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NEXT GENERATION IMAGING TOOLS: RADIOMICS AND ARTIFICIAL INTELLIGENCE SOFTWARE FUTURE PERSPECTIVES

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Abstract

Thanks to the advanced hardware and software technologies present today, we are closer to the introduction of new methods of medical imaging analysis that promise to improve the quality of care for patients and can bring improvements in the work organization by making some worksteps more efficient. Radiomics is a new and constantly evolving field of research that makes extensive use of artificial intelligences. The number of studies concerning this topic is continuously increasing demonstrating a growing interest in this field of study and its promising prospects. In This review we briefly describe the steps involved in radiomic analysis, the current state of this technology, its limitations, its possible uses and the changes it may bring with it as well as the possibilities that it will lead to the figure of the medical doctor.

Keywords: *Radiomics, Radiogenomics, Artificial Intelligence, Machine Learning, Deep Learning, Nuclear medicine radiomics, intra-tumoral heterogeneity.*

Introduction

Computing power has been constantly increasing during the years and software development followed this trend becoming a complex study field. Currently the growing size of any kind of digital database allow for extraction of useful information and many researching fields are taking advantage of this implementing artificial intelligence algorithms.

Artificial intelligence is a very active study field nowadays and AI algorithms are being implemented with success almost everywhere: from industrial maintenance scheduling to face recognition, to autonomous driving, to marketing and many other fields. Therefore, artificial intelligence algorithms will naturally be implemented in future medicine in order to increase treatments quality and efficiency.

Computer aid is crucially involved in modern diagnostics and the number of diagnostic exams is increasing year over year allowing the creation of big imaging databases that can be used to extract new useful information that can result in an important step forward to precision medicine. This process of information extraction from diagnostic imaging through artificial intelligence acquired during the years the name of Radiomics.

Radiomics term was firstly used in 2012 [1] defined as "extraction and analysis of large amounts of advanced quantitative imaging features with high throughput from medical images" [1] [2]. This new field of study uses Artificial Intelligence algorithms on multiple levels in order to gain quantitative parameters that can be correlated to clinical, prognostic and therapeutic information, in order to improve the patient's outcome.

The number of scientific publications associated with the word radiomics has grown steadily over the years, going from 3 in 2012 to 1479 in 2020 on PubMed research results. This study aims to review the current state of this technology and its prospects, along with the changes that may occur in clinical practice with its introduction.

Radiomic Analysis Process

Radiomic analysis is a complex procedure subject to numerous variations, which can be divided into key points that we will briefly describe here.

Image Acquisition

Radiomic analysis start with image acquisition. In Radiomics, image acquisition respects the fundamental rules of the exam with particular focus on standardization. The main diagnostic investigations that lend themselves to radiomic analysis are CT, MRI, PET and SPECT as well as hybrid methods such as CT-PET and CT-SPECT due to the high standardization, high spatial resolution and the characteristic of being operator-independent. [3-7] Artificial intelligence algorithms must be trained to recognize variations in the image; therefore, it is necessary to minimize variations due to acquisition parameters. For this reason, during the acquisition, it is necessary to follow the acquisition parameters specified in the dataset to obtain reliable results: for example, it will be necessary to consider the acquisition time and the type of tracer used in the PET and SPECT images, or the thickness of the layer and others exposure parameters (kilovolts, milliamps, scanning time and pich factor) as well as the characteristics of any contrast media used in CT and MRI investigations. To extract the functionalities in a stable and reproducible way on multiple centers, a unified set of image acquisition protocols is therefore desirable in order to have an archive as homogeneous as possible and to ensure that the image we intend to analyze is adherent to the archive to avoid interpretation problems by the algorithm.

Signal value normalization

One of the cornerstones of radiomic analysis is the production of numerical, quantitative indicators resulting from more or less complex mathematical processing of numerical values associated with the voxels of the image, therefore it is necessary to standardize the values of the voxels [8]. The presence on the market of different models and manufacturers of equipment may introduce variations that can invalidate the result of the analysis, therefore it is necessary to adapt the image

to be analyzed to the characteristics required by the starting dataset. This can be done manually using the appropriate image reconstruction programs or automatically using special algorithms in setting up the image archive.

