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Review article

Radiotherapy modification based on artificial intelligence and radiomics applied to (^{18}F)-fluorodeoxyglucose positron emission tomography/computed tomography

Modification de la radiothérapie basée sur l'intelligence artificielle et la radiomique appliquées à la tomographie par émission de positons/tomodensitométrie au (^{18}F)-fluorodésoxyglucose

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ABSTRACT

Over the last decades, the refinement of radiation therapy techniques has been associated with an increasing interest for individualized radiation therapy with the aim of increasing or maintaining tumor control and reducing radiation toxicity. Developments in artificial intelligence (AI), particularly machine learning and deep learning, in imaging sciences, including nuclear medecine, have led to significant enthusiasm for the concept of "rapid learning health system". AI combined with radiomics applied to (^{18}F)-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]-FDG PET/CT) offers a unique opportunity for the development of predictive models that can help stratify each patient's risk and guide treatment decisions for optimal outcomes and quality of life of patients treated with radiation therapy. Here we present an overview of the current contribution of AI and radiomics-based machine learning models applied to (^{18}F)-FDG PET/CT in the management of cancer treated by radiation therapy.

Mots clés :
Intelligence artificielle
Apprentissage automatique
Apprentissage profond
Radiomique
Radiothérapie

RÉSUMÉ

Au cours des dernières décennies, l'amélioration des techniques de radiothérapie a été associée à un intérêt croissant pour la personnalisation de la radiothérapie afin d'augmenter ou de maintenir le taux de contrôle tumoral tout en réduisant la toxicité des rayonnements. Les progrès de l'intelligence artificielle (IA), en particulier de l'apprentissage automatique et de l'apprentissage profond, dans les domaines de l'imagerie, y compris la médecine nucléaire, ont suscité un grand enthousiasme pour le concept de « système de santé à apprentissage rapide ». L'IA combinée à la radiomique appliquée à la tomographie par émission de positons/tomodensitométrie (TEP/TDM) au (^{18}F)-fluorodésoxyglucose ([^{18}F]-FDG) offre une opportunité unique pour le développement de modèles prédictifs qui peuvent aider à stratifier le risque de chaque patient et guider les décisions de traitement pour des résultats thérapeutiques optimaux et une amélioration de la qualité de vie des patients traités par irradiation. Nous présentons ici une vue d'ensemble du rôle actuel de l'IA et des modèles radiomiques basés sur l'apprentissage automatique appliqué à la TEP/TDM au (^{18}F)-FDG dans la prise en charge des cancers traités par irradiation.

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1. Introduction

Over the past 20 years, nuclear medicine and radiotherapy (RT) have significantly improved, mainly due to material and technological developments. (^{18}F)-fluorodeoxyglucose positron emission tomography/computed tomography ([^{18}F]-FDG PET/CT) is the most widely used nuclear medicine imaging modality in the management of cancer. The development of RT techniques has been associated with a growing interest for individualized RT with the aim of increasing or maintaining tumor control and reducing radiation toxicity.

In clinical practice, including radiotherapy but also in most clinical trials, nuclear medicine images are analyzed mainly visually or semi-quantitatively although they are quantitative. The standardized uptake value (SUV) is the most widely used semi-quantitative index because it reflects FDG uptake in PET/CT, and its value is thought to correlate with the biological aggressiveness of tumors [1]. However, it does not always accurately convey tumor responses. A positive PET finding can be caused by infection or inflammation [2], while false-negative findings can result from low tumor avidity of FDG [3]. There seems to be a growing interest in a better exploitation of these images through a more automatic analysis of medical images coupled with the extraction of multiple features, including some that may not be accessible to the naked eye, even to the trained eye of an expert [4].

Today, we recognize that cancers are molecularly heterogeneous diseases and we believe that understanding the link between underlying biology and clinical behavior is crucial for therapeutic decision-making. Personalized medicine is the goal of modern cancer treatment, which aims to link the genomic and clinical profiles of individual patients for more targeted tumour therapies [5]. The main objective of the improved exploitation of available imaging information is to assess tumour heterogeneity, such as cellular metabolism, necrosis, cancer-associated fibroblasts and specific receptor expression and to integrate these data to influence therapeutic management in the context of precision medicine [6,7].

In this context, medical imaging is expected to play an increased role and become essential beyond staging to encompass therapy planning, as well as therapy monitoring and evaluation, predictive modelling and stratification, to become overall an integral part of future clinical decision-making systems.

