.00%
Liang et al. (2016)	Review the prognostic ability of radiomics features for the staging of colorectal cancer	Textural features	Logistic regression model, Mann-Whitney *U* test, ROC curve	The area under ROC curve: accuracy=0.792; sensitivity=0.611; specificity=0.680
Huang et al. (2016)	Justify the prognostic ability of lymph node metastasis in patients using radiomics nomogram	Textural features	Statistical analysis, multivariable logistic regression analysis	Radiomics nomogram is proved to be useful in clinical settings
Kumar et al. (2016)	Analyse an automatic liver segmentation		Statistical parameter-based approach	It is proven that the proposed method has prognostic capability
Magnetic resonance imaging				
Egger et al. (2013)	Assess the advantages of 3D-Slicer over manual segmentation		Dice similarity coefficient, Hausdorff distance	It is reported that 3D-Slicer is more time-efficient and is statistically comparable to manual segmentation
Zhou et al. (2014)	Determine the differentiating ROIs within the tumour for clinical practices	Textural features	K-NN classifier	K-NN classifier: accuracy=93.75%
Coquery et al. (2014)	Assess the possibility if histologic properties can be extracted based on an automated analysis		Gaussian mixture modelling, *t*-tests, linear discriminant analysis	It is reported that the integration of spatial selection and cluster analysis can be implemented to form information obtained from the multiparametric MRI
Chaddad et al. (2015)	Validate the effectiveness of features extracted from GLCM in glioblastoma phenotypes	Textural features	Nearest neighbour classifier	Accuracy=75.58%; sensitivity=63.95%; specificity=90.69%
Chaudhury (2015)	Validate a new method in the study of heterogeneity in breast cancer	Textural kinetic features	CCC-based random subspace method, naïve Bayes classifier, decision tree classifier, SVM classifier, Kappa statistic	It was concluded that textural kinetic features were more prognostic than features obtained from the whole tumour

To be continued

Table 1

Author (year)	Objective of study	Radiomics features	Techniques used	Performance
Upadhaya et al. (2015a)	Study on multimodal MRI in glioblastoma multiforme	Intensity histogram, textural features	SVM classifier	Accuracy=90.00%; sensitivity=85.00%; specificity=95.00%
Upadhaya et al. (2015b)	Propose a workflow for a predictive model based on textural features	Intensity histogram, textural features	SVM classifier	T1 pre-contrast: accuracy=60.00%; T1 post-contrast: accuracy=82.50%; T2: accuracy=72.50%; FLAIR: accuracy=75.00%; T1 pre-contrast/T1 post-contrast: accuracy=90.00%
Lee et al. (2015)	Identify the correlation of radiomics features with EGFR-driven tumours	Spatial diversity features	Spatial diversity analysis, ROC curve, Brier score	Characterising EGFR-driven tumours, the area under ROC curve: accuracy=0.790
Depeursinge et al. (2015)	Assess the significance of intensity and textural features	Nonlinear features, textural features	Riesz wavelet, concordance index, SVM classifier, Cox-LASSO predictive model	C-index=0.81±0.02. It is concluded that accuracy is better when features are extracted based on solid components of a tumour instead of the entire tumour
Khalvati et al. (2015)	The automatic detection system of prostate cancer using texture features	Statistical features, textural features, Gabor features	Gabor filter, SVM classifier	Proposed technique surpasses conventional model
Velazquez et al. (2015)	Assess the predictive value of glioblastoma automatically segmented and compare it with manual segmentation	VASARI features	The brain tumour image analysis software was utilised, statistical analysis, Spearman rank correlation, CCC analysis, decision tree classifier	It is reported that the automatically segmented datasets have potential in medical imaging research
Guo et al. (2015)	Determine the efficiency of the prognostic outcome when combining genomic and radiomics features	Morphological texture, kinetic curve assessment, enhancement-variance kinetic features	Quantitative radiomics analysis, logistic regression, Benjamini-Hochberg procedure, cross-validation with ROC curve	Radiomics features have prognostic capability in determining pathological stage
Chung et al. (2015)	Present an innovative automated prostate detection algorithm	Intensity histogram, textural features	Radiomics-driven conditional random field framework, Kirsch edge detection, Gabor filters, SVM classifier	Accuracy=91.17%; sensitivity=71.47%; specificity=91.93%
van den Burg et al. (2016)	Analysis of labyrinth	Intensity histogram	Fourier DCT filter, edge detection, gradient orientation filter, entropy filter, Laplacian filter, ridge filter, discrete wavelet transform, image saliency filter, clustering components, morphological components, and binarize colour tone mapping	There was significant statistical difference between normal and patients
Grossmann et al. (2016)	Investigate the correlation of radiomics features and molecular pathways	Volumetric features	Gene expression, pathway analysis	It is noted that radiomics features contain highly significant features

