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# Radiomics in PET imaging: a practical guide for newcomers

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## **Synopsis**

Radiomics has undergone considerable development in recent years. In PET imaging, very promising results concerning the ability of handcrafted features to predict the biological characteristics of lesions and to assess patient prognosis or response to treatment have been reported in the literature. This article presents a checklist for designing a reliable radiomic study, gives an overview of the steps of the pipeline, and outlines approaches for data harmonization. Tips are provided for critical reading of the content of articles. The advantages and limitations of handcrafted radiomics compared to deep learning approaches for the characterization of PET images are also discussed.

**Keywords (3-8):** Radiomics, PET, texture, heterogeneity, harmonization

### **Key points (3-5):**

- In the literature, promising results report links between the radiomic feature values measured on PET images and the biological characteristics of lesions, patient prognosis and response to treatments.
- Each step in the radiomic analysis pipeline influences the feature values and should be carefully reported to allow other teams to reproduce the findings.
- Harmonization methods will play a key role in the development of radiomic models using heterogeneous data and in their deployment for multicenter validation.
- Deep learning methods can be used to extract new features and could bring a new and complementary perspective to current engineered features.

**Technical terms:**

1. Artificial Intelligence
2. Biomarker
3. Cohort
4. Dataset
5. Deep learning
6. Discretization
7. Feature
8. Handcrafted
9. Harmonization
10. Heterogeneity
11. Histogram
12. Medical images
13. Model
14. Multicenter
15. PET
16. Quantification
17. Radiomics
18. Shape
19. Texture
20. Validation

**Must read:**

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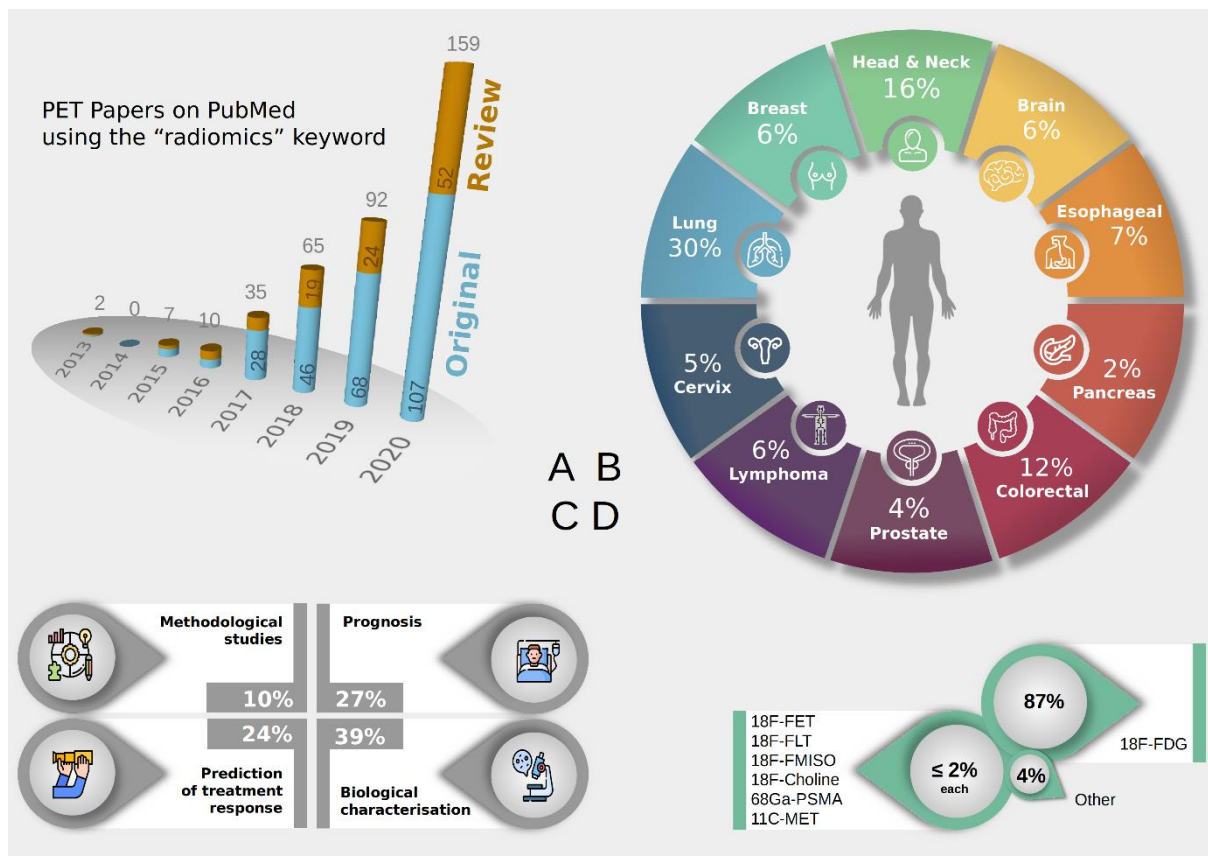
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## Introduction

The term “radiomics” was first introduced in 2010 by Gillies et al.<sup>1</sup> and was later defined as “*the conversion of digital images into mineable high-dimensional data*”<sup>2</sup>. The analysis of these high-dimensional data is intended to provide information on the biological characteristics of tumors, patient prognosis or the response to treatments. These data can reflect the signal intensity distribution, texture or shape of the signal in a given volume of interest (VOI) in the image. Although the term “radiomics” is relatively new, many studies have reported on advanced image analysis in the past and investigated the relationship between sophisticated measurements and biological characteristics. For instance, even before the 2000s, authors were studying the relationship between fractal analysis and striatal dopamine uptake<sup>3</sup> and the use of a co-occurrence matrix to classify lung nodules<sup>4</sup>. Since 2007, the Quantitative Imaging Biomarkers Alliance (QIBA) working groups have also published recommendations “*to advance quantitative imaging and the use of imaging biomarkers in clinical trials and clinical practice*”<sup>5</sup>. Among the 2,970 papers associated with the keyword “radiomics” on PubMed (between 2012-01 and 2020-12), 424 mention PET imaging (Figure 1). These articles mainly concern oncologic applications regarding the lungs (30%), the head and neck (16%), the esophagus (7%), breast cancer (6%) and lymphoma (6%). In these articles, the authors investigated the relationship between radiomic feature values and the biological characteristics of the lesions (39%), patient prognosis (27%) or the response to treatments (24%). In these papers, features were mainly extracted from PET images obtained after injection of 18F-fluorodeoxyglucose (18F-FDG, 87%) but also using other radiotracers such as 18F-fluoroethyl-L-tyrosine (18F-FET, 2%), 11C-methionine (11C-MET, 2%) and 68Ga-prostate-specific membrane antigen (68Ga-PSMA, 2%). A small proportion of articles (10%) report methodological contributions regarding the impact of acquisition and reconstruction parameters of PET images and of the different steps of the radiomic analysis pipeline on feature values based on phantom and/or clinical data.