The aim of the present paper is to provide definitions of artificial intelligence (AI, machine/deep learning) and radiomics and summarize the clinical application of AI and radiomics-based machine learning (ML) models applied to (^{18}F)-FDG PET/CT in the management of cancer treated by RT.

2. Artificial intelligence (AI)

In 1955, the term “artificial intelligence” was introduced and defined as “the science and engineering of making intelligent machines” [8]. Today, AI is rapidly developing in many fields, and definitions are numerous and confusing. Here, we will only refer to machine learning (ML) and deep learning (DL) techniques used in radiomics studies applied to (^{18}F)-FDG PET/CT [8].

ML is a subset of AI that involves computer algorithms. Machine learning algorithms build a model based on training data to make predictions or decisions. Depending on their goals and how the underlying machine is taught, machine-learning algorithms can be divided into three categories: supervised, unsupervised, and semi-supervised [9]. Currently, most ML algorithms under the background of predictive oncology are based on supervised learning. Several classical ML algorithms include random forest (RF), support vector machine (SVM), decision trees, naive Bayes, and k-nearest neighbors [10]. DL is a subcategory of ML, essentially based on the use of neural networks (NNs). NNs can be shallow (1 hidden layer), but far more commonly; they have multiple hidden layers, which has resulted in an explosion of applications utilizing such deep NNs (DNNs) in the field of DL. In the field of medical imaging, research has mainly focused on deep neural network (DNN), including convolutional neural network (CNN) [11]. CNN is a kind of multi-layer neural network with direct progression, while low-level image features are extracted by the first hidden layers, and higher and higher features are learned by successive layers before being classified by different classifiers.

3. Radiomics

Over the past decade, it has been shown that medical images may contain more useful information than that captured by the naked eye that can be obtained by computer extraction and analysis, leading to better disease management. Thus, the introduction of radiomic analysis offers a promising new approach to cancer assessment. In summary, radiomics involves the application of an automatic data characterization algorithm to transform region of interest (ROI) image data into high-dimensional feature data that can be exploited [12]. Quantitative feature extraction includes different features such as histogram-based features, first, second, or higher order features. Each feature has a particular importance in defining the imaging phenotype and revealing key components of the tumor phenotype. Geometric features describe the 3D shape, size, location and dynamic curve characteristics of the ROI. Intensity features indicate the intensity of pixels or voxels in the ROI image. The most important texture features define the pattern and spatial arrangement of the intensities in the ROI. A complete standard radiomics analysis pipeline involves many steps [13]:

- identifying the clinical question and target patient cohorts;
- determining the imaging mode for radiomics analysis;
- standardizing image acquisition and reconstruction;
- segmenting tumor and defining ROI;
- extracting and selecting features;
- building models with different machine learning algorithms;
- training and validating the radiomics model.

More recently, ML methods have become an essential tool in radiomics for the construction and validation of multiparametric models [14,15]. These tools are needed because of the number and diversity of features, with hundreds of radiomic features computed for each region of interest, augmented by clinical data and possibly other omics data, such as transcriptomics and genomics. At the same time, DL techniques in medical imaging have evolved rapidly [16] leading to an evolution of radiomics workflows towards the use of deep neural network (DNN) based techniques. Thanks to these techniques some parts of the radiomics workflow, in particular the detection and segmentation step or the feature extraction process could be improved and automated [17]. In the long run, one could consider automating the whole usual analysis workflow by simply feeding the images into one or more DNNs [18]. Therefore, it has been proposed to subdivide radiomics-based imaging approaches into three broad categories [15,19]: (i) handcrafted (or conventional) radiomics: this consists of explicit extraction from images of predefined radiomic features following IBSI recommendations. Then a univariate analysis (evaluation of the predictive power of each feature) followed by a multivariate analysis using regression or ML algorithms are performed. Following these different steps, a subset of relevant and non-redundant features in the extracted radiomic feature set is obtained. This selected subset of features is then used to form a radiomic model. It can also be combined with additional variables from non-imaging data resulting in so-called

