Radiomics in [^{18}F]FDG PET/CT: a leap in the dark?

W. Noortman
May 10, 2023
University of Twente, Enschede

Promotors:
Prof. L.F. de Geus-Oei, MD, PhD
Prof. C.H. Slump, PhD

Copromotors:
F.H.P. van Velden, PhD
D. Vriens, MD, PhD

Medical images are believed to contain much more information about the biology of the tissue hidden in the myriad of voxels of both lesions and healthy tissue than can be assessed visually or using traditional quantitative measures. Quantification of heterogeneity and other tissue characteristics is studied in the field of radiomics. Radiomics is a form of medical image processing that aims to find stable and clinically relevant image-derived biomarkers for lesion characterisation, prognostic stratification, and response prediction, thereby contributing to precision medicine. Radiomics consists of the conversion of (parts of) medical images into a high-dimensional set of quantitative features and the subsequent mining of this dataset for potential information useful for the quantification or monitoring of tumour or disease characteristics in clinical practice. The field of radiomics can be divided into two areas: handcrafted radiomics and deep learning radiomics (figure 1). In handcrafted radiomics, large numbers of mathematically predefined intensity, shape, and texture features are extracted from a volume of interest and machine learning algorithms are used for feature selection and outcome modelling. Deep learning radiomics employs algorithms that both learn features from raw data and perform modelling, thus without a predefined definition of features.

The possibilities of radiomics seem endless, but, as with the introduction of any new technology, challenges are faced before its added clinical value can be assessed and the new technology can be applied (safely and routinely) into the clinic. Currently, the main challenges of radiomics are limited standardisation in the different steps of the radiomic pipeline and a lack of external validation, hampering its clinical translation. The general aim of this thesis is to provide a deeper understanding of the methodological aspects of handcrafted radiomics in [^{18}F]FDG PET/CT, eventually aiming to bridge the translational gap towards clinical readiness. A specific focus is placed on the robust analysis of small datasets, which is an inherent aspect of nuclear medicine.

Radiomic feature extraction

First, we explored methodological considerations of radiomic feature extraction. Central necrosis can be detected on [^{18}F]FDG PET as an often central region with little to no tracer uptake. Isocontour-based delineation methods inherently exclude central necrosis, but in some studies, subvolumes with central necrosis were added manually to the volume of interest. We assessed the effect of central necrosis on radiomic analysis in patients with non-small cell lung carcinomas and pheochromocytomas and paragangliomas (PPGLs). Volumes of interest were delineated using an isocontour method and, subsequently, volumes of central necrosis were manually added. At least 65% of the radiomic features showed significant differences between delineation methods with and without central necrosis. In the PPGL cohort, performances of the radiomic models to predict the noradrenergic biochemical profile were assessed for both delineation methods, but these were not significantly different. It was recommended that radiomic studies should report whether or not central necrosis was included during delineation.

Then, potential additional information in the temporal domain of dynamic PET scans was explored, as temporal changes in tracer uptake might reveal new aspects of tumour biology. Novel dynamic grey level cooccurrence matrix (GLCM) features were developed to asses if voxel values change from one time frame to the next. Five dynamic GLCM features showed a negligible to moderate correlation with any static feature, suggesting additional information. The clinical benefit of dynamic features should be assessed in larger cohorts, but dynamic features might play a role in total body PET

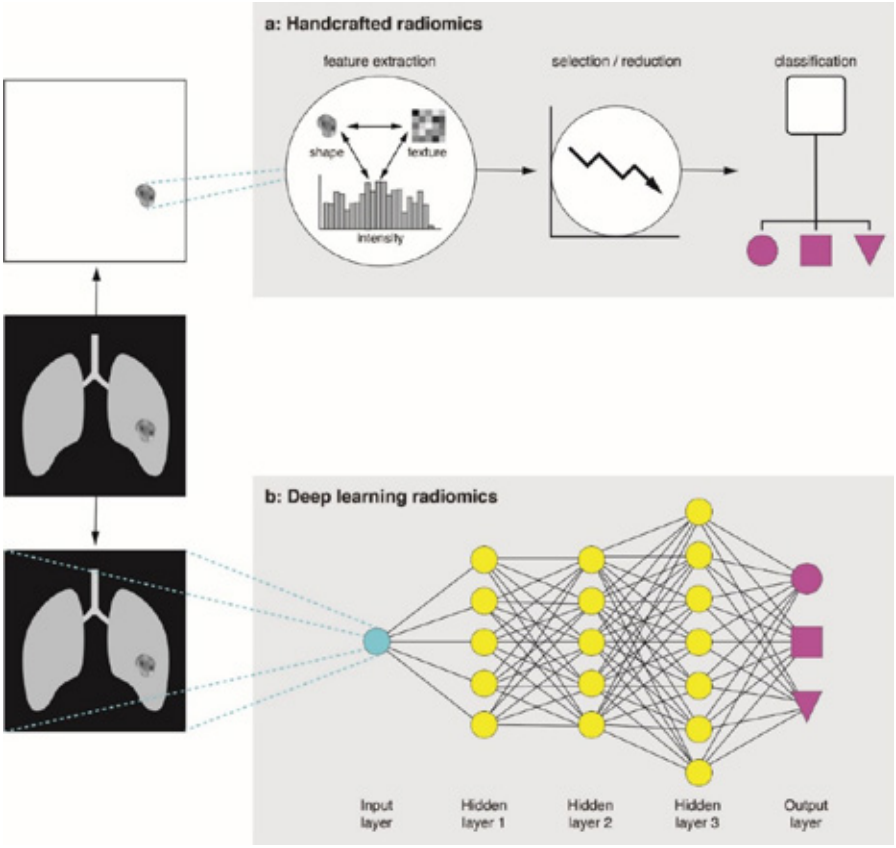
or dynamic contrast-enhanced CT or magnetic resonance imaging.