**Figure 1:** Main characteristics of the published radiomic studies in PET imaging from a search using the keywords "radiomics AND PET" on PubMed (between 2012-01 and 2020-12). A) Number of original papers and reviews per year. B) Percentage of papers according to the organ studied in cancerology. C) Question of interest studied in the papers. D) Distribution of papers according to the tracer used.

Many reviews published in recent years (30% of the papers published in the radiomics field) have explained the potential of radiomics in medical imaging and the current limitations, and interested readers might want to refer to those<sup>6-8</sup>. However, when starting a radiomic study, many practical questions arise.

First, it is important to realize that radiomics includes two approaches. The first approach consists of extracting "handcrafted" features from the images, where handcrafted features refer to features obeying a precise mathematical definition, such as SUVmax, metabolic volume, sphericity or entropy. The resulting radiomic feature values are then used to perform statistical tests relevant to the task of

interest or as an input for a multivariate classifier, most often designed using a machine learning approach, such as the logistic regression, support vector machine, or random forest.

A second approach consists of using images or image VOIs directly as input to a neural network, such as a convolutional neural network (CNN), to obtain a classification or a prediction. This approach can be called deep radiomics as it still treats the images as high-dimensional mineable data (each voxel is an input variable); however, the radiomic features are no longer predefined when using handcrafted features but are learned by the CNN itself as a function of the input images and of the task.

Deep radiomics can also consist of extracting "deep" features using a CNN and then providing these features to a classifier<sup>9,10</sup>. Alternatively, deep radiomics first involves the calculation of radiomic parametric images using the definition of handcrafted features and then inputs these maps into a deep neural network. In short, deep radiomics will be used thereafter anytime a deep neural network is used in a certain step of the radiomic pipeline.

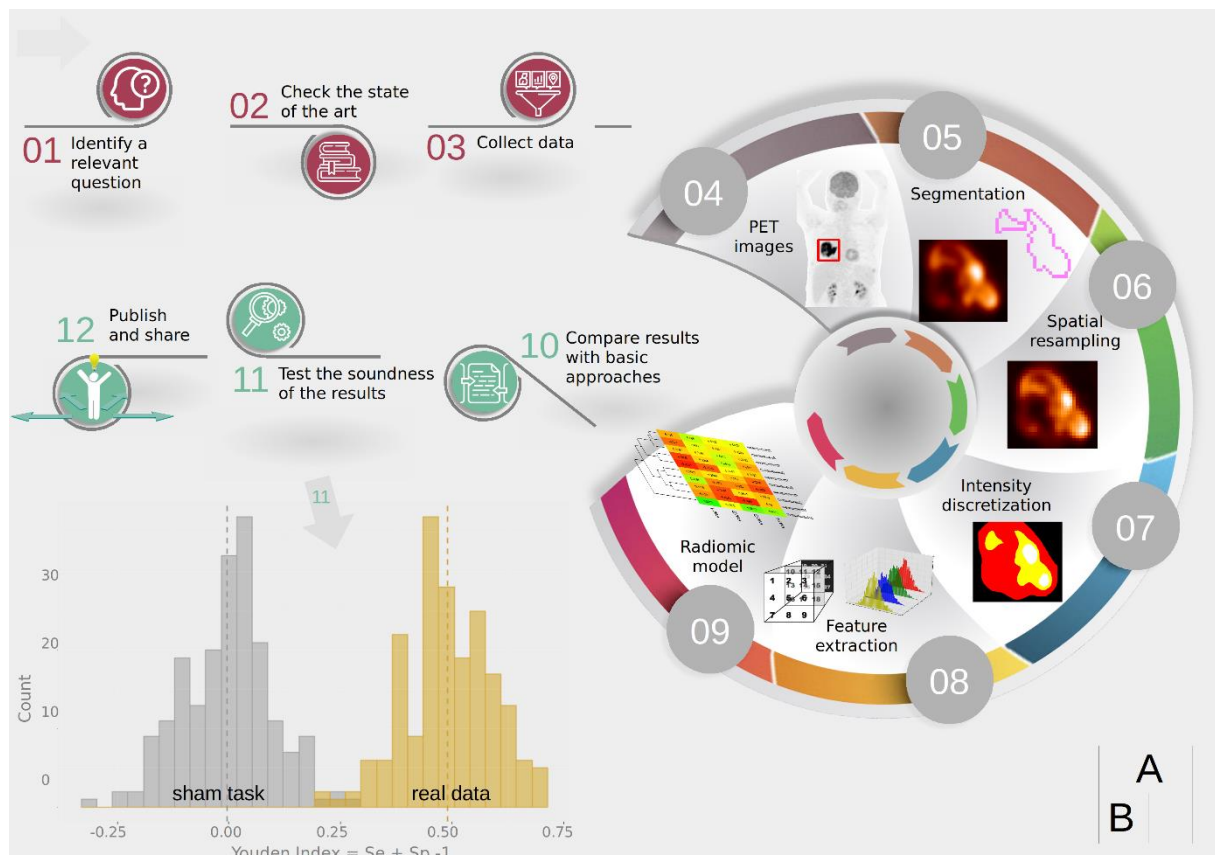
The difficulty for physicians to precisely quantify heterogeneity, the lack of intra- and interobserver reproducibility, and the challenge of coanalyzing many pieces of information at the same time are all arguments in favor of radiomics. Several studies have proven that radiomic indices can quantify the heterogeneity perceived by physicians<sup>11,12</sup> and that the macroscopic phenotypes measured from images are related to the density and spatial organization of cells at the microscopic scale<sup>13-15</sup>. Despite the indisputable potential of radiomics in PET, no model has yet proven its superiority over existing methods based on common features (e.g., SUVmax or metabolic volume) in multicenter and multicohort settings and by different independent investigators. To produce sound radiomic models amenable to clinical translation, a thorough understanding of the impact of the choices made in each step of a radiomic study is absolutely necessary.

Therefore, the main objective of this paper is to offer a practical guide to help interested readers establish a radiomic study involving PET images and "handcrafted" features. In addition, we discuss

key aspects to consider when analyzing the literature in this field. Finally, we explain how deep radiomics can complement handcrafted radiomics.

### Checklist to design a reliable radiomic study

Before initiating a radiomic study, a number of questions should be considered to determine if the study is relevant and feasible. Here, we list the major points to be examined (Figure 2).



**Figure 2:** A) Checklist for a reliable radiomic study. B) Sham test: comparison of the performances using real labels and randomly assigned labels to test the significance of findings.