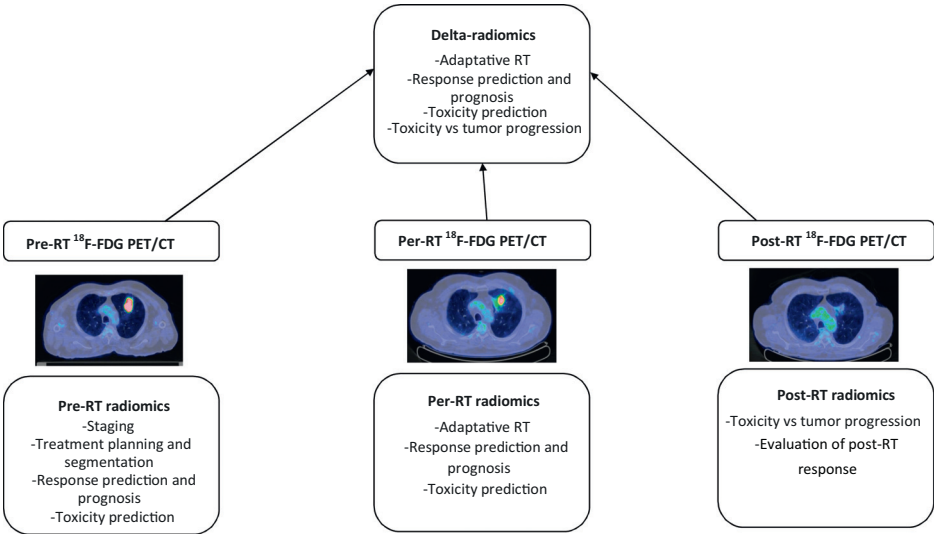

Fig. 1. Clinical applications of radiomics-based machine learning models applied to ^{18}F-FDG PET/CT in cancers treated with radiotherapy.

combined models. In addition, we note that radiomics analysis can be applied at the ROI level, or at a finer scale; e.g., generating a "parametric" image of a given radiomic feature, where feature value at a given pixel/voxel is computed via analysis of a neighborhood of that pixel/voxel [20]; (ii) representation Learning (RL) based radiomics: these are programs whose goal is to automatically discover features and patterns inherent in images, and avoid the use of manually created features. Neural networks (NN) are most often used for this purpose, but other approaches exist such as dictionary learning [21]. Neural networks directly learn from the images, and potentially, from non-imaging data; (iii) hybrid radiomics: this approach involves combining the two above frameworks in different approaches. The most studied are the combination of deep features extracted from a pre-trained DNN and handcrafted features [22] and the use of DLs to generate features (e.g., from an intermediate convolution layer in a DNN or the final fully connected layer) followed by the application of MLs to the extracted features, to achieve a radiomics signature [23].

RL based and hybrid radiomics approaches are also sometimes referred to as the umbrella term deep radiomics, due to the use of deep learning methods at one or more stages of the workflow. Regardless of the approach used, it is necessary to properly define the data needed to develop and evaluate a radiomic model. The dataset used to create the model is referred to as training, development, discovery or exploration data. To evaluate the model, additional data are used that were not used for training and it is necessary to distinguish 2 types of data sets, test data and validation data. A validation dataset is used to optimize the modeling process (e.g., the hyperparameters of a model), whereas a test dataset is only used for the final evaluation of the model. The latter set must be different from the training and validation sets in the sense that it is obtained at a different institution, using a different scanner, during a different period of time or even analyzed by different readers. Thus, its characteristics must be described in detail to verify the generalizability of the model. For example, a test set that differs from the training only in its time period will be less generalizable than a test set from another institution with additional variability factors.

4. Clinical applications

Clinical applications of radiomics-based machine learning models applied to (^{18}F)-FDG PET/CT In cancers treated with radiotherapy are summarized in Fig. 1.

4.1. Staging

In many cancers, the identification of regional lymph node (LN) involvement or distant metastases significantly is a crucial step for optimum treatment decision, particularly for RT.

Yin et al. developed a classification method based on SVM to improve the diagnostic performance of LN involvement in non-small cell lung cancer [24]. The ratio of the maximum of standard uptake value of LN to aortic arch played a major role in their model. They proposed a simplification of their model for transfer to the clinical setting in a scoring system that could help clinicians determine the clinical staging of NSCLC patients relatively easier.

In cervical cancer (CC), LN involvement is a major prognostic factor in locally advanced CC and patients with positive para-aortic LN will be treated with an extended feld of irradiation to the para-aortic region. In a retrospective multicentric study, the authors built and validated a (^{18}F)-FDG PET/CT radiomics-based models with ML to predict para-aortic LN involvement in LACC and guide clinicians in the planning of external beam felds of irradiation, without a surgical staging [25]. Moreover, this is the first study to show the applicability of radiomics-based models from analog PET/CT to digital PET/CT.