To be continued

Table 1

Author (year)	Objective of study	Radiomics features	Techniques used	Performance
Positron emission tomography				
Nair et al. (2012)	Investigate radiogenomics with PET	Textural features	Student's *t*-test, chi-squared test, Fisher's exact test, PCA, SUV, Kaplan-Meier curves	It is noted that there is a correlation between gene signatures and features extracted with ^{18}F-FDG
Leijenaar et al. (2013)	Carry out a stability analysis of radiomics features in non-small cell lung carcinoma	Intensity histogram, textural features	SUV discretisation, ICC, non-parametric ANOVA	Radiomics features possess prognostic capability
Leijenaar et al. (2015)	Determine the importance of a standardised procedure in tumour texture analysis	Textural features	SUV discretisation, Kruskal-Wallis one-way ANOVA	Experiments showed the importance of standardised procedure in tumour texture analysis
Ypsilantis et al. (2015)	Determine if machine learning techniques can predict cancer's metabolic profile and compare the performance of machine learning algorithms with 3S-convolutional neural network	Textural features	Convolutional neural networks, SUV, PCA, SVM classifier, logistic regression	Sensitivity=80.70%; specificity=81.60%. Convolutional neural networks possess better prognostic capability of response to therapy
Tixier et al. (2015)	Compare the results of the visual and prognostic assessment in non-small cell lung cancer	Textural features	SUV, *k*-test, Spearman rank coefficient, Kaplan-Meier method, Cox regression model	The assessments of both visual and prognostic using textural features are not contradictory to each other
Nyflot et al. (2015)	Study the influence of stochastic outcome on textural features	Intensity histogram, textural features	Power analysis	It is concluded that protocols should be implemented to ensure that textural features extracted are standardised
Grootjans et al. (2016)	Investigate the effect of respiratory gating and noises in PET images	Textural features	Fuzzy locally adaptive Bayesian segmentation algorithm, ranking tests	It is reported that textural features in this work are resilient in the existence of respiratory motion
Lian et al. (2016)	Propose a novel methodology for the prognostic tool in PET imaging	Textural features, SUV-based features	SUV, Dempster-Shafer theory for feature selection, ADASYN, K-NN classifier	Proposed methodology showed promising results
Positron emission tomography/computed tomography				
Cheebsumon et al. (2012)	Comparing PET- and CT-based methods to pathology		SUV, statistical analysis	Diameter from PET-based delineation has reported a more similar result with pathology as compared to CT-based delineation
Yoon et al. (2015)	Discover the predictors of tumours for lung adenocarcinoma	Morphological features, histogram-based, regional, and local features	Chi-squared test, Student's *t*-test, SUV, ten-fold cross-validation method	This methodology has potential to be utilised in clinical practice
Oliver et al. (2015)	Investigate the difference of image features between RG and 3D images	Sphericity, spherical disproportion, entropy, sum entropy, textural features	SUV, long axis calculation and rotation analysis	It is reported that features obtained from 3D and RG images are different
van Velden et al. (2016)	Evaluate the impact of reconstruction techniques and the delineation of radiomics features in non-small cell lung cancer	Fractal features, textural features	SUV, statistical analysis, Wilcoxon signed-rank test	It is noted that the performance of radiomics features is better in delineation than that of applied reconstruction technique

