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Radiomics and "radi-…omics" in cancer immunotherapy: a guide for clinicians

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ABSTRACT

In recent years the concept of precision medicine has become a popular topic particularly in medical oncology. Besides the identification of new molecular prognostic and predictive biomarkers and the development of new targeted and immunotherapeutic drugs, imaging has started to play a central role in this new era. Terms such as "radiomics", "radiogenomics" or "radi…-omics" are becoming increasingly common in the literature and soon they will represent an integral part of clinical practice. The use of artificial intelligence, imaging and "-omics" data can be used to develop models able to predict, for example, the features of the tumor immune microenvironment through imaging, and to monitor the therapeutic response beyond the standard radiological criteria.

The aims of this narrative review are to provide a simplified guide for clinicians to these concepts, and to summarize the existing evidence on radiomics and "radi…-omics" in cancer immunotherapy.

1. Introduction

In recent years the concept of precision medicine has become an area of immense interest (Burki, 2017; Ashley, 2016) in medical oncology (Le Tourneau et al., 2018). In this field, emerging mechanisms of resistance (Khan and Spicer, 2019; Lim and Ma, 2019; Narayanan et al., 2020; Kalbasi and Ribas, 2020), financial costs and toxicities (Postow et al., 2018; Porcu et al., 2020; Solinas et al., 2018; Marin-Acevedo et al., 2018; Porcu et al., 2019) are important elements to take into account for guiding treatment decisions, in order to identify ideal candidates that might benefit from a variety of novel and expensive therapies. Besides the identification of new molecular prognostic and predictive biomarkers (Dumitrescu, 2018) and the development of new targeted (Dugger et al., 2018) and immunotherapeutic drugs (Hegde and Chen, 2020; Dobosz and Dzieciątkowski, 2019), imaging has started to play a pivotal role in the evolution towards precision medicine (Acharya et al., 2018).

A fruitful collaboration between radiologists and medical oncologists is essential due to the growing dependency on imaging as a therapeutic biomarker. This is particularly relevant in this new era of cancer immunotherapy with immune checkpoint blockade (ICB) targeting a variety of immune checkpoint molecules that physiologically modulate the immune response (Solinas et al., 2019a; Solinas et al., 2019b; Solinas et al., 2019c; Solinas et al., 2020; ElTanbouly et al., 2020; Rowshanravan et al., 2018). These new drug regimens have a novel mechanism of action. Instead of directly killing tumor cells, they are able to harness the patient's own immune response against cancer, making unique and challenging the assessment of treatment response (Litière et al., 2017; Seymour et al., 2017; Solinas et al., 2017; Porcu et al., 2018). This requires a deep knowledge for the specific features that characterize immune-related phenomena in each organ site. The contribution of imaging is also important for differential diagnosis

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when facing with immune related adverse events (irAEs) (Porcu et al., 2020; Solinas et al., 2018; Porcu et al., 2019).

Radiological sciences are thus moving from a dependency on basic visual features in medical images to new non-visual features buried in the pixel data that are not routinely detectable with the human eye (Gillies et al., 2016). This is obtained thanks to the improvement of computational power of informatic systems and to the use of artificial intelligence (AI) (Obermeyer and Emanuel, 2016), specifically machine learning techniques (Choy et al., 2018) such as deep learning (LeCun et al., 2015).

With their ability to combine quantitative data obtained from imaging together with those derived from genomic analyses, "radiomics" and "radiogenomics" metadata are becoming of common use in clinical research. Hopefully, they will soon be part of daily routine clinical practice with the aim to allow oncologists and radiologists to optimize patient selection and management for medical therapy and to better assess treatment responses (Lambin et al., 2012).

The aims of this narrative review are to provide a simplified guide for clinicians to these new concepts, including some important technical aspects, and to summarize the existing evidence on radiomics in cancer immunotherapy.

2. Definitions

"Radiomics" is defined as the analysis of imaging data through the use of specific algorithms aimed at identifying quantitative features otherwise not identifiable with the simple visual analysis, in order to create enhanced data models for improving medical decision support (Gillies et al., 2016; Lambin et al., 2012). Images from ultrasound (US), computed tomography (CT), magnetic resonance (MR) and positron emission tomography (PET) combined with CT (PET-CT) or MR (PET-MR) can be analyzed with these techniques (Incoronato et al., 2017).

Radiogenomics or "imaging genomics" is the correlation of quantitative data derived from radiomic analysis with genomic expression data (Mazurowski, 2015). With this technique it is possible to create models that are able to deduce the genetic expression of a tumor or tissue sample from a simple CT scan using an imaging based phenotype (Mazurowski, 2015; Bai et al., 2016) or to assess the treatment response beyond the traditional dimensional criteria of tumor size (Litière et al., 2017; Seymour et al., 2017; Solinas et al., 2017; Porcu et al., 2018). Radiomic data can be also combined with other types of data, such as clinical, demographic, laboratory and histological, or data derived from other *"-omics"* sciences, such as transcriptomics (i.e. the study of RNA expression in a tissue sample (Lowe et al., 2017)) in "radiotranscriptomics" (Katrib et al., 2016) and proteomics (i.e. the study of protein expression in a tissue sample (Aslam et al., 2017)) in "radioproteomics" (Djekidel, 2013).

It is important to underlie that the term "radiogenomics" can be referred also to the scientific field that addresses the associations between genetic alterations and response to radiotherapy (Andreassen et al., 2016), but in this review we will focus on systemic treatments (i.e. targeted and immunotherapeutic drugs).

We can grossly identify two distinct phases in radiomic and "radi…-omics" processes: 1) the feature identification and 2) the model development phases.

