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Radiomics and Artificial Intelligence for PET imaging analysis

Andrea d'Amico[1], Damian Borys[1,2], Izabela Gorczewska[1]
[1]Diagnostic PET Department, MSC Memorial Cancer Centre and Institute of Oncology, Gliwice, Poland
[2]Institute of Automatic Control, Silesian University of Technology, Gliwice, Poland

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Abstract

In recent years, processing of the imaging signal derived from CT, MR or positron emission has proven to be able to predict outcome parameters in cancer patients. The processing techniques of the signal constitute the discipline of radiomics. The quantitative analysis of medical images outperform the information that can be obtained through traditional visual analysis. The recognition of neoplasm molecular and genetic characteristics in a non-invasive way, based on routine radiological examinations, potentially allow complete tumor profiling and subsequent treatment customization at practically zero costs. This process is further boosted with the availability of increased computing power and development of artificial intelligence approaches.

KEY words: radiomics; positron emission tomography; artificial intelligence

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Introduction

The initial diagnosis of tumour disease and its molecular profiling are almost always performed invasively by biopsy.

Afterwards, in the great majority of patients who are subsequently subjected to anticancer therapies, non-invasive radiological diagnostics play a fundamental role in staging and monitoring the evolution of the disease and the possible response to treatment, while further biopsies are much less frequent.

In fact, it is universally accepted that radiological evaluable characteristics of the tumour, such as its size, shape, location and metabolism, are associated with prognosis and determine the therapeutic approach [1]. On the other hand, routinely performed CT, MR, PET and SPECT examinations consist of digitized images, which are highly amenable to subsequent analysis based on mathematical algorithms.

It has been proven that features not perceptible to the eye of the reporting physician — such as intra-tumour heterogeneity, distribution of signal values within the tumour area and more — can be indicative of certain biological characteristics of the tissue, such as proliferation, hypoxia, necrosis, angiogenesis and even tumoural genotype [2, 3].

Correspondence to: Andrea d'Amico
Diagnostic PET Department, MSC Memorial Cancer Centre and Institute of Oncology, Wybrzeże Armii Krajowej Street 15, 44–100 Gliwice, Poland
tel: +48 32 2788558; fax: +48 32 2789390
e-mail: adamico@io.gliwice.pl

For this reason, there is an increasing interest in generating algorithms with artificial intelligence methods to analyse a large amount of radiological data. The identification of a sub-group of simultaneously present characteristics can allow for image classification and, consequently, provide answers to specific clinical questions. The field of diagnostic imaging that investigates the creation and application of these algorithms is defined as radiomics, and the group of features that successfully classify the radiological data are defined as the radiomic signature [4, 5].

How to define a radiomic diagnostic algorithm

The definition of an appropriate clinical question is of prime importance [6]. This choice depends on the clinical relevance and the available data. The prognosis and the probability of metastasis, necrosis, hypoxia and resistance to therapy can be evaluated. It is also possible to investigate in a more specific way the definition of variables such as the presence or absence of a specific mutation or the expression of certain receptors.

The typical workflow for the definition of a radiomic signature consists of several steps [7]: i. identification of the series of patients to be studied, ii. image acquisition, iii. definition of lesion contours (segmentation), iv. features extraction and v. model building and clinical validation

Each of these stages presents specific problems in the field of nuclear medicine.

The group of patients must be sufficiently large. To obtain a sufficient number, a certain amount of heterogeneity in the group is acceptable, but it is necessary to remember that the increased inhomogeneity corresponds to an increase in the

number of variables, which can reflect negatively on the strength of the results. Considering that the possible number of features of diagnostic images in nuclear medicine is many hundreds, multi-institutional studies are required — with all the problems of image standardization that this entails.

Image acquisition must be done in a standardized and reproducible way. This is one of the most difficult aspects of the nuclear medicine context, where the acquisition parameters are highly variable and, in fact, they are left to the choice of each operator within the limits defined in the recommendations of national and international scientific societies. Initiatives aimed at standardizing image acquisition, such as the EARL project of the European Association of Nuclear Medicine, should be taken seriously into consideration [8].