To be continued

Table 1

Author (year)	Objective of study	Radiomics features	Techniques used	Performance
Bailly et al. (2016)	Assess the robustness of textural features	Textural features	SUV, coefficient of variation, one-way ANOVA, Tukey HSD test	SUV-based metrics (energy, entropy, RP, and ZP) are found to be robust features
Desseroit et al. (2016)	Initiate a nomogram by blending clinical and imaging features	Textural features	SUV, Kaplan-Meier method, log-rank test	Textural features can be used to create a nomogram but need to be further validated
Positron emission tomography/magnetic resonance imaging				
Vallières et al. (2015)	Develop a joint FDG-PET/CT and MRI texture-based model for early diagnosis of lung metastasis risk	Textural features	SUV, discrete wavelet transform, wavelet band-pass filtering, logistic regression, multivariable analysis, ROC curve	The area under ROC curve: accuracy=98.4%; sensitivity=95.5%; specificity=92.6%
Antunes et al. (2016)	Investigate the capability of radiomics features in FLT-PET and MRI	Filtered-based, entropy and textural features from PET images	Sobel and Kirsch edge filters, Gaussian low-pass filter, SUV, Bhattacharyya distance	Radiomics has potential to be an effective tool for categorising treatment response in PET/MRI
Ultrasonography				
Acharya et al. (2016b)	Propose a novel algorithm to accurately classify non-alcoholic fatty liver disease	DCT	Radon transform, fuzzy sugeno, fatty liver disease index	Accuracy=100.00%; sensitivity=100.00%; specificity=100.00%
Acharya et al. (2016c)	Develop an automated thyroid screening system	Entropies	Gabor transform, statistical analysis, C4.5 decision tree	Accuracy=94.30%
Acharya et al. (2016a)	Assess the reliability and robustness of an automated fatty liver disease and cirrhosis diagnosis system	Higher-order spectra and entropies	Probabilistic neural network, liver disease index	Accuracy=97.33%; sensitivity=96.00%; specificity=100.00%
Acharya et al. (2017)	Evaluate the performance of a new ultrasonography procedure	Second-order statistics	Quadratic discriminant analysis, shear wave breast cancer risk index	Accuracy=93.59%; sensitivity=90.41%; specificity=96.39%
Raghavendra et al. (2017)	Develop a computer-aided diagnosis system to automatically differentiate the different stages of thyroid cancer	Textural features	SVM, thyroid clinical risk index	Accuracy=97.52%; sensitivity=90.32%; specificity=98.57%
Ma et al. (2017a)	Initiate and assess an automated thyroid nodules detection system		Convolutional neural network	The area under ROC curve: accuracy=98.51%
Ma et al. (2017b)	Propose a hybrid approach to automatically classify benign and malignant thyroid nodules		Convolutional neural network	Accuracy=83.02%; sensitivity=82.41%; specificity=84.96%

CCC: concordance correlation coefficient; ROC: receiver operating characteristic; ANOVA: analysis of variance; SVM: support vector machine; GLCM: grey level co-occurrence matrix; CT: computed tomography; BI-RADS: breast imaging reporting and data system; CART: classification and regression tree; PCA: principal component analysis; CBCT: cone beam computed tomography; K-NN: K-nearest neighbour; ROI: region of interest; MRI: magnetic resonance imaging; FLAIR: fluid-attenuated inversion recovery; EGFR: epidermal growth factor receptor; LASSO: least absolute shrinkage and selection operator; VASARI: Visually Accessible Rembrandt Images; DCT: discrete cosine transform; SUV: standardised uptake value; ICC: intraclass correlation; PET: positron-emission tomography; ADASYN: adaptive synthetic; HSD: honest significant difference; FDG: fludeoxyglucose; FLT: fluorothymidine

From Table 1, it is observed that textural features are persistently used in the study of radiomics regardless of the radiological modalities (CT, MRI, or PET). Furthermore, Fig. 2 shows a summary of the various feature extraction techniques implemented based on the literature review (Table 1) and it can be noted that textural-based methods are commonly used.