3. Feature identification in radiomics

Radiomics is based on the discovery of imaging features not identifiable with the simple visual analysis, through the use of specific and sophisticated algorithms (Gillies et al., 2016; Lambin et al., 2012). From a technical point of view, the whole process can be divided into three steps (Gillies et al., 2016; Mazurowski, 2015) (Fig. 1):

1) Image acquisition, database creation and data selection: all imaging examination can be "radiomically" analyzed, including MR, CT, US and PET (Gillies et al., 2016; Lambin et al., 2012; Incoronato et al., 2017). A reasonable rule of thumb is that the minimum number of samples for creating a radiomic database is 10 examinations of the same disease (Gillies et al., 2016).
2) Identification and segmentation of the volume of interest (VOI): once the imaging database has been created, investigators must identify and segment a VOI. This must and can be drawn manually or (semi-) automatically (Polan et al., 2016).
3) Extrapolation of descriptive features (texture analysis): for a given VOI, several mathematical descriptive features can be extracted through the use of dedicated commercially available or in-house software (Varghese et al., 2019; Lubner et al., 2017).

3.1. Texture analysis

In material science, "texture" is a measure of the variation of a surface: a material with rough-textured surface is characterized by a high rate of change between the high and low points of its surface, compared to smooth-textured material (Varghese et al., 2019; Macdonald et al., 2004). In order to understand imaging texture analysis, it should be remembered that medical images, as well as all other images, consist of several thousands or millions of pixels (Richard, 2006). A pixel can be defined as the lowest level of abstraction of an image or the smallest element of an image, whereas the voxel is its 3D counterpart (Richard, 2006; Taira et al., 2010). The principles at the base of medical imaging technologies is to represent body structures as groups of small voxels according to a predefined regular matrix (Richard, 2006; Taira et al., 2010), and every voxel can be identified in the space according to its spatial coordinates (x, y, z), assigning them an intensity value (f) as the function of 3D space, according to the formula (Richard, 2006; Taira et al., 2010):

$$\text{voxel value} = f(x,y,z)$$

The intensity value is visually represented with discrete shades of grey that, as well as dimensions, can vary (i.e. absolute value and range) depending on the technique adopted (CT, MR, US or PET) and the reconstruction methods (Taira et al., 2010).

These are the elements needed to understand the concept of imaging texture analysis. In analogy to what happens in material sciences, the imaging texture analysis allows to mathematically study the distribution and the differences in grey-scale of the pixel/voxels of a given image, and to automatically extract up to hundreds of quantitative features (Varghese et al., 2019; Lubner et al., 2017). The features extracted from texture analysis can be typically divided into four different types (Incoronato et al., 2017; Rizzo et al., 2018) (Table 1): a) shape-based; b) first-order statistics; c) second-order statistics; d) higher-order statistics.

Shape-based features are the most intuitive, and they collect quantitative data regarding the geometric features of the VOI. Examples include: volume, surface area, spiculations and compactness (Incoronato et al., 2017). Some typical shape-based features are listed in Table 2.

First-order statistics are generally histogram-based and describe the distribution of pixels inside a VOI without spatial relationship information (Incoronato et al., 2017); examples of this type of statistics include mean, standard deviation, range, entropy, skewness and kurtosis (Incoronato et al., 2017). Some examples of first order statistics are listed in Table 3.

Second-order statistics, also called texture-based metrics (Incoronato et al., 2017; Rizzo et al., 2018; Kolossváry et al., 2018; Davnall et al., 2012; Haralick and Shanmugam, 1973; Galloway, 1975; Tixier et al., 2011; Thibault et al., 2014; Amadasun and King, 1989; Sun C, Wee WG, 1983) analyze the spatial relationships between voxels with similar intensity values within a VOI and providing information about the heterogeneity within the lesion (Lambin et al., 2012;

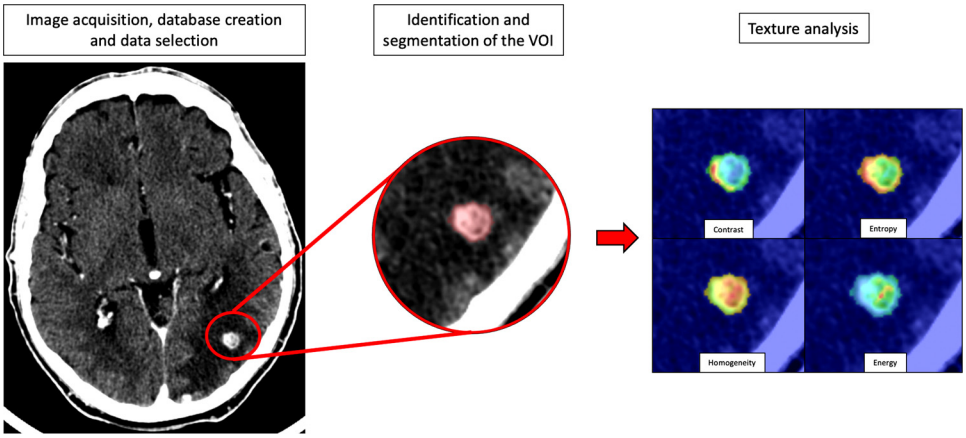

Fig. 1. The steps of the feature identification in radiomics.

Table 1
Features extractable from texture analysis (Incoronato et al., 2017; Taira et al., 2010).

Features extractable from texture analysis
Shape based features
First-order statistics
Second-order statistics
Higher-order statistics

Incoronato et al., 2017; Kolossváry et al., 2018). This kind of metrics are expressed in terms of matrices, signifying that statistics are calculated not from the values themselves but from the relationships between two voxels (Incoronato et al., 2017; Taira et al., 2010; Kolossváry et al., 2018), and several other sub-features are mineable from each matrix (Incoronato et al., 2017). Examples of second-order statistics are represented by the gray level co-occurrence matrix (GLCM) (Rizzo et al., 2018; Haralick and Shanmugam, 1973), the grey-level run-length matrix (GLRLM) (Rizzo et al., 2018; Kolossváry et al., 2018; Galloway, 1975), the gray-level size-zone matrix (GLSZM) (Tixier et al., 2011), the gray-level distance-zone matrix (GLDZM) (Thibault et al., 2014), the neighborhood gray-tone difference matrix (NGTDM) (Amadasun and King, 1989) and the neighboring gray-level dependence matrix (NGLDM) (Sun C, Wee WG, 1983). The main second order statistics and their meaning is reported in Table 4.