Clinical datasets

Next, radiomic analysis was performed in four clinical datasets. First, the potential utility of [^{18}F]FDG PET/CT radiomics supplementary to clinical characteristics and the SUV_{max} was investigated for the identification of the genetic cluster in 40 PPGLs. The PET radiomic model performed best, but a simplified model with only SUV_{max} performed almost similarly (multiclass AUCs in the test set of 0.88 and 0.85, respectively). Therefore, a model with SUV_{max} alone might be preferred clinically, weighing model performances against the laborious radiomic analysis.
In addition, a clinicoradiomic model based on [^{18}F]FDG PET radiomic features and clinical characteristics was built to predict overall survival in patients with head and neck squamous cell carcinoma (HNSCC) treated with neoadjuvant afatinib. In a clinicoradiomic model, a clinical model, a radiomic model, and a model that combines both (clinicoradiomic) are compared. Radiomic analysis of two relatively small but independent multicentre clinical studies of 20 and 34 patients was performed, where each cohort served once as training and once as an external validation set. The clinicoradiomic performed best with validation concordance-indices of 0.71 and 0.82, respectively. Although assessed in two small cohorts, [^{18}F]FDG PET radiomics seemed promising for the prediction of overall survival in HNSSC.

Another [^{18}F]FDG PET clinicoradiomic model was created to identify peritoneal and distant metastases in 206 patients with locally advanced gastric cancer. Neither of the models could identify metastases with AUCs of 0.59, 0.51, and 0.56, for the clinical, radiomic, and clinicoradiomic model, respectively. Subgroup analysis of intestinal and mixed-type tumours resulted in poor AUCs of 0.67 and 0.60 for the clinical and radiomic model, and a moderate AUC of 0.71 in the clinicoradiomic model. However, this slight improvement in model performance does not outweigh the laborious radiomic analysis. Therefore, [^{18}F]FDG PET-based radiomics showed no added value compared to clinical characteristics in the analyses of the complete dataset, nor in the subgroup analyses of intestinal and diffuse type tumours.

Lastly, radiomic analysis was performed on 84 [^{18}F]FDG-positive nodules of the EfFECTS trial, a randomised controlled multicentre trial on the efficacy of [^{18}F]FDG PET/CT in thyroid nodules with indeterminate cytology, with the goal to improve the preoperative differentiation of indeterminate thyroid nodules. With an AUC of 0.45, [^{18}F]FDG PET/CT radiomics did



Figuur 1. Handcrafted and deep learning radiomic pipeline. A: In the handcrafted pipeline predefined features are extracted from a manually or (semi)automatically defined volume of interest (VOI). Feature selection or dimension reduction is performed and these features are consecutively introduced in a statistical or machine learning model. B: Deep learning radiomics does not require VOI delineation, but processes the images in their raw form. The deep learning architecture consists of several hidden layers including convolutional and pooling layers, that extract increasingly complex features and perform feature selection and classification.

not contribute to the preoperative differentiation of [^{18}F]FDG-positive nodules.

Conclusion

In conclusion, this thesis contributes to a deeper understanding of the methodological aspects of handcrafted radiomics in [^{18}F]FDG PET/CT, specifically in small datasets. However, most radiomic papers present proof-of-concept studies and clinical implementation is still far away. At some point in the future, radiomic biomarkers may be used in clinical practice, but at the moment we should acknowledge the limitations of the field and try to overcome these. Only then, we will be able to cross the translational gap towards clinical readiness. Future research should focus on standardisation of feature selection, model building, and ideally a tool that implements most or all of these aspects. In such a way, radiomics may redeem the promise of bringing forth imaging biomarkers that contribute to precision medicine. ♦