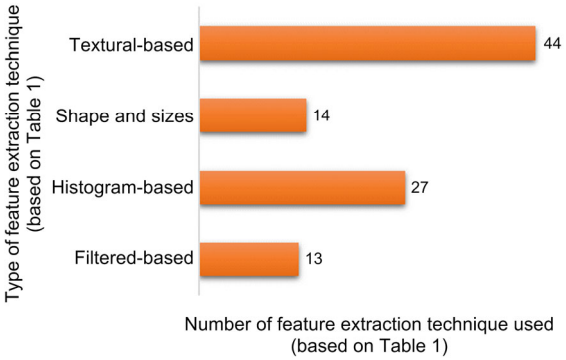

Fig. 2 Types of feature extraction methods used

Generally, the feature extraction process produces a huge number of features; among them few features are redundant. Therefore, feature reduction or selection is performed to identify useful features from the pool of features extracted. This step significantly boosts the performance of the classifier by selecting only the highly significant features and eliminating redundant features. In addition, statistical tests, namely analysis of variance (ANOVA), Benjamini-Hochberg procedure, chi-squared test, Cox regression model, Friedman test, Kaplan-Meier analysis, Kruskal-Wallis test, Mann-Whitney test, Student's *t*-test, Tukey honest significant difference (HSD) test, and Wilcoxon test, are performed to select highly significant features for optimal performance.

These statistical tests are used based on different conditions (SPSS Tutorials 2017; https://www.spss-tutorials.com). Hence, there are different types of statistical tests to implement based on the conditions of the dataset. ANOVA is used for a three-class or more problem with the assumption that the input data are normally distributed. Benjamini-Hochberg procedure is used in a three-class or more problem and when the data are independent of each other. Chi-squared test is a distribution-free test and can be used only when the two-class problem data are independent of each other. Cox regression model works on a normally distributed two-class problem data. Friedman test can be used in a three-class or more problem that does not assume that the data are normally distributed. Also, the Kaplan-Meier analysis can be used in a three-class or more problem in abnormally distributed data. Kruskal-Wallis test is used when there is a three-class or more problem and the data are assumed to be skewed; Mann-Whitney test, also known as the Wilcoxon rank sum test, is used when the data are independent and assumed to be non-normally distributed. Wilcoxon signed rank test, on the other hand, is used when the two-class problem data are dependent and assumed to be non-normally distributed. Student's *t*-test is used only when the two-class problem data are assumed to be normally distributed. The Tukey HSD test is used when the three-class or more problem dataset is assumed to be normally distributed.

2.4 Analysis

In the final stage, the selected highly significant features are fed into classifiers for further analysis and assessment. These extracted radiomics features are then examined together with clinical data obtained from other 'omics' studies in order to analyse the mutuality of clinical features (information) and radiomics features (Narang et al., 2016). The combination of data is known as multilevel data. Classifier models are machine learning algorithms for making accurate predictions based on the training dataset and on the features extracted from radiological images.

Machine learning uses algorithms to analyse data, learn the data, and make a prediction with the data. The machine is 'trained' with a huge amount of data using algorithms to extract information from the data and to analyse them. Moreover, with the advancement and improvement of machine learning, a subset of machine learning known as deep learning is established. Deep learning is inspired by the anatomy and function of the brain and it involves neural networks with at least three or more hidden layers (Chen et al., 2014). The difference between deep learning and conventional machine learning is in the segmentation and feature extraction processes. Deep learning does not require any algorithm to select ROI or to extract significant features for classification. This technique can learn to focus on the right features with least guidance; hence, the potential of deep learning

in high-throughput medicine is straightforward (Angermueller et al., 2016). However, deep learning is relatively new and has tremendous potential waiting to be explored. Nevertheless, Ma et al. (2017a, 2017b) reported the potential by implementing deep learning (CNN) in their work.