Higher-order statistics work by imposing filter grids on an image, in order to extrapolate repetitive and/or non-repetitive patterns (Incoronato et al., 2017). The filters most frequently employed in radiomic studies are (Incoronato et al., 2017): the laplacian of Gaussian (Marr and Hildreth, 1980; Ferreira Junior et al., 2018), the Gabor (Fogel and Sagi, 1989), the wavelet transform (Mallat, 1989; Chaddad et al., 2018) and the fractal dimensions (Cusumano et al., 2018; Lopes and Betrouni, 2009; Aerts et al., 2016) filters (Table 5). Filtered images are then processed in order to extract first- and second-order statistics (Incoronato et al., 2017).

A more comprehensive technical and mathematical description of the different features that could be extracted from texture analysis has been addressed in other articles (Lambin et al., 2012; Incoronato et al., 2017) and is beyond the scope of this review.

3.2. Critical points in radiomic analysis

Some major critical points that could interfere with the final results and the creation of a reliable model can be recognized in radiomic analysis.

Among them, the database composition is crucial for the correct creation of predictive and analytic models (Gillies et al., 2016; Incoronato et al., 2017; Taira et al., 2010). Databases for radiomic studies should be comprised of a minimum of 100 patients, although larger cohorts could provide more statistical power (Gillies et al., 2016).

In addition to the size of the database, the quality of the data is also important: wide variations in protocol acquisition of imaging investigations and the lack of standardization of these protocols across manufacturers and sites do not generally represent a problem in routine identification of radiomic features (Gillies et al., 2016). However, variations in image acquisitions could introduce biases due to the fact that reconstruction parameters might introduce changes that are not related to the underlying biologic effects (Gillies et al., 2016).

Finally, besides the lack of standardization of image acquisition, the type of segmentation of the VOI can interfere with the final results of radiomic analysis (Gillies et al., 2016; Lambin et al., 2012; Incoronato et al., 2017). In oncology the VOI is usually represented by the tumor lesion(s) (single or multiple). It should be remembered that the

Table 2
Examples of shape-based features (Lambin et al., 2012; Incoronato et al., 2017).

Examples of shape-based features			
Features	Formula	Formula values	Significance
Volume	;	V = volume of the VOI; N = number of voxels within the segmented VOI; vs = voxel size	Volume of the VOI - information on the size of the lesion
Surface area	$A = \sum_{i=1}^{NT} \frac{1}{2} \lvert \overrightarrow{a_i b_i} \times \overrightarrow{a_i c_i} \rvert$	A = surface area of the VOI; NT = number of triangles derived from the triangulation of the tumor surface; a_i, b_i,c_i = vertices of the i-th triangle	Surface area of the VOI - information on the size of the lesion
Compactness	$c = 36\pi \frac{V^2}{A^3}$	c = compactness; V = volume; A = surface area	How much a VOI differs from a sphere
Spherical disproportion	$spherical\ disproportion = \frac{A}{4\pi R^2}$	A = surface area of the VOI; R = radius of a sphere with the same volume of the VOI	Measures of how much the volume resembles a sphere
Sphericity	$sphericity = \frac{(36\pi V^2)^{\frac{1}{3}}}{A}$	A = surface area of the VOI; V = Volume of the VOI	

Table 3
: Examples of first-order statistics (Lambin et al., 2012; Incoronato et al., 2017).

Examples of first-order statistics			
Statistics	Formula	Formula values	Significance
Range	$range = \max(X) - \min(X)$	max(X) = maximum intensity value of the voxels of the VOI; min(X) = minimum intensity value of the voxels of the VOI	The range of mean intensity values
Mean	$\overline{X} = \frac{1}{N}\sum_{i=1}^{N} X(i)$	X = mean intensity value of the voxels of the VOI; N = number of voxels within the segmented VOI; X(i) = gray value of the ith voxels of the VOI	Average intensity value of voxels within a VOI
Standard deviation	$\sigma = \sqrt{\frac{1}{N-1}\sum_{i=1}^{N}(X(i) - X^{-})^2}$	Σ = standard deviation; N = number of voxels within the segmented VOI; X(i) = gray value of the ith voxels of the VOI	The widening of intensity value variation
Entropy	$entropy = -\sum_{i=1}^{N_i} P(i)\log_2 P(i)$	N = number of voxels within the segmented VOI; P = first-order histogram of the VOI computed on N_l bins	Randomness within a data sample
Skewness	$skewness = \frac{\sum_{i=1}^{N}(X(i) - \overline{X})^3}{N\sigma^3}$	σ = standard deviation; N = number of voxels within the segmented VOI; X(i) = gray value of the ith voxels of the VOI	Asymmetry of a given histogram around the mean
Kurtosis	$kurtosis = \frac{\sum_{i=1}^{N}(X(i) - \overline{X})^4}{N\sigma^4}$	σ = standard deviation; N = number of voxels within the segmented VOI; X(i) = gray value of the ith voxels of the VOI	Degree of peakedness of a given histogram
Root mean square	$RMS = \sqrt{\frac{\sum_{i}^{N} X(i)^2}{N}}$	RMS = root mean square; X(i) = gray value of the ith voxels of the VOI; N = Number of voxels within the segmented VOI	The square root of the mean of squares of all voxels intensity

Table 4
Typically used second-order statistics and examples of features mineable from each matrix (Lambin et al., 2012; Incoronato et al., 2017).