Austrian authors have shown, through the acquisition of a NEMA phantom in 13 different sites following the local acquisition protocols, that almost all features are very sensitive to the conditions of image acquisition. The use of the point-spread function, the reduced values of the voxel size and a narrow Gaussian post-filtering have proved useful in minimizing feature variations [9]. The size of PET voxels is higher than in MRI and CT images. A greater volume is therefore necessary to assess tumour heterogeneity. For example, Brooks et al. demonstrated that in PET images of cervical tumours with volumes less than 45 cm^3, the radiomic methods have a greater chance of bias [10].

The segmentation of the tumour has not yet been uniquely defined. For example, for PET, different segmentation methods are possible, based on the value of the SUV, on the percentage of accumulation of the tracer compared with the point of greatest signal intensity, on the ratio to the signal of an organ considered as standard or, finally, with mathematical processing methods (adaptive segmentation) [11, 12]. None of these methods has been validated clinically. Recently, an approach has been proposed for evaluating data on physiologically distinct regions of the tumour (for example by distinguishing the area with cellularity from the oedema and the necrotic part), with extraction of radiomic data from each of these regions [2].

Data extraction must include the definition of large series of values. Features are divided into semantic and non-semantic: the first type concerns data such as diameter, volume and shape of the tumour, whereas the second one concerns data extracted from the mathematical elaboration of the image. Features can also be distinguished according to their definition mode. First-order variables concern the signal values of the tumour voxels independently of their spatial distribution, while second-order data concern the analysis of the spatial distribution of the signal: the so-called texture analysis. Texture is defined as "a regular repetition of an element or pattern on a surface with the characteristics of brightness, colour, size and shape". There are also features concerning the spatial characteristics of the tumour: shape-based features. Finally, different data sets can be calculated by analysing the tumour with the use of fractals: fractal-based features. The data must be subsequently selected to identify the non-redundant, stable and relevant ones, which have the greatest possibility of defining models with good diagnostic performance [13]. In particular, stability can be calculated by evaluating the consistency of the data in tests repeated at different times or with different methods of tumour segmentation.

Once the most suitable data have been identified, it is necessary to define an algorithm for their processing in order to obtain a response to a given clinical question. The population is divided into two subsets, the first to develop the model (training group) and the second to validate it (testing group). Depending on whether the answer is a discrete or continuous variable, different mathematical methods can be used.

Possible clinical applications and future scenarios

An increasing number of authors are exploring the possible clinical applications of radiomics. The segmentation of head and neck tumours based on textural features can be applied to radiotherapy planning and tumour distinction from surrounding healthy tissues, with a possible increase in accuracy [14, 15].

Images of pulmonary solitary nodules from an 18F-FDG PET investigation can be studied with fractal-based algorithms, which have shown good accuracy in distinguishing between malignant lesions and non-aggressive nodules. Furthermore, unlike analysis based on the maximum SUV values, this approach does not seem to be affected by the size of the nodule [16].

The application of radiomics to FDG PET investigations in patients with lung and oesophageal tumours and sarcomas has been shown to have a high prognostic value [17–20].

The clinical validation of radiomic signatures for PET is probably only a matter of time. The process of standardizing the methods of acquisition and reconstruction of PET images currently appears to be the major obstacle. However, the potential clinical advantages are obvious, and a work of education of the medical-nuclear community could be the first step to be taken in this direction.

One step further: deep learning

Recent studies in the field of artificial intelligence have also developed new, fundamentally different methods of image analysis. The so-called deep learning algorithms provide a "non-deterministic" analysis, where the features are not defined a priori but the algorithm itself defines features, selects them and reaches the final classification (diagnosis). All these operations with deep learning algorithms are conducted simultaneously during the training phase. The quantitative features derived from this analysis, on the other hand, are intrinsically difficult to describe and are not intuitively linked to tumour biology.