From the literature review (Table 1), it can be seen that the different classifiers, namely bagging (Parmar et al., 2015b), Bayesian (Parmar et al., 2015b), boosting (Parmar et al., 2015b), classification and regression tree (CART) (Wang et al., 2015), decision tree (Hawkins et al., 2014; Chaudhury, 2015; Parmar et al., 2015b; Velazquez et al., 2015), discriminant analysis (Balagurunathan et al., 2014b; Coquery et al., 2014; Parmar et al., 2015b), generalised linear (Parmar et al., 2015b), K-nearest neighbour (K-NN) (Zhou et al., 2014; Chaddad et al., 2015; Parmar et al., 2015b; Lian et al., 2016; Wu et al., 2016), logistic regression (Guo et al., 2015; Parmar et al., 2015a; Vallières et al., 2015; Ypsilantis et al., 2015; Coroller et al., 2016; Huang et al., 2016; Liang et al., 2016), naïve Bayes (Chaudhury, 2015; Emaminejad et al., 2016; Wu et al., 2016), neural network (Parmar et al., 2015b), random forest (Parmar et al., 2015b; Wu et al., 2016), and support vector machine (SVM) (Zhou et al., 2014; Chaudhury, 2015; Chung et al., 2015; Depeursinge et al., 2015; Khalvati et al., 2015; Parmar et al., 2015b; Upadhaya et al., 2015a, 2015b; Ypsilantis et al., 2015; Mattonen et al., 2016), are used. Fig. 3 depicts a summary of the types and times of the classifiers used in various studies.

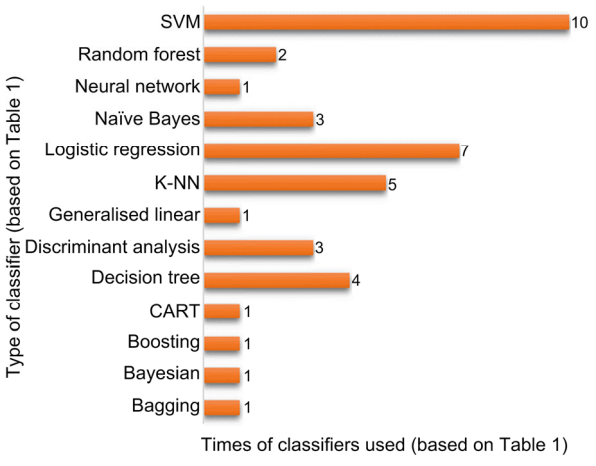

Fig. 3 Types of classifiers used

SVM: support vector machine; K-NN: K-nearest neighbour; CART: classification and regression tree

3 Discussion

In this review, the results of radiomics and various radiomics-based studies conducted using various radiological images such as CT, MRI, PET, and ultrasonography are discussed. The findings of those studies are summarised in Table 1.

Cho et al. (2015) experimented on an automated screening of melanoma and noted that radiomics improved the overall efficacy of characterising benign from malignant melanoma. They achieved an accuracy of 82.4% using 367 dermal radiomics features with the random forest classifier. In the oesophageal cancer review paper by van Rossum et al. (2016), they reported that textural radiomics features proved to be correlated to the underlying physiologic processes as textural features are valuable characteristics used to extract subtle information from ROIs (Haralick et al., 1973).

Some researchers have studied the reproducibility and resilience of radiomics features in CT images and concluded that radiomics features can be reproducible (Hunter et al., 2013; Balagurunathan et al., 2014a, 2014b; Fried et al., 2014; Zhao et al., 2016). Hunter et al. (2013) utilised two different CT scanners obtained from 59 non-small cell lung cancer patients in their experiment to single out radiomics features that are highly significant, non-redundant, and reproducible across the scanners. They found that average derived image features showed superior inter-machine reproducibility as compared to end-exhale and breath-hold images, as well as cine 4D-CT compared to helical 3D-CT. Mackin et al. (2015) also evaluated the repeatability of radiomics features in images acquired from different scanners and found that there was inter-scanner variability in the mean CT numbers and noise for the 17 CT scanners. In addition, Oliver et al. (2015) reported a difference between the radiomics features extracted from a static CT image and a respiratory-gated CT image, thus exhibiting the effect of respiratory motion on radiomics features. Hence, we can comment that radiomics features reproducibility and redundancy are dependent on the CT scanners and the type of CT image, as well as the standardisation of image acquisition and reconstruction.