Typically-used second-order statistics		
Statistics	Feature description	Examples of features mineable from each matrix
Grey Level Co-occurrence Matrix (GLCM) (Taira et al., 2010; Davnall et al., 2012)	It describes how frequently voxels with similar intensity value are located next with each other along a given direction and distance	Autocorrelation, cluster shade, cluster prominence, homogeneity, entropy, inverse difference normalized, sum average
Grey-Level Run-length Matrix (GLRLM) (Taira et al., 2010; Rizzo et al., 2018; Haralick and Shanmugam, 1973)	It describes how many voxels with the same intensity value are located next to each other	Short run emphasis, gray level non-uniformity, run percentage, short run high gray level emphasis, run length variance
Grey-Level Size-Zone Matrix (GLSZM) (Galloway, 1975)	It describes the amount of homogeneous connected areas within a VOI, of a given size and intensity	Small area emphasis, large area emphasis, intensity non uniformity, zone percentage, high intensity small area emphasis
Grey-Level Distance-Zone Matrix (GLDZM) (Tixier et al., 2011)	It describes the amount of homogenous connected areas within the VOI, of a given intensity and distance from the shape borders	Small distance emphasis, intensity non-uniformity, zone percentage, intensity variance, distance zone variance
Neighborhood Grey-Tone Difference Matrix (NGTDM) (Thibault et al., 2014)	It describes the differences between the intensity of a given voxel and the average intensity of neighboring voxels within a given distance	Coarseness, contrast, busyness, complexity, strength
Neighboring Grey-Level Dependence Matrix (NGLDM) (Amadasun and King, 1989)	It describes the relationships between the intensity of a given voxel with the intensity of all its neighboring voxels at a given distance	Small dependence emphasis, grey-level non uniformity, low grey-level emphasis, dependence variance, dependence entropy

Table 5
Filters usually used in radiomic studies for higher-order statistics (Incoronato et al., 2017).

Filters usually used in radiomic studies for higher-order statistics	
Filters usually used in radiomic studies	Function
Laplacian of Gaussian (Sun C, Wee WG, 1983; Marr and Hildreth, 1980)	This filter highlights the regions of rapid intensity change, commonly used for edge detection
Gabor filters (Ferreira Junior et al., 2018)	These filters permit to detect edges of images in different directions and widths
Wavelet transform (Incoronato et al., 2017; Fogel and Sagi, 1989; Mallat, 1989)	This transform allows to decouple textural information of the image into low- and high-frequency coefficients; these coefficients can be considered as the projections of the signal of the original voxels onto multi-resolution subspaces
Fractal dimensions (Chaddad et al., 2018; Cusumano et al., 2018; Lopes and Betrouni, 2009)	Fractal dimensions estimates the complexity of an image by measuring the self-similarity grade of the structures of the analyzed image

characteristics of the tumor can change overtime, representing a further source of variability (Gillies et al., 2016). In addition, it is often difficult for a researcher to identify and to correctly segment the VOI because not infrequently tumors have indistinct margins with the surrounding structures. In this situation, segmentation can be the most variable portion of the radiomic analysis, due to the fact that slight differences in VOI segmentation can heavily interfere with final results (Gillies et al., 2016; Lambin et al., 2012; Incoronato et al., 2017). However, although the debate about the reproducibility of segmentation is still ongoing (notably the inter-operator variability in semi-automated techniques), there is general consensus that maximum reproducibility is achievable by using computer-aided edge detection followed by manual correction (Gillies et al., 2016).

4. The model development in radiomics and "radi…-omics"

Once radiomic and non-radiomic features (such as those derived from histologic, genomic, proteomic or transcriptomic analyses) are collected, they can be used for data mining, representing the process of discovering patterns in datasets (Gillies et al., 2016; Incoronato et al.,

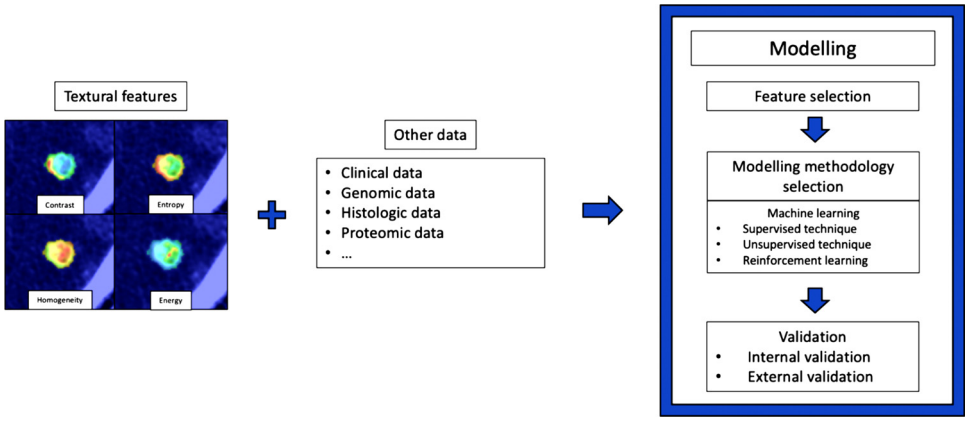

Fig. 2. The steps of the model development.

2017). By exploring the mutual relationships between radiomic and non-radiomic features with a selected outcome variable, AI modeling can be used to develop models that, once validated, could be used for different purposes. As an example, starting from imaging, these models could be used to predict the genotype of a tumor, the overall survival (OS) or the response of a disease to a given treatment or to assess the response to a treatment beyond the classic radiologic criteria (Gillies et al., 2016; Lambin et al., 2012; Incoronato et al., 2017; Lo Gullo et al., 2020). Change detection between temporal time points provides treatment response criteria beyond the classic radiologic criteria by measuring temporal changes of radiomic features from a time series of images (for example pre- and post-treatment) (Chang et al., 2019; Fave et al., 2017). This "modelling" process involves three aspects: a) feature selection, b) modelling methodology selection and c) validation (Lambin et al., 2012). All the process that brings to the model development are reported in Fig. 2.

4.1. Feature selection

The feature selection should be data-driven due to the large volume of data elements that must be taken into consideration (virtually unlimited), including the radiomic characteristics seen above (Gillies et al., 2016; Lambin et al., 2012; Incoronato et al., 2017). Considering all the possible features in the model could result in overfitting, which may make the model less useful when tested on new data (Lambin et al., 2012). Initial data analysis should include reduction of relatively insignificant variables in the model, selecting the archetypal features through dimensional reduction techniques, such as principal component analysis, clustering, least absolute shrinkage and selection operator (LASSO) and automatic relevance determination (ARD) (Lambin et al., 2012; Muthukrishnan and Rohini, 2016a; Muthukrishnan and Rohini, 2016b). Multi-factorial data models are ideally analyzed using machine-learning techniques (Gillies et al., 2016; Lambin et al., 2012; Incoronato et al., 2017).