### **1) *Identify a relevant question***

As with any scientific study, the question of interest will determine the impact of the investigation. From a clinical point of view, the question of interest may relate to patient management (for instance, the prediction of patient response or survival) or to a better understanding of a disease (for instance, the distinction between different molecular subtypes from phenotypic data). The level of performance that would make the radiomic approach appealing compared to state-of-the-art approaches should be indicated or, alternatively, the reason why a radiomic approach would be desirable. From a physics point of view, the goal might be to better understand radiomics or the factors that can influence feature values and/or to propose corrections or improvements for enhanced radiomic models. The relevance of the question and the contribution of the investigation should be carefully inspected based on a bibliographic search.

### **2) *Review the state-of-the-art***

In radiomics, there is at least as much value in confirming a previously published result as in establishing a new model<sup>16</sup>. As obvious as this may seem, the first instinct should be to review the existing literature on the subject of interest to determine whether the question has already been addressed by others and how. In particular, it is useful to know if a clinical question has already been investigated using conventional features (for instance, SUVmax, metabolic volume, and total lesion glycolysis) and which added value is expected from the use of more sophisticated radiomic features. If a clinical question has already been dealt with using radiomics, the first step could be to try to reproduce the findings. Indeed, at the moment, although hundreds of radiomic models are published, publications that independently validate radiomic models published by others are scarce, if they even exist<sup>16</sup>. This lack of reproducible results is certainly the greatest bottleneck for advancing the field, and it is an essential prerequisite for clinical translation.

### **3) Collect data**

Once the question of interest has been identified and well defined, the availability of the data needed to conduct the study with the expected statistical power should be checked. Needless to say, the data should comply with the legislation regarding data privacy (for instance, it should be GDPR-compliant in Europe). When collecting the data, the inclusion/exclusion criteria should be precisely defined and later clearly reported in any publication. In the vast majority of cases, images alone are insufficient; and additional data has, such as that on age, sex, cancer subtype, comedication, and treatment, have to be accessible and collected as these factors can influence the measurements made from the images. For example, the age of patients can influence the radiomic feature values measured in breast cancer lesions<sup>17</sup> and thus be a confounding factor. For supervised learning, a ground truth or surrogate ground truth must be available and can be based on histological analysis (e.g., subtype and the presence of mutations), radiological evaluation (e.g., response to treatment evaluated via RECIST) or follow-up (e.g., recurrence, progression-free survival, and overall survival). In practice, this ground truth might be imperfect, especially when it is derived from a physician's diagnosis, and this might influence the performance of the model and its generalization.

The quantity of images needed for a specific investigation does not obey a simple rule. It depends on the difficulty of the task, the complexity of the mathematical model and the approaches used (handcrafted or deep radiomics). If the biological signal is weak or the data have high heterogeneity, several hundred or even thousand patients may be needed. If the biological signal is well reflected by the radiomic features, fewer than 100 patients might be sufficient to build and validate a handcrafted radiomic model using cross-validation<sup>18</sup>. Moreover, the required number of images may grow when several hundred radiomic features are investigated to account for an increased false discovery rate. A downsampling strategy can be used to obtain some insights into how the performance evolves as a function of the number of patients and the number of patients needed to achieve a given performance<sup>19</sup>. Overall, as the definition of handcrafted features is fixed, a smaller number of patients

is typically needed in handcrafted radiomics compared to when designing models based on deep features. In deep learning, a recent meta-analysis<sup>20</sup> for detecting disease from medical images reported that all sound and well-validated models were built using cohorts involving at least 800 patients.

#### ***4) Include a comparison with basic approaches***

Even when the question of interest has not been addressed or reported previously, a good practice is to always compare and report the performance of a radiomic model with that obtained using current approaches that may involve visual analysis (for instance, the visual 4-point “Lizarraga” scale for brain tumors<sup>21</sup>) or when building a model based on usual PET features such as SUVs and/or metabolic volume only.

#### ***5) Test the soundness of the results***

To ensure the stability of the results, the investigators should check if the findings remain similar when using slightly different statistical methods. Indeed, if information relevant to the task is actually captured by some radiomic features, it is unlikely that it can only be found using a single model or a single set of features<sup>22</sup>. Using a cross-validation design when building a model is a good approach to select the model and test the stability of the results as a function of the validation fold and makes it possible to compare the consistency of the models identified based on the different training sets. This procedure can be repeated several times (eg, using so-called nested cross-validation) in order not to be biased by the random drawing of the folds. When using cross-validation, once the average performance and their variability have been characterized based on the different folds, the final model should be retrained using all the patients of the training set to be later deployed. The practice of “cherry picking”, which consists of carrying forward only the best results obtained with a single approach while omitting contradictory results obtained with a slightly different approach, is strongly discouraged. The reliability of a set of results or of a model should ideally be tested by evaluating the model on an independent dataset, i.e., on data that have neither contributed to the model design nor been kept aside from the original dataset. It is recommended that these data be external data, i.e.,

acquired on a different device or from a different center to validate the performance in slightly different conditions, to better demonstrate the validity of the findings. Another useful evaluation approach is to test the extensive model building or data analysis pipeline using sham data<sup>19</sup>. This involves randomly assigning the real labels to the actual data and comparing the performance with that obtained when the labels are correctly assigned. For this approach to be informative, the complete analysis process should be applied to the sham data (including the feature selection process, if any), and several sham datasets (corresponding to several random drawings) should be used so that the statistical distribution of the relevant figures of merit can be determined in sham conditions. The figures of merit measured on the real data can then be compared to those statistical distributions to establish the significance of the results (Figure 2). Other approaches such as image simulations<sup>11,23</sup> can be used to check the robustness of the results and/or the interpretation of features.

The use of a hypothesis-driven approach can help to minimize false discovery. For example, this is the case when a new feature is designed to quantify a characteristic perceived by physicians as predictive or prognostic (for instance, the quantification of the presence of severity of a necrosis in a tumor). The investigation of the biological plausibility of a radiomic model by deciphering the information reflected by the different features and the associated weights improves the confidence in the results. The use of unsupervised feature selection methods, test-retests, or studies investigating the influence of segmentation methods can eliminate irrelevant or insufficiently robust variables and thus reduce false discoveries.

## **6) *Publish and share***

A scientific study should be replicable, and its impact will actually depend on the ability of independent researchers to confirm the findings. To make that possible, the steps used to produce the results should be precisely described (see below), and the images (or extracted radiomic feature values) and/or the algorithm could be shared whenever possible. If the source code does not have to be shared, an executable or information regarding how to access a prototype implementing the model

can be sufficient. This allows colleagues to challenge and hopefully confirm the results on the same data or test the classification or prediction model independently on other data. The huge importance of data sharing was recently well illustrated by Welch et al.<sup>23</sup> who were able to demonstrate the spurious interpretation of a previously published prognostic signature through an independent reanalysis of the data provided by the authors.