4.2. Treatment planning and segmentation

4.2.1. Target volume definition

Even if the majority of radiomics papers considered tumor volume as a whole, DL-based automatic segmentation techniques are increasingly used to improve the accuracy and reproducibility of VOI delineation [26,27]. Iantsen et al validated in a multicenter study an automatic segmentation based on a U-Net architecture method on (^{18}F)-FDG PET/CT in LACC. In addition, this approach could facilitate the deployment of a fully automated radiomic pipeline in heterogeneous multicenter cohorts [26].

4.2.2. Subvolumes definition for dose painting implementation

Even if the majority of radiomics papers considered tumor volume as a whole, some papers applied classification tasks at a voxel scale with the goal to improve tumor delineation and associated treatment planning.

A first study showed that radiomic analysis of tumor subregions on (^{18}F)-FDG PET/CT imaging has the potential to predict progression free survival in 128 patients with nasopharyngeal carcinoma, which also provides complementary prognostic information for

traditional predictors and outperfomed the analysis of whole tumor [28].

Another study of 32 patients treated with RT for non-small cell lung cancer evaluated the potential benefits of (^{18}F)-FDG PET/CT radiomic feature maps (RFMs) for delineating target volumes for radiation therapy [29]. The authors showed the relevance of second-order PET features for accurate identification of tumor volume with very good correlation with 40% of SUV_{max} volume and delineation of intratumor heterogeneity with identification of tumor subvolumes. These results could have potential advantages for dose painting. However, further research is needed to assess and validate their clinical application in practice.

4.3. Response prediction and prognosis

The majority of articles evaluated radiomics as a prognostic or response prediction tool [30–33]. Predicting the outcome is an essential step for the patients' management because it is crucial to detect patients with a higher probability of recurrence who may benefit from more aggressive local or systemic treatments.

It was the first clinical application that used both deep learning features and handcrafted features extracted on the (^{18}F)-FDG PET/CT images to predict outcomes. Peng et al. have evaluated the value of deep learning on (^{18}F)-FDG PET/CT-based radiomics to select patient who could be benefit of induction chemotherapy in advanced nasopharyngeal carcinoma before concurrent chemoradiotherapy [34]. They found a radiomic signature that outperformed standard clinical parameters for predicting disease-free survival and for selecting high-risk patients who might benefit from induction chemotherapy.

It was also the first clinical application that used delta-radiomics to predict outcomes. A retrospective study reported a significant improvement in prediction of locoregional recurrence with delta-radiomics feature-based models compared to single-modality models, whether trained with pre-, post-treatment radiomics features.

4.4. Toxicity prediction

Very few studies have focused on the ability of (^{18}F)-FDG PET/CT textural features to predict radiation toxicity. Among them, the most interesting [35] studied the risk of xerostomia in patients irradiated for head and neck cancer. The authors reported a significant improvement in the prediction of xerostomia at 12 months with pre-treatment PET radiomics features compared to the reference model based on gland dose.

4.5. Adaptative radiation therapy

Radiomic expression – which may be linked to the appearance and behavior of disease – may encode traces of therapeutic response that can be computationally measured in individual patients. These intra-treatment radiomics can be evaluated alone or in comparison with pre-treatment radiomics, these longitudinal changes in radiomic features are named delta radiomics, and can be used in making clinical decisions such as early prediction of therapy response.

A prospective study has investigated the prognostic potential of intra-treatment PET radiomics data in 64 patients undergoing definitive chemoradiation therapy for oropharyngeal cancer. They found that pre-treatment radiomics were not prognostic whereas intra-treatment radiomic expression was intrinsically associated with both residual/recurrent disease ($P = 0.03$) and RFS (HR = 7.53, 95% CI = 2.54–22.3; $P = 0.02$) [36].

4.6. Differential diagnosis toxicity vs. tumor progression

Differentiating radiation pneumonitis from residual/recurrent disease to avoid delay in treatment is a challenging issue after RT [37]. These may have a similar appearance on CT [38–40]. Also, increased metabolism due to inflammation is common in (^{18}F)-FDG PET/CT images [40,41], which may decrease the accuracy of SUVs. To distinguish these two entities, Suga et al. showed that two conventional radiomics features outperformed SUV (AUC = 0.83–0.82 vs. 0.63–0.64) but not MTV (AUC = 0.86) [37].