4.2. Modeling techniques

The modeling process usually exploits machine-learning techniques (Choy et al., 2018). Machine-learning can be defined as a method of data science based on computer algorithms able to learn complex relationships from data without being programmed with explicit rules and to make accurate decisions (Choy et al., 2018; Wang and Summers, 2012). Machine-learning techniques can be broadly classified into three subcategories: a) supervised, b) unsupervised and c) reinforcement learning (Choy et al., 2018; Deo, 2015).

Supervised learning techniques are used to learn a general rule in order to map inputs and outputs, exploiting labeled input data and learning known patterns (Choy et al., 2018). Unsupervised learning techniques exploit unlabeled data in order to learn unknown patterns to find the hidden structure of the data, separating them into different clusters (Choy et al., 2018). Reinforcement learning techniques exploit labeled input data in order to learn a series of actions from the consequences of the interactions with an environment (Choy et al., 2018; Zhang et al., 2018). These techniques can be used also in combination (Gillies et al., 2016; Lambin et al., 2012; Incoronato et al., 2017). A list of the principal machine learning techniques is provided in Table 6.

Artificial neural networks are a subset of machine-learning methods inspired by the functioning of the central nervous system, that consist of a large number of processing elements called neurons (or nodes or cells) highly interconnected between them (Choy et al., 2018; Dayhoff and DeLeo, 2001). Neurons are organized in layers: an input layer, one or different "*hidden*" layers, and one output layer (Choy et al., 2018; Dayhoff and DeLeo, 2001); all the neurons of a layer are fully interconnected with all the neurons of the previous layer (Choy et al., 2018; Dayhoff and DeLeo, 2001).

Deep learning, also known as hierarchical learning, is a subset of artificial neural networks algorithms that typically contain several hidden layers (Choy et al., 2018; LeCun et al., 2015; Saba et al., 2019). This technique attempts to model high-level abstractions in data that make them directly applicable to computer vision and image recognition (Choy et al., 2018; LeCun et al., 2015). Deep learning models used for imaging analysis can be further divided as typical, in which input data are in the vector form (nonstructured; one-dimensional) and convolutional neural networks (CNNs) in which input data are structured in the two-dimensional or three-dimensional form (Choy et al., 2018).

CNNs are feedforward artificial neural networks containing multiple hidden layers that consist of convolutional (including filter elements called kernels) or pooling neurons, in addition to normalization and fully connected layers (Choy et al., 2018). Convolution is a mathematical operation that can be applied to find patterns in signals or filter signals, and the convolution layers in the network are the principal components (Choy et al., 2018). On the other hand, pooling layers are used to reduce overfitting and gain computational performances by reducing spatial dimensions (Choy et al., 2018). Thanks to these properties, CNNs are particularly useful for feature extraction from images and they currently represent the most used machine learning technique in medical imaging (Choy et al., 2018; Saba et al., 2019; Kohli et al., 2017).

A CNN trained for a specific application can be directly applied to a different but related task. This offers significant time advantage when developing a model for a new application in which a pre-trained model can be trained on a smaller dataset relevant to the new application. For example, a CNN pretrained on a given dataset for nonmedical images can be applied also in medical imaging (Choy et al., 2018). This machine learning approach is known as transfer learning (Choy et al.,

Table 6
List of principal machine learning techniques (Choy et al., 2018; Zhang et al., 2018).

List of principal machine learning techniques		
Category	Algorithm category	Algorithm
Supervised learning	Classification	Decision trees K-nearest neighbors Support vector machine Random forests Naïve Bayes classifier
Algorithms able to learn a general rule in order to map inputs and outputs, exploiting labeled input data and learning known patterns.	Regression	Linear/non-linear regression Local regression (LOESS) Ordinary least squares regression Neural networks
Unsupervised learning	Cluster analysis	Hierarchical clustering K-means clustering
Algorithms that exploit unlabeled data to learn unknown patterns to find the hidden structure of the data, separating them into different clusters.	Dimension reduction	Linear discriminant analysis Principal component analysis
Reinforcement learning	-	Q-learning State-Action-Reward-State-Action
Algorithms that exploit labeled input data in order to learn a series of actions from the consequences of the interactions with an environment.		Deep Deterministic Police Gradients Normalize Advantage Functions Asynchronous Advantage Actor-critic

2018; Grapov et al., 2018), and has been used in many applications including prostate cancer classification (Yuan et al., 2019) and lung nodule classification (Nishio et al., 2018).

4.3. Validation of the model and evaluation of its performances

The performance of a machine-learning model must be reproducible on new data in order to be accepted both in the scientific and clinical communities. The process of validation defines the models performance by using new internal and/or preferably external data (Choy et al., 2018; Lambin et al., 2012; Park et al., 2019). Internal validation methods, such as split sample or bootstrapping, assess how well the experiment is conducted, particularly when evaluating the relationships between variables (Park et al., 2019; Cook and Campbell, 1979). External validation assesses the "generalizability" of the model, i.e., whether the model maintains a level of performance when tested on new data, especially that which avoids any deliberate selection bias (Park et al., 2019; Ferguson, 2004).

The model performances can be measured in different ways, in particular in terms of calibration and discrimination (Lambin et al., 2012). Discrimination is the ability of the model to correctly classify cases that match a given outcome from those who do not match that outcome, and it can be typically measured in terms of sensitivity and specificity by using the receiver operating characteristic (ROC), i.e. the area under the ROC curve (AUC) (Lambin et al., 2012; Metz, 1978). Calibration can be defined as the agreement between model predictions and observed outcomes, and it is typically reported by using a calibration plot and calibration-in-the-large/slope (Lambin et al., 2012; Steyerberg et al., 2010).