It is necessary to underline, however, that the theoretical bases of the deep learning process are not intuitive. In fact, the fundamental paradigm of scientific research, whose paternity is traditionally attributed to European astronomers of the fourteenth and fifteenth centuries (Copernicus, Galileo), consists of so-called hypothesis-driven research.

As we have all studied in high school, this foresees firstly the observation of data, preferentially by means of quantification tools, followed by a hypothesis formulation about the laws regulating the system in which the phenomenon occurs. Finally, the hypothesis must be confirmed by reproducible experiments. In medical sciences, typical hypothesis-driven research involves the evaluation of a given variable (i.e. a drug) by analysing its effect on a population compared with a control group.

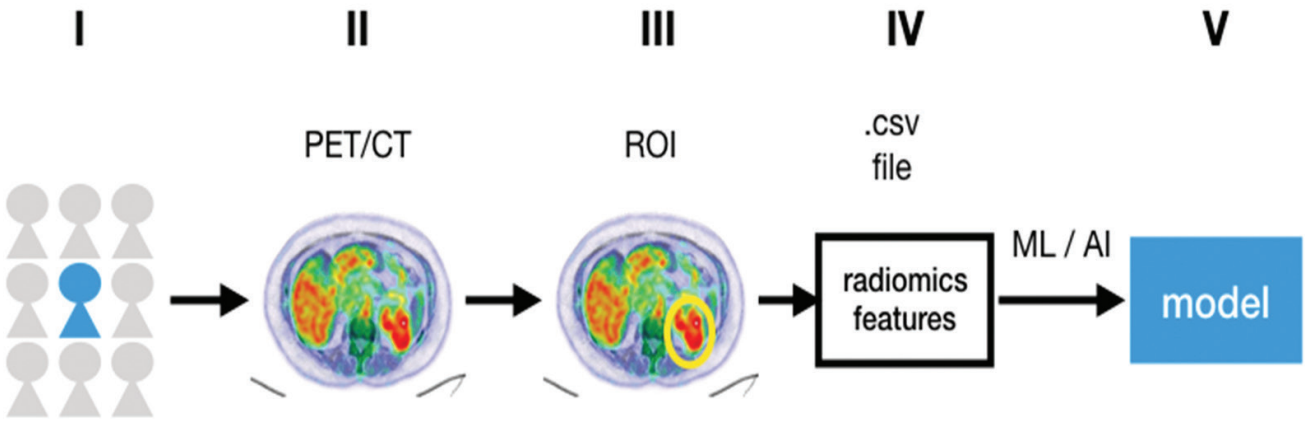

Figure 1. Illustration of the typical workflow for Radiomics signature development: I group selection, II Data acquisition, III Image segmentation, IV Feature extraction, V model validation

The mass of radiomic data currently exceeds the possibility of testing all the possible features with this type of approach. An alternative strategy is coming into play: the so called "data-driven hypothesis". In this scenario, the undifferentiated collection of enormous amounts of data (data mining) is followed by the generation of signatures capable of separating two or more groups, but without specifying in advance what the determining elements are and without using specifically selected data [21, 22].

Actually, deep learning applications are used in automatic speech and image recognition, drug discovery, commercial advertising, financial fraud detection and for military purposes. A deep learning model is conceptually extremely different from the traditional method of subjective image interpretation, since an artificial neural network autonomously defines and extracts features in order to classify the input data. This unavoidably will increase doctors' reluctance to accept in clinical practice the therapeutic decision-making paradigms based only on opaque quantitative characteristics. On the other hand, the recent catastrophic effects related to the hasty application of artificial intelligence in the field of civil aviation [23] provide a more than reasonable justification for the distrust of clinical radiologists.

Hopefully, radiomic models should try to be readable in correlation with more established radiology models [24]. At this stage, a combination of traditional radiological interpretation models with radiomic functionalities could increase diagnostic accuracy in oncology and would seem to be a reasonable compromise.

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