ROI segmentation

Once the data has been collected and organized, a ROI (Region of Interest) will be defined and taken into consideration for radiomics analysis. The delineation of the margins of the ROI can be defined manually, but the need for a high consistency to have a reliable result, combined with the speed of the automatic process, makes the automatic segmentation (Autosegmentation) preferable. Self-segmentation based on artificial intelligence has had interesting developments in recent years thanks to the experience gained with the different methods of analysis of the data [9]. Recently, efforts to develop self-segmentation solutions using deep learning models have produced promising results [10,11]. The effectiveness of self-segmentation is very important, since the manual modification of an ineffective self-segmentation, as often happens, for example, in tumors with poorly defined margins, introduces additional variability which, albeit minimal, can invalidate the result of the analysis. The adoption of automatic methods in the radiomics workflow should result in more solid radiomics results, since the variability of the observer will be mitigated and the segmentation time will be significantly reduced compared to manual or semi-automatic segmentation. [11]

Analysis and Feature Extraction

Feature Extraction represents the actual analysis of the ROI content, during which the numerical values of the individual voxels and the relationships between adjacent voxels are analyzed using complex mathematical calculations to obtain numerical data from the image, whether simple (First Order) or reworked (Higher Order) [8]. These are the Image-Based Biomarkers (IBB), [12] which allow, through statistical inference, to associate the morphology of the image and the data derived from it to its biological equivalent or to prognostic probabilities, thus providing discrete, quantifiable and objective data that can provide the doctor with an easier classification of the patient in categories of treatment, in order to improve the outcome. [13] This process is carried out by training the algorithm analyzing the numerous images in the archive (Dataset) and validation of the result, needed to test the algorithm operation using a second image archive to verify the results achieved. A great number of features is extracted from the images, however many carry redundant information therefore a selection of the most useful ones is necessary [14].

Image Based Biomarkers

A biomarker is "a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacological responses to a therapeutic intervention" [8]. Image based biomarkers consist of both qualitative biomarkers, which require a trained eye interpretation, and quantitative biomarkers based on mathematical definitions. Several authors have tried to divide the numerous radiomic features into classes [8,15], however no common agreement has yet been reached on their subdivision. For the purpose of this review we will briefly describe the different classes.

First Order features are often classified as morphological features that describe the geometric aspects of a region of interest (ROI), such as area and volume, but also include more complex parameters. Some examples of first level characteristics are: Shape, Size, Localization, Sphericity, Asphericity, Major Axis Length, Minor Axis Length, Degree of Vascularization, Inhomogeneity of Margins, Area Density, Volume Density, Compactness, Symmetry, Repeated patterns.

Second order features include features obtained from the analysis of the quantitative value of to the single voxel, that is, the smallest unit making up the image, returning the distribution of the latter in the form of histograms or numerical data resulting from complex calculations. Some examples of second level characteristics are: Average, Maximum, Minimum, SUVpeak, SUVmax, Standard Deviation,

Kurtosis, entropy, Energy, Uniformity, Variance, Area Under the Curve (AUC).

Third order features are derived from the analysis of the correlation between neighbouring voxels. This category contains dozens of parameters and can be divided into several sub-categories based on the degree and type of processing that is carried out. This category also includes the Features derived from signal filtering, with the possibility of eliminating disturbing factors such as background noise or the signal deriving from structures close to the lesion. Among the main analyzes of this category used in Radiomics we have: Gray Level Co Occurrence Matrix (GLCM), Gray-Level Run Length Matrix (GLRLM), Gray-Level Size Zone Matrix (GLSZM), Gray-Level Distance Zone Matrix (GLDZM), Neighborhood Gray-Tone Difference Matrix (NGTDM), Wavelet Transform, Laplace Transform, Fourier Transform.

Model Building

Once the extraction of the features has been finalized and the most useful ones selected, it is possible to create radiomic models using a wide range of machine learning algorithms to find statistical associations between extracted characteristics and diagnostic, predictive and prognostic data. These features with significative associations with outcome are the Image Based Biomarkers (IBB). A Large set of features highly associated with patient's outcome is obtained through training and validation of the algorithm on two different datasets. Subsequently, the characteristics most strongly associated with the outcomes are selected to provide a signature of the pathology allowing the analysis of subsequent images with greater efficiency making this processing compatible with use in clinical practice.