Sharing the data and methods should prompt the investigators to clearly define the limitations of their findings, including the description of the situations in which they expect their model to fail or conclusions not to be true. Reporting negative results is essential to avoid the misuse of algorithms or excessive generalization of results<sup>16</sup>.

### **How to read an article reporting a radiomics study**

As in any scientific discipline, reading an article in the radiomics field calls for the reader's critical sense. The Materials & Methods section is as important as if not more important than the results and scrutinization of the supplemental data is often needed to avoid misinterpretation. The reader should in particular pay attention to whether the data are homogeneous (well defined patient cohort, same acquisition protocol for all patients, same treatment, etc.) and, if not, to the strategy implemented to rule out or account for possible confounding factors caused by that heterogeneity. The validation approach used in the paper should be examined carefully to determine whether the corresponding results support the claim. The positioning of the results with respect to clinical practice or previous work addressing the same topic should be reported so that the findings are put into perspective. Last, whether the conclusion can be checked by others will actually determine the impact of the findings.

Recently, a Radiomic Quality Score (RQS) has been proposed to assess the quality of radiomic studies<sup>24</sup>. This score, including 16 criteria related to the acquisition protocol up to data sharing, is provided in order to *“both reward and penalize the methodology and analyses of a study, consequently encouraging the best scientific practice”*<sup>24</sup> according to the authors. However, this score does not

necessarily reflect the reliability of the results and of their interpretation. Indeed, the study by Aerts et al.<sup>25</sup> had a score of 55.6% according to <sup>26</sup>, which is higher than all other papers mentioned in this article (range: [0-50%]). However, it was still highly biased, including a spurious interpretation of the findings<sup>23</sup>. Other checklists not specifically dedicated to radiomic studies, such as Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis (TRIPOD)<sup>27</sup> and Checklist for Artificial Intelligence in Medical Imaging (CLAIM)<sup>28</sup> for example, can also be considered when conducting radiomic studies, as they include good practice rules that are also very relevant to radiomic studies.

Therefore, the best way to judge the quality of a radiomic study is to become familiar with the various steps of the pipeline and to understand their influences on the results. We thus explain these different steps hereafter.

### **Handcrafted radiomics**

A handcrafted radiomics pipeline can be described using five steps. The investigator builds a database of medical images, and VOIs are defined. This is followed by a spatial resampling step and an intensity discretization step (except for shape features) before the calculation of radiomic features (Figure 2). As many different practices have been reported in the literature<sup>29</sup>, an international consortium named the Image Biomarker Standardization Initiative (IBSI) involving 25 teams<sup>30</sup> has been established to precisely define the different options for each step and provide benchmark data to check that different radiomic software programs provide the same value for specific well-defined features. This standardization step remains a fundamental prerequisite to ensure that the calculated radiomic values follow a reference standard that others can replicate. The IBSI has produced a reference guide<sup>31</sup> with definitions of features and has listed most options for the preprocessing steps. Reference to this guide is then extremely useful to explain how a specific step (e.g., interpolation) in the radiomic feature calculation process is performed. However, based on this guide, it may be difficult to choose the optimal setting among all the available options since it depends on the type of medical images that are

analyzed, the device used, the imaging protocol, the type of cancer, and the question of interest. Many methodological choices remain the responsibility of the investigator. Based on our experience and the data from the literature, here we present some guidelines to perform radiomic analysis in PET.

- ***Segmentation***

There is no consensus regarding how the structure of interest should be segmented before subsequent radiomic analysis<sup>32,33</sup>. However, it has been widely demonstrated that radiomic features are sensitive to the segmentation method used<sup>34–38</sup>, with an intraclass correlation coefficient that can vary from 0.0 to 1 depending on the segmentation methods and the radiomic features. For the sake of reproducibility, it therefore seems preferable to use an automatic or semiautomatic method rather than manual segmentation. In addition, the impact that the segmentation method has on the radiomic model performance should be systematically analyzed, unless the radiomic features involved in the models have already been demonstrated not to be sensitive to the region delineation (eg, SUVmax).

In tumor imaging, the primary tumor is usually segmented, and radiomic analysis is performed using this single VOI. However, extending the radiomic analysis to the peritumoral area (sometimes called ring) at the interface between the lesion and the surrounding healthy tissue<sup>39</sup> to possibly capture relevant information related to the tumor environment has been proposed. When multiple tumor sites are present, there are no rules as to how to combine the radiomic features measured in different lesions, and specific features reflecting the distribution of lesions can then be extracted<sup>40,41</sup>.

In cancer patients, there is an increasing interest in studying metabolism and its heterogeneity in “healthy” organs, especially lymphoid organs, to determine whether such features might actually provide valuable information to prognostic or predictive models. This is often performed by locating a small volume of a fixed size (on the order of a few ml) in the organ of interest, such as the liver, spleen, bone marrow or adipose tissue, to derive radiomic features<sup>42</sup>.

To reduce the variability in radiomic feature values due to the VOI definition, the rule of thumb is to use the same strategy for all patients in the cohort (e.g., the same threshold corresponding to 40% of

SUVmax or the anatomical contour based on CT or MR images). When this is not possible, the influence of the difference in VOI delineation should be considered in the analysis of the results. For biological characterization (e.g., to distinguish between tumor subtypes), focusing on the tumor VOI may be sufficient. Conversely, if the objective is to predict the response to treatments (especially in the case of immunotherapy) or the survival of the patients, considering radiomic features measured in organs other than the tumors might be useful<sup>43</sup>.

- ***Spatial resampling***

For example, when the algorithm uses neighboring voxel values to compute a texture feature, it is implicitly assumed that the voxels are isotropic, that is, that all the neighbors of a voxel are located at the same distance in the three directions. Spatial resampling is thus needed when this is not the case. This makes the extraction of textural features rotationally invariant. In addition, the size of the voxels strongly influences the values of some features<sup>44,45</sup>. Therefore, feature values should be compared only if they are calculated from images with the same voxel size. Spatial resampling involves interpolation, such as nearest neighbor, trilinear, tricubic convolution, and tricubic spline interpolation; and the choice of the method influences the feature values<sup>46</sup>. For this resampling step, there is no single best option. For instance, if the voxel size in the original image is 1x1x3 mm<sup>3</sup>, it is possible to resample them to 1x1x1 mm<sup>3</sup>, 2x2x2 mm<sup>3</sup> or 3x3x3 mm<sup>3</sup>, but it would not make sense to resample to 0.1 or 10 mm. The rule of thumb is to choose the same isotropic voxel size with the same interpolation method for all patients in the cohort. After a resampling strategy is used and a successful model is validated, it is always recommended that whether the model performance is highly dependent on the resampling settings be checked.