To date, there is still limited study on radiomics features using MRI and its reliability. One of the diseases that have been studied is glioblastoma multiforme

(GBM), a highly malignant neurologic tumour in the brain exhibiting complex intra-tumoural and inter-patient heterogeneity. Hence, because of the difficulty in obtaining representative biopsies, the underlying radiomics features extracted by processing radiological imaging data are hypothesized to provide detailed phenotypic information (Lambin et al., 2012). Narang et al. (2016) found two main approaches used to develop radiomics features in GBM. Firstly, the standardised semantic features scored by radiologists are used. The features include tumour location, lesion size, proportion enhancing, proportion necrosis, proportion oedema, and definition of enhancing margin. Secondly, fully computational derived features using imaging and statistical techniques are extracted from the images. Semantic features are known to be highly correlated with clinical outcomes, as shown in a study by Lacroix et al. (2001) on 416 patients with GBM. They found that necrosis and tumour enhancement were a strong prognostic indicator. A Visually Accessible Rembrandt Images (VASARI) feature set comprising 30 semantic features was used to standardise radiological assessment of GBM (https://wiki.cancerimagingarchive.net/display/Public/VASARI+Research+Project). The neuroradiology domain experts agreed that these distinct VASARI features could quantify the phenotype comprehensively and robustly, and these measurements and assessments can be reproducible to provide clinically meaningful and biologically relevant information (Gutman et al., 2013). These VASARI features can be extracted using automated phenotype quantification, i.e. radiomics.

PET is progressively being used for analysis, cancer staging, and therapy response assessments in tumours (Boellaard, 2009; Kato and Nakajima, 2012; Rahim et al., 2014). In addition, radiomics features extracted from PET images have been used to broaden clinical parameters such as the standardised uptake value (SUV) used to aid visual interpretation (Thie, 2004) in clinical practices (Chicklore et al., 2013; Tixier et al., 2015). Most PET studies included SUVs in their work (Cheebsumon et al., 2012; Nair et al., 2012; Leijenaar et al., 2013, 2015; Oliver et al., 2015; Tixier et al., 2015; Vallières et al., 2015; Yoon et al., 2015; Ypsilantis et al., 2015; Antunes et al., 2016; Bailly et al., 2016; Desseroit et al., 2016; Grootjans et al., 2016; Lian et al., 2016; van Velden et al., 2016). Leijenaar et al. (2013) reported a high test-retest stability of approximately 71% using radiomics features in the analysis of non-small cell lung carcinoma (NSCLC) from PET scans. Moreover, the performance of analysis using radiomics features outperformed inter-observer's diagnosis. Furthermore, Tixier et al. (2015) compared inter-observer's analysis with the analysis made with radiomics for NSCLC, and concluded that a computer-aided diagnosis system using radiomics has a higher prognostic capability and can reduce subjective diagnosis. Tixier et al. (2012) in another study on oesophageal cancer found that for some textural features such as entropy, dissimilarity, homogeneity, size variability, and intensity of homogenous tumour areas (regional characterization) had reproducibility similar to or better than that of simple SUV measurements. However, several studies found that PET radiomics features are susceptible to reconstruction parameters and the type of image acquisition. Galavis et al. (2010) in their cohort study of 20 patients with various solid tumours found that 40 out of 50 features tested demonstrated large variations (>30%) when the number of iterations, grid size, reconstruction algorithm, and/or post-reconstruction filter were changed. Their findings were further supported by van Velden et al. (2016) and Yan et al. (2015). Respiratory motion artefact is also a well-known concern in any imaging modality. Grootjans et al. (2016) and Oliver et al. (2015) studied lung cancer with PET and reported that respiratory motion has a considerable effect on the quantification of tumour heterogeneity. From these recent studies, we can conclude that PET radiomics features can be reproducible; however, interpretation of the images and results must be done carefully bearing in mind that there are limitations.