Artificial Intelligence and Radiomics

In the last decade, publications containing the term "Artificial Intelligence" have seen an exponential increase, thanks to the interest developed in relation to the growing awareness of the potential associated with this research method. The definition of Artificial Intelligence has been constantly redefined during the years since the term "intelligence" is not itself well defined in a universally accepted way by the scientific community and because the capabilities of these technologies are constantly evolving. Today we already interact daily with artificial intelligences in various ways, often without realizing it: for example on a smartphone, in the car or while surfing the Internet. The study of artificial intelligence plays an important role in the radiomics research process, requiring the presence of highly specialized professionals in the research team. In fact, there are many artificial intelligence algorithms and new methods of analysis are introduced continuously thanks to the commitment that the scientific society has been investing in these technologies in recent years. For each application, an artificial intelligence algorithm can be more accurate or more performant to achieve a set goal: using different data analysis methods greatly influences the result of the analysis and it is therefore necessary to select the right algorithm based on the size, homogeneity and classification characteristics of the dataset available, as well as based on the task that we intend to entrust to the machine.

Future applications

The future applications of radiomics include interesting applications in the oncology field, but also in the cardiology field and various other areas such as denoising, the construction of attenuation maps for a precise calculation of the decay factor in nuclear imaging, or to increase the efficiency of screening programs. Virtually any medical imaging can be analyzed.

Oncological

Oncology is a very active research field where personalized treatments where personalized treatments are necessary to ensure the best chance of survival for patients. One of the major reasons for therapeutic failure is intratumoral heterogeneity [16]. With current knowledge, it is difficult to be sure that two tumors, staged and classified as molecularly identical, have the same biological behaviour [17]. This is because by its nature, a tumor

has a significant genetic instability that it brings to a high number of mutations, which follow each other phylogenetically and progress into distinct cell lines with different morphology and a behavior in relation to the genetic alterations they bring with them. This also applies to tumor metastases. This different behavior of the various cell populations in the context of the tumor mass corresponds to a different behavior towards the therapy [18].

Considering that the cell is a complex functional ecosystem regulated by proteins, it appears evident that a modification of genes, their expression and their product, produce alterations both in the cellular morphology and in the of tissue morphology. The possibility, of associating the morphological characteristics of a tumor mass with its biological behavior, would be extremely useful in the decision-making process that ultimately makes the difference in the patient's outcome. Radiomics can make a great contribution in this field allowing for in-vivo lesion characterization before the anatomo-pathological analysis thus potentially changing the approach to the patient. [19-21]

Lung Cancer

Lung cancer is the most common malignancy in the general population and is the leading cause of cancer death worldwide [22]. In lung cancer, radiomics has shown potential utility in the characterization of the solitary pulmonary nodule (SPN). A solitary pulmonary nodule (defined as a focal opacity <3 cm in diameter) is a very frequent radiological finding in clinical practice and often poses problems of differential diagnosis [23-24]. In this field radiomics can help giving a reliable characterization of the solitary polmonary nodule consequently reducing the workload in radiology [25]. Radiomics also proves very promising in the non-invasive definition of EGFR mutational status: various studies aim to find a set of features able to identify a radiomic signature of the mutational state of the EGFR [26,27]. Non-invasive EGFR status characterization could be useful to identify patients candidates for EGFR target-therapy where traditional invasive characterization is ineffective or not possible for various reasons such as tumor position or size, poor health state of the patient.

Breast Cancer

Breast cancer is the most common malignancy in women [28]. Several studies have investigated the effectiveness of radiomics in various areas with encouraging results. [29-34] Areas of major interest in this field are diagnosis, non-invasive identification of the molecular subtype of the tumor and HER2 and ki67 mutational status, response to treatment prediction, relapse predition and patient prognosis. [35,36] Most of the studies report good performance of the algorithms [37-43].