5. Radiomics and "radi…-omics" in cancer immunotherapy

Radiomics could be a helpful tool in cancer immunotherapy for optimal patient selection (El Naqa I, Ten Haken RK, 2018). It may act as a non-invasive digital biopsy technique able to quantify tumor T-cell infiltration, to support personalized immunotherapy interventions, and to longitudinally monitor the therapeutic response above the traditional dimensional criteria (Solinas et al., 2017; Porcu et al., 2018). In particular, digital biopsy thorugh the combination of radiomics and pathomics features (i.e. data derived from the analysis of imaging data of pathological samples, in analogy with what seen for radiomics (Gupta et al., 2019)), represents a promising technique that could improve the diagnosis, prognosis and outcome prediction in the optic of personalized medicine (Banna et al., 2019a).

One of the first attempts to create and validate a radiomic signature able to discriminate the different tumor immune-phenotypes (inflamed *versus* immune-desert) and to be associated with a benefit from anti-Programmed Cell Death-Ligand 1 (PD-L1) ICB, was performed on a retrospective multicohort study (= 4 independent cohorts) including patients with advanced solid tumors (Sun et al., 2018). The development of the radiomic signature of $CD8^+$ T cells was accomplished with the use of CT scans, RNA sequencing and genomic data (from tumor biopsies). Remarkably, patients treated with anti- Programmed Cell Death-1 (PD-1) and PD-L1 drugs, experienced major benefit from ICB (i.e., objective response or stable disease and improved survival) in the presence of a high baseline $CD8^+$ T cell radiomic score (Sun et al., 2018). In order to understand the progresses in this field and how these models would be valuable tools in daily clinical practice for the correct management of oncologic patients, several radiomic studies focused on immunotherapy in different types of tumors (particularly in non-small cell lung cancer (NSCLC)) have been conducted. Ongoing clinical trials testing radiomics in immunotherapy are listed in Table 7).

5.1. Radiomics in immunotherapy for non-small cell lung cancer

Immunotherapy is one of the options approved in clinical practice for the treatment of NSCLC (Herbst et al., 2018). Interestingly AI has been widely applied in NSCLC research, from optical biopsy to histopathology and genomic classification (Rabbani et al., 2018). AI was further employed in different radiomic studies, with some of them creating models able to distinguish responders and non-responders, to stratify prognosis and to monitor the effects of treatment in patients undergoing cancer immunotherapy.

To identify responders to immunotherapy, starting from the hypothesis that local tumor immune-environment would be associated with patient outcomes and responses to treatments, in their retrospective study *Tang C et al.* (Tang et al., 2018) applied radiomics by creating a model able to forecast the tumor immune-environment of primary NSCLC. The authors firstly divided patients into two groups, a training (114 patients) and a validation group (176 patients) (Tang et al., 2018). In both groups they analyzed the tumor immune-environment on the surgically resected primary tumor by analyzing the expression of PD-L1 on tumor cells and the density of tumor-infiltrating $CD3^+$ (T) lymphocytes through immunohistochemistry (IHC) and automated cell counting. They further analyzed the correlation between the 5 year-overall survival (OS) and the tumor immune-environment

Table 7
Ongoing clinical trials of radiomics in immunotherapy. Source: ClinicalTrials.gov ; cut-off date: 11/07/2020. CT = Computed Tomography; iRADIOMICS = imaging-based RADIOMICS analysis of FDG PET/CT data; NSCLC = Non-small celllung cancer; PET = positron emission tomography.

Ongoing clinical trials of radiomics*					
Identifier	Study type	Status	Study title	Intervention(s)	Outcome measures
NCT03305380	Observational	Recruiting	Radiomics to Identify Patients at Risk for Developing Pneumonitis, Differentiate Immune Checkpoint Inhibitor-induced Pneumonitis From Other Lung Inflammation and Distinguish Tumour Pseudo-progression From Real Tumour Growth, in Patients With Non-Small Cell Lung Cancer Treated With Anti-PD-1 or Anti-PD-L1	Diagnostic test: radiomics	Cause of pneumonitis Predictive accuracy of radiomics for determining the cause of pneumonitis. Three subgroups of immune checkpoint induced pneumonitis: Immune checkpoint-induced pneumonitis from tumour progression Immune checkpoint-induced pneumonitis from other types of pneumonitis Patients with interstitial lung disease that are at risk to develop immune checkpoint-induced pneumonitis and those who are not. Radiomics will be used to predict the cause of pneumonitis
NCT01302626	Observational/ Prospective	Completed	Radiomics: a Prospective Study of Outcome in Lung Cancer	Diagnostic test: radiomics in patients receiving different treatments (e.g., surgery, chemotherapy, radiotherapy, any systemic therapy and supportive care)	Lung tumor tissue Lung normal tissue
NCT04007068	Observational/ Prospective	Active/not recruiting	FDG PET/CT Radiomics Analyses of Lung Cancer Patients Treated With Immunotherapy	Diagnostic test: FDG PET/CT	Correlation of iRADIOMICS with survival
NCT04079283	Retrospective	Completed	Radiomics of Immunotherapeutics Response Evaluation and Prediction (RIREP)	Diagnostic Test: Clinical Diagnostic Test: Semantic Diagnostic Test: Radiomic	Area Under Curve (AUC) of each diagnostic model Disease Control Rate of immunotherapy Incidence of immune-related adverse events
NCT04193956	Observational/ Prospective	Recruiting	Towards Patient-tailored Cancer Immunotherapy Supported by a Multifaceted Predictive Signature Composed of Integrative Omics and Molecular Imaging	Other: Standard of care procedures Study procedures: patients will undergo tumor biopsies, venous blood sampling and feces sampling in combination with a food questionnaire before, during and at the end of standard of care anti-PD-1 treatment	Predictive signatures based on multi-omics for PD-1 antibody treatment response as assessed by RECIST1.1 Predictive signatures based on multi-omics for PD-1 antibody treatment toxicity as assessed by CTCAE 4.03
NCT04364776	Prospective	Recruiting	Radiomic Signature as Predictive Marker of Response to Chemoradiation and Durvalumab in Stage III NSCLC	Drug: Durvalumab	Progression-free survival Overall survival
NCT04452058	Observational/ Retrospective	Recruiting	CT-based Radiomic Algorithm for Assisting Surgery Decision and Predicting Immunotherapy Response of NSCLC	Other: Radiomic algorithm	Pathological subtype Objective Response Rate Progression-Free Survival Overall Survival Clinical Benefit Rate
NCT04243720	Observational/ Prospective	Not yet recruiting	Immune Resistance Interrogation Study	Diagnostic test: radiomics	Radiomic changes associated with primary or acquired resistance to immunotherapy given alone or in combination in patients with advanced solid tumors** Radiomic changes associated with subsequent anticancer therapies in patients with advanced solid tumors who have progressed on immunotherapy** Fecal microbiome changes associated with primary or acquired resistance to immunotherapy given alone or in combination in patients with advanced solid tumors**

