Editorial, PET/CT.

Radiomics in PET/CT: Numbers Can Tell What Cannot Be Seen!

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INTRODUCTION

The past decade has witnessed the rapid evolution of the "big data era", which has been introduced into clinical practice with the aim of rendering the concept of "precision medicine" possible [1, 2]. It is the future of medicine, being personalized in terms of screening, risk stratification, treatment tailoring and response assessment, a ship that needs smart tools under conscious control to steer it quickly, accurately and judiciously in the right direction for maximum effectiveness [3-5].The adoption of precision or personalized medicine concept has speeded up the progression of high throughput quantitative metrics with substantial methodological advancement in technologies interrogating biological systems and paving the way for "omics" development [6]. "Omics" is defined as analyzing large amount of structural and functional data at cellular and subcellular level in a systematic manner [7]. Multi-omics integration has aided in constructing a relationship between molecular signatures and phenotypic manifestations of a particular disease [8, 9]. "Radiomics" is one of the "omics" harvesters. It is a digital transformation of medical imaging through which numerous quantitative invisible features could be extracted using methods from bioinformatics [10, 11]. The extracted digital features are handled through handcrafted or recently machine learning and/or deep neuronal techniques to build synergistic models [12]. Such models carry diagnostic and/or prognostic information and are capable of non-invasively capture tissue and lesion characteristics providing a powerful tool in precision medicine [13].

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Radiomics was initially put forward in CT and radiotherapy applications for treatment planning and was first proposed by ***Philippe Lambin*** in 2012 [(14)]. Later on, thousands of studies were carried out to investigate different radiomics signatures as the shape, intensity, and textural features in PET images to predict outcome in a very small number of patients then further studies enrolled larger number of populations were performed for correlation with tumor histology, prediction of therapy response, differentiation of different lesions and subtypes of tumors, as well as survival prediction [(15, 16)]. Even with the presence of limitations as the lack of external validation sets, the small study populations or even the variable medical imaging protocols, Radiomics research has opened up a broad horizon for researchers to study new dimensions of medical imaging that appears to have an impact on clinical decision-making from an entirely new perspective [(17,18)]. Hence Joint EANM/SNMMI has published a guideline on radiomics in nuclear medicine to provide comprehensive information on best practices for robust radiomics analyses for both hand-crafted and deep learning-based approaches [(19)]. The standard workflow of radiomics mainly consists of five processes:

(1) High quality Image acquisition and reconstruction.

(2) Tumor segmentation either automated or manually by an experienced radiologist or nuclear medicine physician.

(3) Extraction of features from the segmented tumor.

(4) Features selection based on their independence from other traits, reproducibility and prominence on the data; and (5) customized informatics analyses for model generation that predicts specific endpoint [(20)]. The aim is to provide precise risk stratification by integrating imaging features into prediction models of therapy outcome or any other assessed endpoint and determining their additive value to commonly used predictors [(21)]. Since the emerge of radiomics in the field of PET/CT its diagnostic and prognostic role has been extensively investigated in several tumors [(10)]. A number of studies were carried out in patients with brain tumors investigating the potential of PET radiomics or combined PET/MRI radiomics using a variety of PET tracers such as 2-[^{18}F]-fluoro-2-deoxy-D-glucose (FDG), [^{18}F]-3′- deoxy-3′-fluorothymidine (FLT), [^{18}F]-fluoromisonidazole (FMISO), and amino acid PET tracers such as [11C]-methyl-L-methionine (MET), and O-(2-[^{18}F]-fluoroethyl)-L-tyrosine (FET).

Textural features analyses and prediction models were generated evaluating gliomas proliferative activity, WHO grades, different genes mutation and deletion, differentiating true from pseudo-progression and treatment related changes from tumor residue or recurrence as well as survival prediction [22, 23]. Textural analysis has also demonstrated preliminary evidence suggesting clinical utility in head and neck tumors as regards benign versus malignant tissue classification, HPV status; loco-regional control and failure; risk of distant metastasis, and therapy outcome [24,25]. Likewise, applications of PET/CT radiomics in lung tumors were either cross sectional studies determining specific characteristics of a lesion as to discriminate benign versus malignant lesions , predict histological subtypes, and biomarker expression where previous studies built and validated radiomics models for prediction of tumor microenvironment, gene expression and mutation status in NSCLC patients. Other longitudinal studies were performed for prediction of survival, response to Immunotherapy and adverse events correlated with Immunotherapy [26]. PET-based machine learning radiomics/radio-genomics predictive models revealed a promising non-invasive perspective of a more accurate and high-efficient diagnostic model for breast cancer with recent studies evaluated dynamic radiomics to [^{18}F]-fluoro-3'-deoxy-3'-L-fluorothymidine ([^{18}F]FLT) data for the assessment of treatment response in breast cancer patients and [^{18}F] FDG-PET for evaluation of Neoadjuvant chemotherapy efficacy [27]. Applications of Artificial Intelligence have extended to prostate cancer with prediction models were able to predict post-surgical Gleason score and ISUP grade and predicting biochemical recurrence in patients with prostate cancer using [^{68}Ga]Ga-PSMA-11, [^{18}F] fluoro-methylcholine, and [^{18}F]-DCFPyL PET/tracers [28]. PET radiomics were also investigated in several other tumors as lymphoma, neuroendocrine tumors, hepatocellular carcinoma, gastric carcinoma, colorectal carcinoma, pancreatic cancer, cervical carcinoma, multiple myeloma, soft tissue and bone sarcomas [11]. Derived radiomics signatures, whether tested alone or linked to other "-omics" commonly the genomics, have outperformed conventional metabolic and morphological parameters and correlated well with tumor grade and aggressiveness, risk for metastases and clinical outcomes [13].

Beyond oncological indications, radiomics has also been tested for other benign etiologies as pancreatitis and visualization of epileptogenic lesions. However, the authors recommended further evaluation in larger cohort to assess its clinical performance (29, 30). As a general summary, one can easily state that recent years have been marked by rapid developments in the field of artificial intelligence, and radiomics has become an important sub-field and a very quickly evolving field of research as machine learning algorithms has greatly facilitated its existence in the real world [(12)].

Meanwhile, further steps are still required to establish and standardize these techniques appropriately and which would pave the way for their introduction into routine clinical practice, these steps include larger prospective studies with a large number of patients, standardizing imaging protocols, acquisitions and segmentation methods, expansion and standardization of user-friendly software, with resorting to reliable AI-based techniques for appropriate processing of this comprehensive data as well as external validation of prediction models [(15)].

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