Colorectal

Colorectal cancer It is the second most common cancer diagnosed in women and third most in men [44]. In this context, radiomics studies were carried out to identify the mutational status of the neoplasm and histochemical characteristics [45], to predict outcomes and assess the probability of complete pathological response (pCR) in Locally Advanced Rectal Cancer (LARC) [46,47] and the probability of lymph-node distant metastasis [48-53].

CNS Cancer

In the area of Central Nervous System Tumors, several studies have reported the possible usefulness of using a radiomic approach to overcome some clinical difficulties. [54] The field in which radiomics has proved promising is the non-invasive identification of glioblastoma. [55] The Revised World Health Organization (WHO) Classification of Tumors of the Central Nervous System of 2016 is the first tumor classification based on both molecular markers and histology. [56] Radiomics aims to allow a rapid and non-invasive way of diagnosis and characterization of CNS lesions. [57] Radiomics studies have been carried out regarding the ability of artificial intelligences in ki67 mutational state identification, in differentiating the necrotic tissue from relapse after radio-chemotherapy and the differentiation between primary SNC tumor and brain metastases [58-60].

Radio-Genomics

Genomics and Proteomics are currently the main disciplines that make a clinical contribution to precision medicine, allowing a valid patient stratification, despite the limitations of biopsy. Radiomics is, although very promising, still a field under study, and will not be usable in the clinic until the Standardization limits are exceeded and an acceptable reliability is achieved. The goal of radiomics is to relate to genomics, in order to identify, through tissue morphology, what is the genetic asset of the tumor even before resorting to biopsy, with all the advantages that this entails. When this result is achieved, it will be possible to have accurate estimates of the pathology in question without the need to use invasive methods [61].

Screening

Being able to obtain an analysis algorithm with a maximum Sensitivity, even at the expense of Specificity, could be extremely useful in screening programs, this because safely excluding negative tests could reduce the working hours necessary for the radiologist to analyze them, allowing, for the same number of working hours, the analysis of a greater number of overall exams, with the possibility of using resources more efficiently by extending the screening to a greater number of people. [62,63]

Hardware

Rradiomics analysis tools will probably be available as processing software, not differently from those currently used in clinical practice. More specifically, these software will be provided in compatibility with the machines already available in the facilities, and will require higher computing power than the software currently used in clinical practice due to the type of calculations performed, which are more complex. However, this type of calculations is particularly speeded up using graphics processing units (GPU: Graphics Processing Unit) which are particularly suitable for performing these calculations (Data Mining) due to their architecture, allowing the analysis time to be compatible with daily use. The current machines (computers) available on the market are already able to provide the performance necessary for daily use with relatively low costs and therefore, it is reasonable to say that in the future, with the increase of the calculation capacity, the analysis will be faster, cheaper and more complex. From costs perspective, the machines used for the analysis do not differ from the common computers used in every work environment and do not require peripherals built ad hoc, benefiting from the economy of scale and requiring development costs limited mainly to the software. As a result of these considerations, it is possible to imagine how this analysis tool can easily be implemented where required, allowing a wide and rapid distribution of this technology on the territory when it is mature.

Nuclear Medicine Imaging

Despite the limitations due to low spatial resolution, in the field of nuclear medicine radiomics is developing on par with traditional radiology, taking advantage of the functional information it can offer. [64] In particular, Positron Emission Tomography (PET) is the most promising exam and several studies suggest that PET Radiomics can provide valuable support in the diagnosis, [65] staging [66] and characterization of various tumors. [67] In FDG-PET scans, the Standardized Uptake Value (SUV) is the main element routinely used. [68] SUV is calculated from a single voxel within the lesion (SUVmax) or from a ROI which represents the highest metabolic activity in the tumor (SUVpeak). Other quantitative parameters used in PET imaging include Total Lesion Glycolysis (TLG) and Metabolic Tumor Volume (MTV). [69] Radiomics has the technical potential to detect even the slightest changes in repeated scans over time and to compare them. This ability would allow us to intervene at an early stage of progress or relapse [70]. PET is increasingly used quantitatively. This requires that intensity values, can be compared between repeated measurements, between different scanners, and between centers in multicenter studies. In this regard, it must be considered that radioisotopes have a decay time