*Source: ClinicalTrials.gov - Cut-off date: 11/07/2020.
** Listed only the ones that are related to radiomics.

features by distinguishing the: 1) immune activated tumors (characterized by a greater quantity of $CD3^+$ lymphocytes and a lower percentage of tumor cells expressing PD-L1) and the 2) immune-inhibited tumors (characterized by a lower quantity of $CD3^+$ lymphocytes and a greater percentage of tumor cells expressing PD-L1). Remarkably they found that patients from the immune activated tumor-subgroup had the highest 5 year-OS when compared with those belonging to the immune-inhibited-subgroup (Tang et al., 2018). Authors then extracted 12 radiomic features from the pre-treatment CT scans of the training group and developed an immune pathology-informed model by using a hierarchical clustering algorithm (Choy et al., 2018; Tang et al., 2018). Specifically, the authors found that the favorable outcome group was characterized by low CT intensity and high heterogeneity, i.e. the group with a favorable immune activated state, characterized by low PD-L1 count and higher CD3 infiltration (Tang et al., 2018).

The prediction of PD-L1 expression on tumor cells in NSCLC through the use of radiomics was also investigated by *Jiang M et al.* (Jiang et al., 2019) in ^{18}fluorodeoxyglucose (^{18}F-FDG) PET/CT. PD-L1 expression was measured in surgical specimens by using IHC (Jiang et al., 2019). Also in this case authors divided patients into two cohorts (a training and a testing cohort). Clinical and radiomic features derived from CT, PET and PET/CT data were extracted from the training cohort and filtered by applying ARD and LASSO. Single predictive models for CT, PET and PET/CT features were realized by applying a logistic regression classifier and a random forest classifier to find the PD-L1 expression status from the filtered features (Choy et al., 2018; Muthukrishnan and Rohini, 2016a; Muthukrishnan and Rohini, 2016b; Jiang et al., 2019). This model was tested in the testing cohort, applying the ROC for estimating model performances, leading to good results in terms of AUC especially for models derived from CT and PET/CT images (Jiang et al., 2019).

Also *Mu W et al.* (Rabbani et al., 2018) developed models able to predict the clinical outcome of NSCLC patients treated with immunotherapy from baseline pretreatment ^{18}F-FDG PET/CT scans. Also in this case, radiomic features were extracted from PET, CT and PET/CT images from a training cohort in order to create/test a multiparametric radiomic signature to be validated either in a retrospective and in a prospective test cohorts, able to predict durable clinical outcome with good results (AUC: 0.86 for training, 0.83 for retrospective and 0.81 for prospective test cohorts) (Mu et al., 2019).

Another approach for developing models predicting OS and responses to immunotherapy was used by *Khorrami et al.* by exploiting delta-radiomics (Khorrami et al., 2020). In this study, the authors retrospectively analyzed data from 139 patients with NSCLC divided into a discovery set and into two independent validation sets (Khorrami et al., 2020). Radiomic features were extracted within and outside tumor nodules from pre- and post-treatment CT scans, and the relative differences were computed (Khorrami et al., 2020). Subsequently, a model to predict treatment responses according to the commonly used response evaluation criteria in solid tumors (RECIST) (Nardone et al., 2020) was developed by using a linear discriminant analysis (LDA) classifier (Choy et al., 2018; Khorrami et al., 2020). This model was shown able to distinguish responders from non-responders with high AUC values (0.88 ± 0.08) (Khorrami et al., 2020). A similar approach was used more recently by *Nardone V et al.* in patients with metastatic NSCLC treated with the anti-PD-1 nivolumab (Eisenhauer et al., 2009).

Finally, an example of more complex predictive model created by integrating radiomic and several types of non-radiomic data (patients demographics, clinical and hematological data, and driver mutations) was presented in the research by *Tunali I et al.* (Tunali et al., 2019). Authors created a model for identifying rapid disease progression phenotypes in patients affected by NSCLC treated with ICB by including not only histological and radiomic data derived from pre-treatment contrast-enhanced CT scans (600 radiomic features extracted from the largest lung lesions and tumor border regions), but also considering patient demographics, clinical and hematological data, and driver mutations (Tunali et al., 2019). Also in this case they were able to identify parsimonious clinical-radiomic models able to predict rapid disease progression phenotypes, even if these models have been not tested in a validation cohort (Tunali et al., 2019).

So far, the majority of clinical trials that test the potential of radiomics in immunotherapy involve patients with NSCLC (Table 7).

5.2. Radiomics in cancer immunotherapy (other types of tumors) and adverse events to immunotherapy

Similar to NSCLC, other types of cancer have been investigated in radiomic studies for the potential development of models able to predict and monitor the responses to immunotherapy.