- ***Intensity discretization***

Intensity discretization is a mandatory step to calculate some radiomic features in order to group close gray levels together to reduce the impact of noise. In the literature, two techniques are mostly used: relative discretization, corresponding to setting the number of gray levels or bins; and absolute

discretization, corresponding to setting the bin size. This step greatly influences the values of the features<sup>47,48</sup>, and it is important to understand what each approach implies. The relative discretization consists of grouping the gray levels in a fixed number of bins between the minimum (SUV<sub>min</sub>) and maximum intensity (SUV<sub>max</sub>) of each lesion:

$$R(x) = \text{floor} \left( NBin \times \frac{I(x) - SUV_{min}}{SUV_{max} - SUV_{min}} \right) + 1$$

where R(x) is the resampled value in voxel x, I(x) is the value in voxel x in the original image, and NBin corresponds to the number of bins.

For example, let us consider two lesions with uptakes between 3 and 7 SUV for lesion 1 and between 2 and 12 SUV for lesion 2 (Figure 3). Setting the number of bins to 4, after discretization with the relative method, lesion 1 has 4 bins of size 1, and lesion 2 has 4 bins of size 2.5. The first bin corresponds to uptake between 3 and 4 SUV for lesion 1 and uptake between 2 and 4.5 for lesion 2, so a bin number does not encompass the same SUV range for all lesions.

The absolute discretization consists of grouping the gray levels in bins of a fixed size between two bounds (Bound<sub>min</sub> and Bound<sub>max</sub>):

$$R(x) = \text{floor} \left( NBin \times \frac{I(x) - Bound_{min}}{Bound_{max} - Bound_{min}} \right) + 1$$

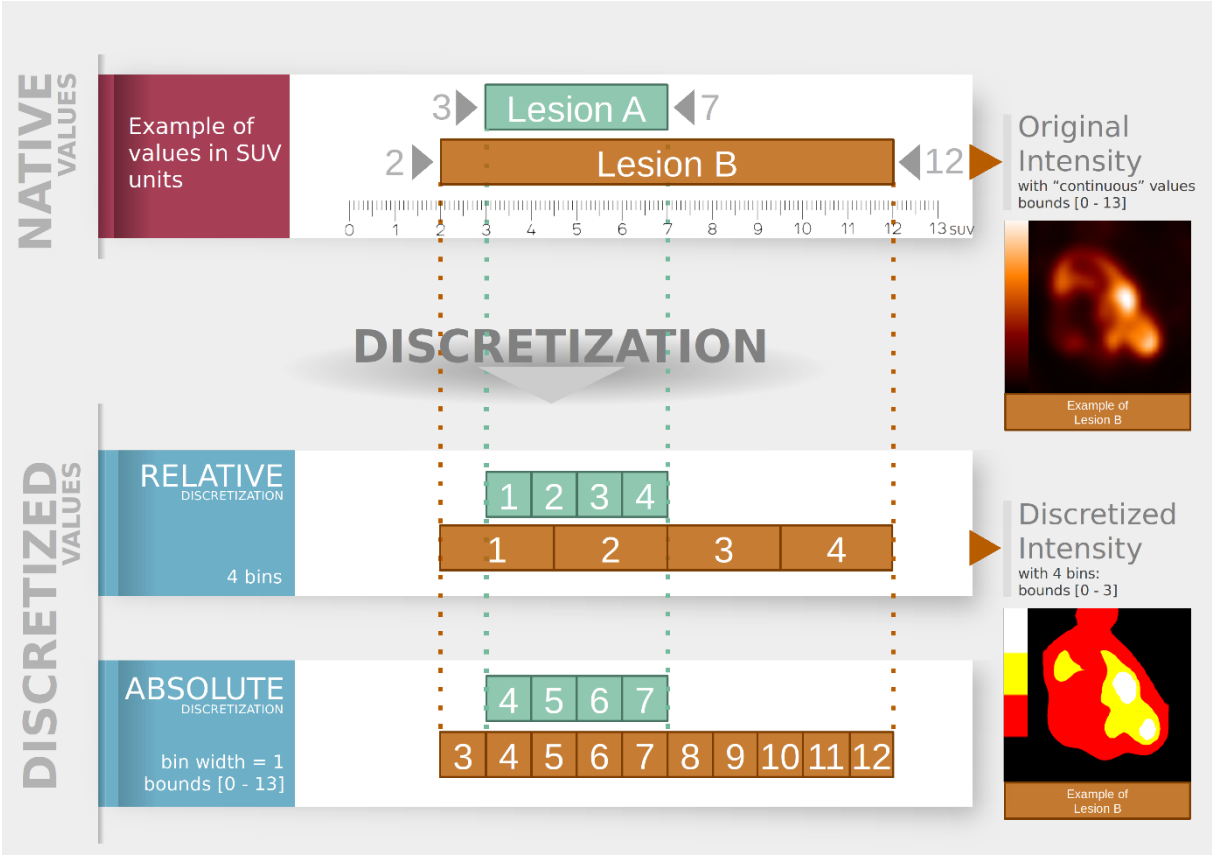
The number of bins and the bin size are related by the following equation:

$$Bin \text{ size} = \frac{Bound_{max} - Bound_{min}}{NBin}$$

Using the previous example, if the bin size is set to 1 between 0 and 13 SUV, lesion 1 has 4 bins of size 1, and lesion 2 has 10 bins of size 1 (Figure 3). Therefore, a bin number corresponds to the same SUV range for all lesions. For instance, bin 4 corresponds to an uptake between 3 and 4 SUV for all lesions.

These two methods lead to different correlations of the radiomic feature values with the metabolic volume or SUV. In<sup>48</sup>, VOIs were segmented in a homogenous phantom, lung lesions and healthy liver

tissue. With relative discretization, the entropy values are highly correlated with metabolic volume and are not different between the three regions (phantom, lung lesion and liver region), whereas visually, the heterogeneity is quite different. With absolute discretization, the entropy values are different between the three regions (with higher values for the tumor than for the liver tissue and higher values in the liver compared to the phantom), and the features are much less dependent on the volume but are more correlated with SUVs. As seen from this example, in PET, features calculated using absolute discretization thus better reflect visual impression. The choice of the bin size influences the results<sup>44</sup>. A trade-off must be found between the quantification of the heterogeneity and the influence of noise. For instance, in PET images, a difference in 0.01 SUV unit is meaningless, so using a bin size of 0.01 SUV unit does not make sense. We therefore recommend, for example, setting the bin size to 0.3 SUV unit between 0 and 20 SUV units (representing 64 bins) or between 0 and 40 SUV (i.e., 128 bins) if some lesions have a SUVmax greater than 20. The rule of thumb is to use the same range and bin size for all patients.



