2 SPECT Radiomics: The Current Landscape, Challenges, and Opportunities

Faiq Shaikh and Francisca Mulero

2.1 Introduction

Radiomics as a medical image analysis technology is coming of age in the realms of clinical practice and clinical development. Quantitative image analysis has been used as a methodology to evaluate disease processes using medical images for a few decades now; radiomics is a newer approach that involves intricate feature extraction and classification techniques and leverage sophisticated statistical approaches, such as machine learning (ML). Standard structural imaging modalities, such as computed tomography (CT) and magnetic resonance imaging (MRI), were first to be used for radiomic analysis efforts and still comprise the majority of scientific work being done in this space. More recently, a significant body of scientific literature has been accumulating for radiomics performed on positron emission tomography (PET) images. Meta-analysis of these early PET studies has shown that radiomic analysis lacked in reproducibility given its high sensitivity to variations in voxel size, segmentation and reconstruction algorithms used, which is why standardized uptake value (SUV) still remains the gold standard for PET signal measurement [1]. Single photon emission computed tomography (SPECT) is another functional imaging modality where radiomics can play a role in extracting more information than what meets the eye. However, there are concerns with the reproducibility and reliability of SPECT-based radiomic analysis similar to those seen with PET. This is both a challenge and an opportunity. And while AI-driven approaches, of which radiomics is one, can be very promising for all imaging, including SPECT, the challenges related to data availability, annotation, and medicolegal considerations thereof need to be addressed for the application of radiomics to become mainstream [2]. In this chapter, we review the landscape of the recent efforts in SPECT radiomics and discuss the challenges and opportunities that abound its applications in clinical practice and development.

2.2 Radiomics as a Methodology

Conceptually, radiomics is an analytical process of using medical images to extract microstructural or "microfuncitional" information by extracting data from each boxes, which may then be useful for disease classification, stratification, therapy response assessment, and prognostication. In that sense, it is a non-invasive alternative to molecular and other histopathology-based disease assessments. Developing imaging-based biomarkers for these purposes is a sophisticated process that

F. Shaikh (✉)
Advanced Imaging, Image Analysis Group, Philadelphia, PA, USA

F. Mulero
Molecular Imaging, Centro Nacional de Investigaciones Oncologicas (CNIO), Madrid, Spain
e-mail: fmulero@cnio.es

H. Ahmadzadehfar et al. (eds.), *Clinical Applications of SPECT-CT*,
https://doi.org/10.1007/978-3-030-65850-2_2

involves choosing the right medical images and employing adequate ML approaches that deliver useful radiomic signatures of clinical significance. Typically, these radiomic signatures are based on the morphology and tissue heterogeneity, but when using functional modalities, such as PET and SPECT, these signatures provide insights into the physiologic or biochemical processes and perturbations there of [3]. AI/ML models developed for radiomic analysis are improving in their accuracy and predictive power when compared to conventional interpretive approaches. Radiomics is being considered as a potential quantitative analysis methodology to be applied to SPECT imaging in the realm of neurologic, cardiac, oncologic, and immunologic diseases [4].

The basic steps involved in the radiomics methodology (see Fig. 2.1) are as follows:

- *Image acquisition*: This is the first step in this process. In most settings, radiomic analysis can be performed on medical images acquired as per standard clinical protocols. However, modified protocols that render higher spatial resolution or "richer" raw data can be useful. The main concern is to have a standardized acquisition protocol across the cohort in order to minimize variations in the feature extraction process [1]. Furthermore, post-acquisition processing, including filtering techniques and iterative reconstruction, should also be standardized in order to minimize inter- and even intra-centre variability. Filtering techniques are used to improve results [1].
- *Lesion detection and segmentation*: This is a key requisite step in this methodology. It is critical to identify the right lesion(s) and segment them in a way to include the whole lesion while removing the surrounding or background tissue [5]. The process of segmentation may be manual, whereby a radiologist identifies the lesion and drawing a region/volume of interest (ROI/VOI). Alternatively, it may be semiautomated, whereby the lesion is manually selected and the algorithm identifies its boundaries and draws a VOI. There are also fully automated segmentation software programs that can identify the lesion and draw an ROI/VOI. All these