The combination of CT and PET imaging is an established diagnostic imaging tool in oncology (Tixier et al., 2015; Lu and Chen, 2016). PET-CT has an advantage over just PET or CT scan only as PET-CT provides additional information on a tumour (Lu et al., 2015). Also, a combination of MRI and PET-CT has been reported (Vallières et al., 2015; Antunes et al., 2016). Vallières et al. (2015) proposed a collaborative study with PET and MRI to analyse lung metastasis risk in soft-tissue sarcomas. It was concluded that the radiomics features extracted from

the fusion of PET-MRI possess additional prognostic characteristics and could reveal the underlying details from the ROI. It is also noted that there are very few radiomics-based studies using ultrasound modality mainly due to the subjectivity and operator-dependent nature of this modality.

As mentioned here, there are very few studies using ultrasound modality mainly due to the subjective and operator-dependent nature of this modality. However, there have been several attempts with very good results (Acharya et al., 2016a, 2016b, 2016c, 2017). It is anticipated that more studies will be embarked on this area. Acharya et al. (2016b) proposed a novel technique to distinguish fatty liver disease using discrete cosine transform and radon transform. They have achieved 100% accuracy, sensitivity, and specificity with the fuzzy sugeno classifier. Also, they developed a fatty liver disease index using a single number to differentiate normal from the fatty liver disease class. Moreover, they extended their work to a three-class problem to differentiate normal, fatty liver disease, and cirrhosis (Acharya et al., 2016a). They also formulated a fatty liver disease index to mathematically distinguish the three classes. Further, Acharya et al. (2016c) explored the possibility of thyroid lesion classification obtained from ultrasound images. They implemented Gabor transform on the images and then extracted entropy features. They attained a performance rate of 94.30% with C4.5 decision tree classifier. In their later work (Acharya et al., 2017), they also studied the classification of breast lesion in shear wave ultrasound. In their work, they devised a shear wave breast cancer risk index to distinguish benign and malignant breast lesions. They reported a performance of 93.59% accuracy using a quadratic discriminant analysis classifier.

Raghavendra et al. (2017) explored the fusion of different texture features and extracted various entropies for the discrimination of benign and malignant thyroid lesions. Similarly, they constructed a thyroid clinical risk index to distinguish the two classes using numerical values. Also, Ma et al. (2017a, 2017b) proposed CNN-based automatic thyroid nodule detection system. These high performances confirm the application of CNN in developing robust computer-aided diagnosis systems using medical images.

4 Radiogenomics

However, utilising radiomics alone is insufficient to qualify as or achieve the goal for precision medicine. More information is needed to consider individual variability in genes for more accurate diagnosis and treatment. Nevertheless, studies have demonstrated that there is a correlation between genomics, proteomics, and radiomics (Segal et al., 2007; Zinn et al., 2011; Aerts et al., 2014; Sala et al., 2017). Furthermore, genomics and proteomics have brought overwhelming progress in medicine (Wanichthanarak et al., 2015; Aerts, 2016). They belong to the 'omics' data which have facilitated the state-of-the-art analysis of diverse organismal and molecular processes (Horgan and Kenny, 2011; Wanichthanarak et al., 2015). Thus, the term radiogenomics was coined as it highlights the synergistic combination of genomics and radiomics. Radiogenomics signifies the broadening of clinical imaging into genomic and molecular imaging (Kuo and Jamshidi, 2014) as it focuses on the relationship between features obtained from radiological images and biomolecular markers.

Yamamoto et al. (2014) performed a radiogenomic analysis in non-small cell lung cancer and achieved an accuracy of 78.8%, a sensitivity of 83.3%, and specificity of 77.9%. They concluded that the molecular phenotype and CT imaging, when combined, can distinguish tumours from non-tumours. Moreover, Yamamoto et al. (2015) conducted another radiogenomic study on breast cancer to investigate the correlations between MRI phenotype, quantitative imaging, and RNA expression. Their experiment showed the potential of radiogenomics in identifying early metastasis.

Although radiogenomics is still in its infancy, radiogenomic analysis does possess the potential to reveal a predictive radiomic signature and underlying gene expression patterns. Therefore, for radiogenomics to be formally introduced to clinical settings, radiomics must be firmly established first.