**Figure 3:** Intensity discretization consists of converting continuous values into discretized levels. Two approaches are commonly used: relative discretization, which sets the number of bins (for instance, number of bins = 4); and absolute discretization, which sets the width of the bin (for instance, bin width = 1). Here, we illustrate the discretization step for two lesions (A and B) whose intensities vary between 3 and 7 SUV and 2 and 12 SUV, respectively, before discretization.

- **Handcrafted features**

The calculation of the radiomic features is performed in the segmented region after spatial resampling and intensity discretization, except for “native” features that do not need any binning to be calculated, such as the SUVmax, SUVmean, SUVpeak intensity features, or the Metabolic Volume (MV) or Total Lesion Glycolysis (TLG). The goal is to quantitatively characterize the intensity distribution of voxel values, the shape of the VOI and the spatial relationship between voxel values within the VOI. To do this, three types of features can be used.

So-called shape features include the volume, the surface of a region of interest and its sphericity or compactness. In the case of the segmentation of several tumor volumes, it is possible to characterize the spatial distribution of tumor foci using dedicated features, by measuring, for example, the distance between the two most distant foci<sup>41,49</sup> or the volume of the bounding box including all segmented tumors<sup>40</sup>. These features are much less dependent on the acquisition and reconstruction parameters than first- or second-order features. However, some of them are highly dependent on the segmentation method.

The first-order or histogram features describe the distribution of values of individual voxels without accounting for spatial relationships. The histogram features are therefore not textural features. From the histogram, the minimum, maximum (different from the SUVmax, obtained before intensity discretization), mean (respectively SUVmean), median, first quartile, third quartile, standard deviation, skewness, kurtosis, energy and entropy can be calculated, among other values.

The third category corresponds to textural features. They describe spatial interrelationships between voxels with similar (or dissimilar) values. In the literature, four matrices are often used: the gray-level co-occurrence matrix (GLCM), gray-level run length matrix (GLRLM), gray-level zone length matrix (GLZLM) and neighborhood gray-level dependence matrix (NGLDM). All these matrices were initially designed to be computed for 2D images. To extend their use to 3D volumes of interest, several options are possible, as listed in the IBSI guide; and the most common option consists of calculating 13 matrices in 13 directions (to cover all space without redundancy), extracting the features from each of the matrices and then taking the average of the 13 values. As texture analysis consists of studying the relationships between voxels, small lesions composed of only a few voxels can be a challenge. Some authors recommend not performing texture analysis below a certain volume (5, 10 or even 45 ml)<sup>50-52</sup> because below this cutoff volume, the features would mostly depend on the volume and would not reflect the texture. Other authors do not set limits. What matters is the number of voxels and not the volume in ml because the algorithm does not consider the size of the voxels and only considers the number of voxels. If the VOI is 3 by 3 by 3 voxels, only the voxel at the center has 26 neighbors in 3 dimensions; therefore, it is the only voxel contributing to the computation of texture matrices in all directions. It might not be robust to calculate a texture based on 1 voxel only. We thus recommend calculating textural features in regions that contain at least 64 voxels, which corresponds to 4 by 4 by 4 voxels for cubic regions. When several VOIs are segmented for the same patient, the textural features can be calculated for each VOI independently or by merging the contributions of each VOI within the same texture matrices. The use of several VOIs in texture analysis is still marginal and does require special attention, as there is currently no best way to aggregate values measured in each VOI.

Finally, histogram and textural features can be calculated from the original images or after initial image filtering, such as using wavelets or Gabor filters. Given the number of possible wavelet and Gabor filters, such prefiltering considerably increases the number of calculable features. Few results using such filters on PET imaging are currently available<sup>53</sup>, and the definition of these filters is the subject of ongoing effort by the IBSI consortium.

- ***Radiomic models***

Radiomic feature extraction is usually followed by designing a model to solve a classification, prognostic or predictive task. Given the initially high number of features, a preliminary step of variable selection is often used to reduce overfitting and build more parsimonious models that might be easier to interpret in a clinical context and that also might better generalize to other data. Feature selection can be based on one or more of the following criteria:

- the redundancy: a single feature from a group of highly correlated radiomic features is selected or dimensionality reduction techniques such as principal component analysis can be used;
- the robustness of the features: by pre-selecting only radiomic features that have been previously shown to be robust with respect to different segmentation methods or based on test-retest studies for instance;
- the importance of the features for the task of interest: for instance, for a 2-group classification task, only radiomic features that are significantly different between the 2 groups (eg, p-value of the Wilcoxon test lower than 5%) can be retained (so-called univariate feature selection).

Feature selection can also be integrated into the training of the model, for instance using recursive feature elimination<sup>54</sup> or the Least Absolute Shrinkage and Selection Operator (LASSO)<sup>55</sup>.

A radiomic model can then be trained using different machine learning approaches such as Logistic Regression, Support Vector Machine, Random Forest or Neural Networks to mention just a few. The performance of the model often depends on the variable selection method and machine learning approach. For example, when designing a prognostic model using radiomic features extracted from CT images of head and neck cancer patients, Parmar et al.<sup>56</sup> observed an area under the ROC curve (AUC) ranging from 0.50 (un-informative model) to 0.79 (fair performance) when combining 13 feature selection methods with 11 classification methods. To compare several models and select the best performing, investigators can use different performance metrics such as the Akaike Information Criterion (AIC), the Bayesian Information Criterion (BIC), the accuracy (or balanced accuracy in case of

class imbalance dataset) or AUC measured on the test set. Each of these metrics has advantages and limitations, and there is no single one that should always be preferred. Different cross-validation techniques<sup>57</sup> can be used to assess the performances: leave-one out, k-fold or bootstrap for example. As mentioned above, the cross-validation procedures must be repeated several times in order not to be biased by the random selection of folds. Finally, at a similar or near-similar level of performance, a more parsimonious model may be considered preferable as it might be easier to interpret and possibly more generalizable on new data. For this purpose, it is possible to apply the "one-standard-error-rule"<sup>58</sup>, consisting in selecting the most parsimonious model (ie, the model with the lowest complexity) whose performance is no more than one standard error below that of the best performing model.

Given the different steps involved in radiomic feature calculation and the development of a radiomic model, it is necessary to report how radiomic features were calculated and combined (see Table 1) so that other teams can evaluate published radiomic models while ensuring they process the data as reported in the original studies.

<b>Minimum information to be provided</b>
<b>Name of the software, version number and IBSI-compliance (yes/no)</b>
<b>Segmentation method used</b>
<b>Interpolation method and voxel size (before and after resampling)</b>
<b>Discretization method (absolute or relative) and parameters (bin size and bounds)</b>
<b>Feature selection and classification method used including metrics on test set and cross-validation scheme</b>

**Table 1:** Checklist of information to be reported in radiomic papers.

Even when radiomic features are calculated in exactly the same way as described in a publication and using the same feature selection and classification method, the evaluation of a radiomic model on a different cohort of data often leads to different, often not as good, results. One possible reason might

be differences in the image properties (spatial resolution, contrast, and signal-to-noise ratio) that affect the feature values. This calls for addressing the issue of heterogeneous data.