(half-life), which varies depending on the isotope considered. In the case of PET these radioisotopes have a very short half-life, for example 18F has a half-life of 109.7 minutes. It follows that the intensity of the signal generated will depend on the time elapsed from radiopharmaceutical preparation and the scan, the amount of injected radiopharmaceutical, the acquisition time, and the radioisotope used. [71] Therefore, during the acquisition of the intensity it will be necessary to apply a Correction Factor (Decay Factor) that considers all these variables to avoid having a false numerical data. In nuclear medicine, therefore, the use of Artificial Intelligences in the generation of valid Attenuation Maps remains an active field of study [72] . Application of Artificial Intelligence in Denoising is an important point both to help the diagnosis by improving the quality of a full dose image, and to reduce the Collective Effective Dose, i.e. the total amount of radiation artificially introduced into the population, due to the increase in prescribed diagnostic tests (with obvious benefits), cannot be ignored. [73]

Actual Limitations

At present, most of the studies therefore report encouraging results, but the authors suggest further verifications to confirm the results obtained from the studies paying attention to standardization in order to achieve reproducible and reliable results. From the perspective of evidence-based medicine, it is indeed necessary to achieve accurate and reliable results in order to integrate them into clinical practice. To date, the limit of radiomics is precisely technical standardization, because the methods of analysis are numerous and an optimized protocol applicable for each type of analysis has not yet been set, furthermore the number of studies is, even if exponentially growing, still insufficient to provide adequate results for introduction into clinical practice. The choice of a suitable algorithm for the construction of models is an active and important research field as it is not yet clear which algorithm is more suitable for each type of analysis in terms of performance, but it is certainly clear that based on the type of task and to the type of dataset, some algorithms prove better than others. Most likely it will be necessary to involve professionals specialized in the study of artificial intelligence to achieve the best possible results given the complexity achieved by the AI sciences.

Discussion

We are at the gates of a radical change in medical imaging. Understandably, the rapid evolution of artificial intelligence technologies can be perceived as a threat to the physician, but it can also be seen as an opportunity to play a pioneering role in the health sector and to actively model this transformation process [74].

Machines are still very far from the processing capability of the human mind, however, their superiority in "Task Oriented" tasks is indisputable: to date we have countless examples of how machines help humans in areas where the latter does not excel: precision, repeatability, scalability. In this perspective, the machine can be conceived as a complement that helps to achieve high qualitative and quantitative standards, leaving man more time and energy to devote to what only a human mind can do. [75]

Radiomic analysis, once the current limits have been overcome, will be a very useful tool to complement current diagnostic technologies, due to some characteristics that characterize it:

Radiomics is a Non-Operator Dependent Method.

Radiomic analysis will be performed on PET, SPECT, CT and MRI scans, methods now considered highly standardized and characterized by a low operator dependency factor, being then processed by a computer, it will provide accurate and reproducible results. Radiomic analysis can therefore also be considered a non-operator dependant process.

Radiomics is a Non-Invasive Method.

Radiomics analysis is a software processing performed on the raw data of scans, and as such, can be performed after the scan and more times on the same scan, for example, to provide different sets of features, without the need to repeat the acquisition when the latter respects adequate qualitative standards and match the required

parameters of the dataset on which the radiomics algorithm is trained.

Radiomics is Repeatable.

Radiomic analysis will have a high precision (precision indicates how close or how repeatable the results are) and therefore the Radiomic Delta (the difference in two analysis carried out on two scans acquired at different times) will be very useful in the follow up of patients to evaluate responses to therapy and disease progression.

Radiomics Provides Objective Parameters.

The result of the radiomic analysis is a set of quantitative parameters (Features) that are the result of a mathematical processing. Features are therefore an excellent support for statistical analysis. Statistical correlation will then be able to attribute predictive and prognostic factors to the individual features or associations of these and will probably be able to provide us with histological-molecular information even before resorting to biopsy.

Radiomics will be easily implemented in clinical practice.

We are still far from the implementation of this technology in clinical practice, however, once fully developed, given the absence of physical limits regarding the equipment, most likely radiomic analysis tools will have a very rapid and widespread diffusion throughout the territory offering a new tool able to reach a better patient care and a more efficient workflow in diagnostic centers.

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