5 Challenges

Radiomics is a new multi-disciplinary field and hence, new challenges are inevitable (Kumar et al.,

2012). Firstly, there is no standardised procedure in image acquisition (Leijenaar et al., 2015; Scrivener et al., 2016). Different protocols have been implemented by different centres for acquisition and analysis of radiological images. The variation of protocol parameters includes, among others, resolution, field of view, and slice thickness of the images. Thus, studies using these heterogeneous radiological images will not produce accurate comparisons across different sets of radiological images.

Secondly, it can be seen from Table 1 that there are numerous techniques and algorithms being used. However, there is no standard methodology being developed and therefore, it is unclear which is the best way forward (Dinapoli et al., 2016). Furthermore, there is a lack of international protocols and standards for validating results (Sala et al., 2017). It is important to validate the re-usability and suitability of a radiomic model to establish rules in this new discipline for a reliable and consistent prognostic tool to be implemented in a clinical setting (Coquery et al., 2014; van Rossum et al., 2016).

Thirdly, sharing of radiological images publicly has always been a problem in clinical research (Nelson, 2009; Gillies et al., 2016). It is beneficial to have shared databases for maximum information to be extracted from radiological images (Gillies et al., 2016). Having an integrated shared database with radiological images and the extracted features will ensure standardisation in radiomic algorithms (Nyflot et al., 2015; Gillies et al., 2016; Wong et al., 2016). Moreover, using the same set of data across various radiomic algorithms will ensure consistency when it comes to inter-comparison and validation of results.

6 Future directions

An important achievement is to correlate 'omics' data with radiomics features extracted from radiological images and integrate them to create a more efficient and robust prognostic model to aid clinicians in practising personalised medicine. The next step is to implement radiomics as an adjunct tool in clinical settings. However, the challenges discussed here must be addressed first before radiomics could be employed in routine clinical settings. Currently, radiomics is at best fragmented with multiple players. Thus, it is imperative to form an international consortium to bring all researchers together for collaboration.

Another focus will be to incorporate deep learning to radiomics as deep learning is currently not being extensively deployed. The deep learning technique reduces the need for feature engineering and thus, it is much more time-efficient and boosts accuracy.

7 Conclusions

The increasing use of biomarkers in cancer diagnosis has paved the way for personalised medicine; however, the accuracy and predictive diagnosis and treatment alternatives are further improved by using imaging biomarkers derived from radiomics. In this review, the potentials of radiomics, the current workflow of radiomics, and employment of radiomics are highlighted. Thus, by introducing radiomics in the clinical setting, significant features can be extracted from the radiological images for subsequent analysis of image phenotypes in order to aid clinical decision-making. However, we need to overcome the challenges before radiomics can be successfully introduced into clinical settings. Further development in radiogenomics will bring us closer towards precision medicine.

Compliance with ethics guidelines

U. Rajendra ACHARYA, Yuki HAGIWARA, Vidya K. SUDARSHAN, Wai Yee CHAN, and Kwan Hoong NG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要

题　目：精准医学发展趋势：从定量成像到放射组学

概　要：放射学（影像学）及影像引导的介入手段能提供多参数的形态学及功能信息，在精准医学中扮演着越来越重要的角色。因此，放射科医生需要理解影像表型，并将这些表型与潜在的疾病相关联，进而描述图像特征。但是为了能理解并描述异质性实体肿瘤的分子表型（基因组学信息），就需要通过活检取得这些组织更进一步的序列信息。因此，放射科医生为了能获得详尽的影像表型，需要从不同视图和角度采集图像，而这就产生了大量的数据。从所有这些影像数据中提取有意义的细节非常具有挑战性，并衍生出了大数据这个命题。因为影像组学有对诊断支持提供有意义的诠释性和预测性信息的潜力，所以近年来对于影像组学的关注越来越多。影像组学是传统的计算机辅助诊断、深度学习和人类技能的结合，因此它能被用来定量描述肿瘤表型。本文对影像组学流程的概览、基于不同手段（如计算机断层扫描（CT）、磁共振成像（MRI）和正电子发射计算机断层扫描（PET））的影像组学研究结果、面临的挑战和影像组学对于精准医学潜在的贡献等方面进行了讨论。

关键词：放射影像学；个体化医学；精准医学；定量成像；放射基因组学；放射组学

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