Liao H et al (Liao et al., 2019), in analogy to other studies (Tang et al., 2018; Jiang et al., 2019), developed a radiomic-based biomarker able to predict cytotoxic $CD8^+$ T-lymphocyte infiltration in hepatocellular carcinoma (HCC) on pre-treatment contrast enhanced CT. The model was developed by using elastic-net regularized regression analysis (Zhang et al., 2017) from radiomic features and IHC data from a training dataset consisting of 100 patients and validated on a validation dataset of 42 patients (Liao et al., 2019). Similarly, *Chen S* et al (Chen et al., 2019) developed a model able to predict the pre-treatment immuno-score (i.e., the intralesional density of $CD3^+$ and $CD8^+$ T lymphocytes (Fridman et al., 2012)) of HCC, starting from IHC data and radiomic features of pre-treatment liver MR examinations performed with Gadolinium ethoxybenzyl-diethylenetriaminepentaacetic acid (Gd-EOB-DTPA) (Wang et al., 2017) of 207 patients who underwent surgical resection for their HCC. 1044 radiomic feature of the tumoral and peri-tumoral regions extracted from the hepatobiliary phase of MR scans were used to generate three different models by using the extreme randomized tree technique in order to predict the immuno-score (Geurts et al., 2006). The model was generated using a training cohort of 150 patients and validation group of 57 patients (Chen et al., 2019). The intratumoral radiomic features of this model showed good performances in predicting the immuno-score (AUC = 0.823). However, performances resulted to be even better with the model generated from both intra-tumoral and peri-tumoral radiomic features (AUC = 0.904) and with the one generated from clinical data combined with selected radiomic features (AUC = 0.926) (Chen et al., 2019).

AI has been further applied for exploring the potential of radiomic features in predicting the responses to immunotherapy in other types of tumor, i.e. glioblastoma (Sinigaglia et al., 2019; Verduin et al., 2018), melanoma (Guerrisi et al., 2020), brain metastases (Galldiks et al., 2020; Bhatia et al., 2019) and also hematopoietic tumors (Cottereau et al., 2020). An example is represented by the retrospective study of *Bhatia et al.* (Bhatia et al., 2019) that identified several MR radiomic features associated with increased OS in a cohort of 88 patients with brain metastases from melanoma that were treated with ICB. Another interesting example is the study by *Cotterau AS et al* (Cottereau et al., 2020) that tested the predictive value of the combination of metabolic tumor volume and radiomic features derived from baseline ^{18}F-FDG PET in evaluating of progression free survival (PFS) and OS in patients with diffuse large B cell lymphoma treated with a drug therapy protocol that included the anti-CD20 rituximab.

Lastly, it is noteworthy to report that researchers are starting to develop models able to predict patients at risk for irAEs. For example, the model of *Colen RR et al* (Colen et al., 2018) was able to identify patients at risk for immune-related pneumonitis (Porcu et al., 2019) by extracting radiomic features from baseline chest CT scans of 30 patients treated with immunotherapy who did not develop immune-related pneumonitis, and those of 2 patients who developed immune-related pneumonitis. For the analysis, six VOIs (one for every lobe of the right lung, and three specular VOIs for the contralateral lung) with radius between 14-15 mm were segmented, and 1860 radiomic features were extracted (Colen et al., 2018). A maximum relevance minimum

redundancy algorithm (Peng et al., 2005) was applied to identify features associated with immunotherapy-induced pneumonitis, and an unsupervised anomaly detection algorithm (Goldstein and Uchida, 2016) was used to develop the predictive algorithm (Colen et al., 2018). This model was able to correctly identify the two patients that developed immune-related pneumonitis (Colen et al., 2018). An ongoing trial (Table 7) is evaluating the relationship between radiomics and adverse events.

6. Current situation and future prospects

Radiomics is changing radiology and oncology (Ha, 2019; Trebeschi et al., 2019; Bera et al., 2018; Du et al., 2019; Banna et al., 2019b), but the process of translation from pure research to clinical practice is facing some difficulties (Park et al., 2020; Deutsch and Paragios, 2019). In a recent article by *Sollini et al* (Choi et al., 2016), authors adopted a phase classification criteria for radiomic studies similar to the one used for drug development, and the relative paucity of phase III and IV trials evaluating radiomic models. They conclude that the results in this field are promising but still not mature enough to be adopted in a routine clinical context.

Besides the intrinsic technical limitations of radiomic analysis and exposed in the above paragraph, this "translation gap" is due to several factors, specifically the quality of science and reports (Waterton and Pylkkanen, 2012; Moons et al., 2015), with the scientific community trying to give some instruments in order to overcome these limitations. Regarding the quality of reporting, *Moons KG et al* (Buckler et al., 2011) proposed that radiomic researches should be reported according to the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD) checklist. Regarding the quality of science, *Lambin et al* (Lambin et al., 2012) developed a system of metric based called "radiomic quality score" (RQS). This consists of 16 components that consider several aspects of the structure of a radiomic scientific research, including modeling technique, feature reproducibility, biologic/clinical validation and performance index. A recent study by *Park JE et al* (Park et al., 2020) that evaluated the radiomic studies present in literature by applying RQS (Lambin et al., 2012) and TRIPOD (Buckler et al., 2011) evidenced that both the scientific and reporting quality is generally insufficient, particularly the scientific quality. However, the scientific community is making great efforts to bridge this gap. An example is represented by the activation of national and international initiatives such as the quantitative imaging biomarkers alliance (QIBA) promoted by the Radiological Society of North America (RSNA) and by the National Institute for Biomedical Imaging, and the European Imaging Biomarkers Alliance (EIBALL) sustained by the European Society of Radiology (ESR), whose main goal is to standardize quantitative imaging (Gillies et al., 2016; Sollini et al., 2019; Alberich-Bayarri et al., 2019).

It is reasonable to speculate that all these efforts and the technological improvements in computer science will bring soon to the introduction of several radiomic models in clinical practice.

In the coming future, hopefully radiomics would represent an important predictive or prognostic tool in medical oncology. However, nowadays it is too premature to derive definitive conclusions from published works, that together with the ongoing studies are almost observational (either prospective and retrospective, as reported in Table 7). Prospective trials comparing a specific treatment to a control in patients having or not a particular radiomic biomarker would help addressing these questions and making these tools available in clinical practice (Bogowicz et al., 2019).

7. Conclusions

Radiomics and "radi…-omics" techniques leverage imaging information beyond those attained through visual inspection. In the field of cancer immunotherapy, radiomics has already shown value in characterizing the tumor immune-environment and to stratify prognosis by easily evaluating the baseline imaging investigations.

Even though the process of translation of these models from pure research to clinical practice is still in progress, they represent an innovative tool that once applied in clinical practice will help clinicians in the correct management of the oncologic patient.

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