5. Opportunities and challenges

The potential of AI and radiomics-based ML models applied to (^{18}F)-FDG PET/CT in the management of cancer treated by RT. In recent years, there have been two important developments in radiomic studies. The first one is the advent of a much more standardized context compared to previous years, primarily through the efforts of IBSI [42]. This has made it easier to understand and compare studies, and even to reproduce them. The second is the rapid evolution of DL in all areas of imaging sciences, including of course nuclear medicine and radiomics. DL-based methods are increasingly being considered to speed up or facilitate certain steps in the radiomic workflow or to solve specific problems such as image harmonization as a preprocessing step. In addition, DL is increasingly considered as an alternative to standard radiomics, directly training DNNs to predict specific parameters from input images without going through all the usual steps of the classical radiomics approach (i.e., tumor detection and segmentation, extraction and selection of specific handcrafted features, and then modeling). Although this raises other issues such as the need for large databases to efficiently train models or technical solutions to help networks learn with limited amounts of data, as well as the ability to explain and interpret the resulting models, this evolution will likely continue in the near future. Despite theoretical considerations about the greater expressive power of "deep features" compared to "handcrafted features", it has been shown that some handcrafted features are difficult to capture by limited depth CNNs given limited learning data [43]. Furthermore, CNNs can be negatively biased in capturing shape information [44], which can be important for a range of clinical tasks [17]. Consequently, handcrafted radiomic features may be complementary to deep features.

Radiomics presents several challenges. Several studies have successfully trained models to perform specific tasks to personalize patient management, including predicting treatment response or prognosis (e.g., survival) after RT. But this area of research is still in its infancy. As we have seen, few studies have included an independent validation or test data set, which carries a high risk of overfitting results. To consider clinical application of radiomics, the robustness and repeatability of imaging markers must be improved. To improve technical repeatability and reproducibility, one solution could be to create a large multi-agency cooperative database covering a variety of imaging protocols and equipment, clinical settings and patient characteristics. However, it may be difficult to impose acquisition protocols on several centers. Thus, more and more studies are proposing an alternative to address this issue. This consists of validating models in large multicenter cohorts [45] using different harmonization techniques, but choosing the best method remains an open area of research, with several candidate approaches under investigation, including deep learning-based image synthesis [46].

The most appropriate machine learning algorithms and feature selection methods are still unknown, as we have not yet discovered the significant feature combinations with the greatest prognostic power. Integration of data from peritumoral regions or even outside

the tumor boundaries may provide additional prognostic information. Given the whole-body assessment with DL, it may be more powerful in this regard.

Another important future development should lie in the combination of radiomics with other areas of omics and other types of data, including but not limited to histopathology, genomics, or dosimetry, which clearly raises further modeling and validation issues. As radiomics evolves, a better understanding of these features and their relationship to the underlying biology will be needed, building on and expanding existing studies.

First radiomic studies in nuclear medicine have focused on PET, however given that SPECT images are now also quantitatively reliable [47], applying radiomics to SPECT is also feasible and relevant [22]. Radiomics can of course be applied to PET/MRI in the same way as to PET/CT, at least with respect to the PET component, but we have focused here on PET/CT. Concerning PET/CT, several radiotracers have been studied to improve patient management in the field of radiotherapy alone or in combination with systemic therapies. Thus, radiomic studies applied to PET using other radiotracers than (^{18}F)-FDG have already been performed. For example, a quantitative imaging metric has been described in a preclinical study indicating that radiation-resistant subvolumes in head and neck cancers can be detected by ADC and FMISO clusters using a PET/MRI combination, which are potential targets for future functional image-guided RT dose painting approaches and require clinical validation [48]. However, many other radiotracers have not been investigated which pave the way for many more studies.

6. Conclusion

Radiomics and artificial intelligence are considered as potential non-invasive decision-making tools for the management of cancer treated by RT in the future, but the clinical transferability of results is an urgent problem to be solved. At present, there are several initiatives and recommendations to regulate the standardization of research reports. In the future, multicenter, prospective, larger cohort research is necessary.

Disclosure of interest

The authors declare that they have no competing interest.

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Author contributions

F.L.: methodology, writing – original draft, review and editing; R.H., R.L.P., O.P., P.Y.S., U.S., V.B., P.L.: writing – review and editing.

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