### **How to manage heterogeneous data**

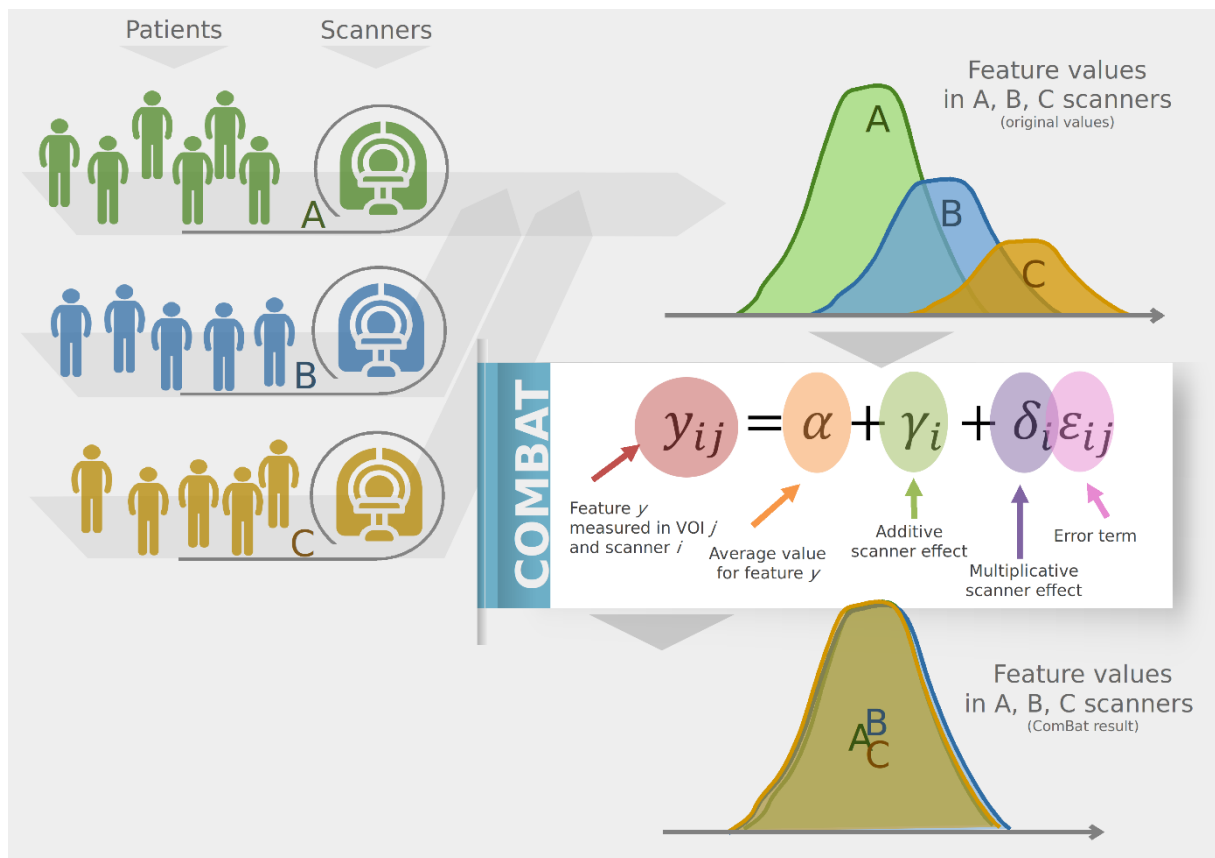
To increase the number of patients and hence the statistical power, pooling data from different centers or imaging protocols can be an option. However, feature values are sensitive to the acquisition and reconstruction parameters<sup>59-63</sup> such as the reconstruction algorithm, the number of iterations, or postreconstruction smoothing, if any. The consequence is that a radiomic model developed on data from one PET scanner applied to data acquired with another device of a different generation might not perform well<sup>64</sup>, especially when the model involves some features that are very sensitive to the center effect, such as the entropy. It is thus always useful to assess the impact of the center effect on the features involved in the model. This can be achieved easily using unsupervised analysis such as principal component analysis or by observing the statistical distribution of each feature in a reference region (e.g., cerebellum and healthy liver) where it is assumed to be the same for all patients wherever they have been scanned.

The way the center effect can be handled depends on whether the study is retrospective or prospective. In prospective studies, imaging protocols can be harmonized before data acquisition by following, for example, the EARL recommendations<sup>65,66</sup>. In retrospective studies, this is not always possible as this would require access to the scanners to perform phantom acquisitions. It is sometimes even complicated to access the images directly.

When the data cannot be harmonized prior to acquisition, the center effect should be accounted for in the statistical analysis, for example, by introducing a covariate. A method initially described in Genomics<sup>67</sup>, ComBat, can also reduce the center effect. ComBat was designed to correct for the batch effect, which is a technical source of variations caused by the handling of samples by different laboratories, different technicians and on different days. ComBat harmonization has then been used to normalize cortical thickness measurements from MR images<sup>68</sup>. In the radiomics field<sup>69</sup>, ComBat

assumes that the values of one feature are the sum of an average value, an additive scanner effect and a multiplicative scanner effect. ComBat estimates the model parameters using a maximum likelihood approach based on the set of available observations. ComBat thus determines one transformation for each feature separately and for each type of tissue (for instance, different transformations for tumors and healthy liver tissue). Schematically, ComBat consists of adjusting and translating a distribution so as to make the distributions overlap (Figure 4). ComBat has many advantages. The method is easily available and fast. The transformations are estimated based on the observed feature values without the need to return to images or to perform phantom experiments, and no learning set is needed. If the patient groups have different characteristics (for instance, different proportions of healthy subjects and diseased patients), the covariates of interest may be used in the ComBat method to account for this difference. A limitation of the method is that it is necessary to have at least 20 patients per batch or per imaging protocol to correctly estimate the transformations. Other approaches using Generative Adversarial Networks (GANs) in particular are currently under development<sup>70</sup>. These techniques that process the images (unlike ComBat, which only needs the feature values) aim to convert an image measured using a scanner into the same image but with image properties (noise, contrast, and spatial resolution) similar to those of images acquired using a different scanner (or protocol).

Even with careful feature extraction, the signal captured by handcrafted features may not be sufficient to answer the clinical question of interest. Deep features might be able to capture other types of information, as now discussed.



**Figure 4:** Harmonization using the ComBat method that realigns the distributions of feature values obtained in different centers considering additive and multiplicative scanner effects.

### Handcrafted vs deep features

The training of deep neural networks consists of iterative optimization of tunable network parameters. In this process, deep features that help recognize these salient and persistent patterns become encoded within the network. The type of features that the network learns is determined by the training data, neural network architecture, and optimization algorithm.

This ability to learn disease-relevant deep features from the data is what gives deep learning its power. In contrast to handcrafted features, automatic feature learning eliminates the need to perform feature engineering or selection for a particular task. Feature selection is replaced by the selection of a deep

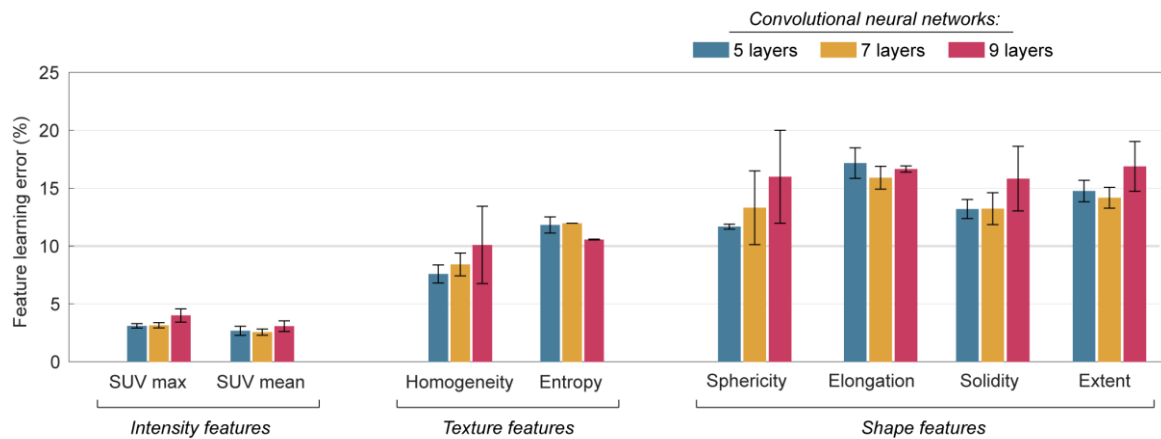
architecture. In addition, feature learning and predictive modeling can be performed in one step (referred to as “end-to-end” training). Another possible advantage of deep learning approaches is that neural networks might automatically identify the parts of the image that are most relevant for the task of interest; in more advanced architectures, this is achieved using the so-called “attention” modules<sup>71</sup>. Thus, there is no need to perform image segmentation prior to analysis, in contrast to handcrafted features where an ROI/VOI needs to be specified for feature extraction. The associated drawback is the need for added training data given the large collection of voxels being considered, as discussed below.

The limitations of deep learning features are closely related to their advantages. First, not having to perform feature selection comes at a price of requiring more data. Second, deep learning methods often require significant tuning to perform adequately. Moreover, learned features may not have a clear physical or biological meaning, so that the resulting model is often seen as a “black-box” without any simple interpretation. Yet, the black box aspect of deep features and associated networks should not be a show-stopper as more and more research is dedicated to providing means to decipher these complex models. In addition, these models might ultimately provide evidence of sophisticated information “hidden” in the data that could be turned into new hypotheses later amenable to testing using dedicated experiments. In fields other than nuclear medicine, model-agnostic interpretation methods have led to new discoveries, such as differences in the retina observed between men and women<sup>72</sup>, or the importance of areas previously ignored by experts that were found to have prognostic values (for instance areas within the stroma in pathological sections were found to have prognostic value for mesothelioma patients<sup>73</sup>). Finally, learned features may capture image characteristics that are not related to the diagnostic objective. For example, they may capture image properties related to a particular scanner or imaging protocol<sup>74,75</sup>. Algorithmic methods that can examine which image regions contribute to a decision produced by a neural network exist and will contribute to a better understanding of the models, although that sometimes produce unreliable results<sup>76</sup>.

Since deep features are determined in large part by a particular dataset, they are subject to population biases and may show poor descriptive performance when applied to a different dataset<sup>77,78</sup>. The relative generalization capacity between the deep and handcrafted radiomic features is still debated. In this context, the advantage of handcrafted features is that their computation can be standardized; however, no standards or standard libraries currently exist for deep radiomic features.

An important question to consider when planning an image analysis study is the relative expressive power of deep and handcrafted radiomic features. Theory suggests that deep neural networks have much greater expressive power than handcrafted radiomics. This follows from the universal approximation theorem<sup>79</sup> and implies that all handcrafted features are merely a small subset of deep radiomic features. However, despite theoretical considerations, some handcrafted features may be difficult for neural networks to learn in practice: there may be significant limitations with respect to the required number of training samples or the number of neurons in the network. In other words, simply because a neural network can act like any handcrafted feature does not mean that it can learn to do so from given data (it may need significant depth in its layers and/or significant training data).

Because datasets are limited in practice and neural networks have finite sizes, they may be biased to the types of deep radiomic features that can be learned from a given set of images. In a recent work, we trained CNNs to function like common handcrafted features of the tumor intensity, texture and shape<sup>80,81</sup>. In other words, we tested how well the deep networks can learn these features. We found that CNNs were negatively biased in capturing shape information (Figure 5). This finding may have significant implications for CNN-based quantitative medical image analysis since shape features represent an important subset of handcrafted radiomics<sup>30</sup>. Thus, deep features may not be as effective as handcrafted features at capturing and leveraging certain lesion properties that have previously been associated with clinical outcomes. Therefore, handcrafted radiomic features appear to be complementary to deep radiomic features rather than redundant – although additional studies in this area are needed.



**Figure 5:** Feature learning errors for CNNs with 5, 7 and 9 convolutional layers, expressed in % of the ground truth values of handcrafted features. The names of the tested handcrafted features are given on the x-axis. The CNNs were trained on 4,000 synthetic 2D PET images containing realistic lesions and tested on a separate set of 500 images.

Ultimately, the choice between handcrafted and deep radiomic features depends on the study objectives and data availability. Handcrafted features can be recommended for inference studies, where the objective is to establish a link between biologically meaningful features and a particular clinical metric. These studies can be performed with a relatively low number of samples, which can be determined based on the required power of the study. If a very large number of samples is available, deep radiomics might achieve higher performance than models based on handcrafted features.

## Summary

Radiomic analysis of PET images is a promising approach to extract subtler information and continuously evolves with advances in artificial intelligence. Using deep learning methods, new disease-specific deep features can also be learned directly from data and appear to complement conventional handcrafted features. However, in order to create models that can be clinically translated and benefit patients, investigators should be aware of the ins and outs of each step of the radiomic pipeline. Particular attention must be paid to the comparison of the results obtained with state-of-the-

art approaches and to the findings previously reported in the literature in order to advance knowledge in the field.

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