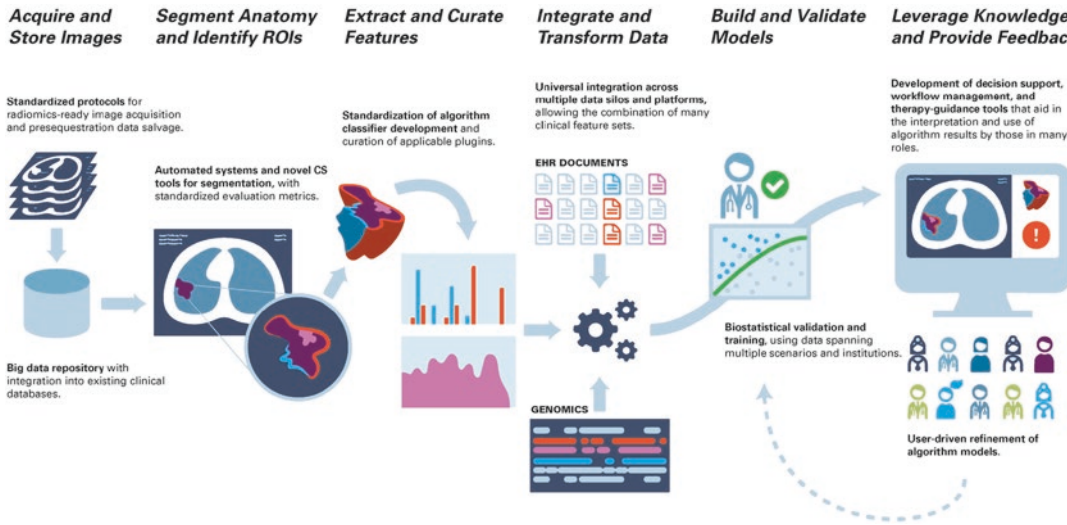

Fig. 2.1 Typical radiomics workflow. The basic steps include image sequestration and preacquisition data salvage, data transfer and repository maintenance, image segmentation, feature extraction and classification, covariance matrices and data modelling, integration into clinical decision support systems, and biostatistic and outcome analysis. ROI, region of interest. (Used under CC license from Technical Challenges in the Clinical Application of Radiomics. Faiq A. Shaikh, Brian J. Kolowitz, Omer Awan, Hugo J. Aerts, Anna von Reden, Safwan Halabi, Sohaib A. Mohiuddin, Sana Malik, Rasu B. Shrestha, Christopher Deible. JCO Clinical Cancer Informatics. 2017;1:1–8.)

methods allow for manual readjustment to ensure correct lesion demarcation with human oversight. Whichever method adopted, precise, consistent, and accurate segmentation of all lesions is critical for a reliable and reproducible delta radiomics assessment.

- *Feature extraction*: This is the core step of the radiomics technique in which a large set of features (which are mathematically determined based on the values within a voxel) are extracted from these images. The size of the feature set depends on the modality, and there are a variety of libraries available for each. The radiomic signatures can be created using features extracted in a "pre-engineered" or "handcrafted" fashion or through a "black-box" approach that depends on ML [6–8]. Radiomic features are based on the morphology, histogram, or texture analysis. These features may be semantic (providing description about shape, size, tissue relation to surrounding material, surface area and volume) or agnostic (providing histograms and texture-based features). These extracted features are highly variable, and feature reduction is applied to reduce redundancy. LASSO (least absolute shrinkage and selection operator) is a regression analysis technique that performs variable selection and regularization to improve prediction and accuracy and can be employed in this step to extract a smaller subset of features that is more likely to yield the radiomic signature of interest [8]. Second-order radiomic analysis has been most commonly applied across all modalities as it provides valuable information regarding the local spatial distribution of voxel values, calculating local features at each voxel within the in-plane image and deriving parameters from the distributions of the local features. A number of texture features can be derived that provide a measure of intralesional heterogeneity.
- *Feature classification and model development*: The extracted radiomic features are "raw data" that needs to be classified into signatures of statistical value. These signatures are critical in the development of non-invasive biomarkers that can quantify tissue-level changes otherwise not visualized in the medical image. Correlation heat maps of the extracted radiomic features are created and those with high variance are used (see Fig. 2.2). Feature classification is performed

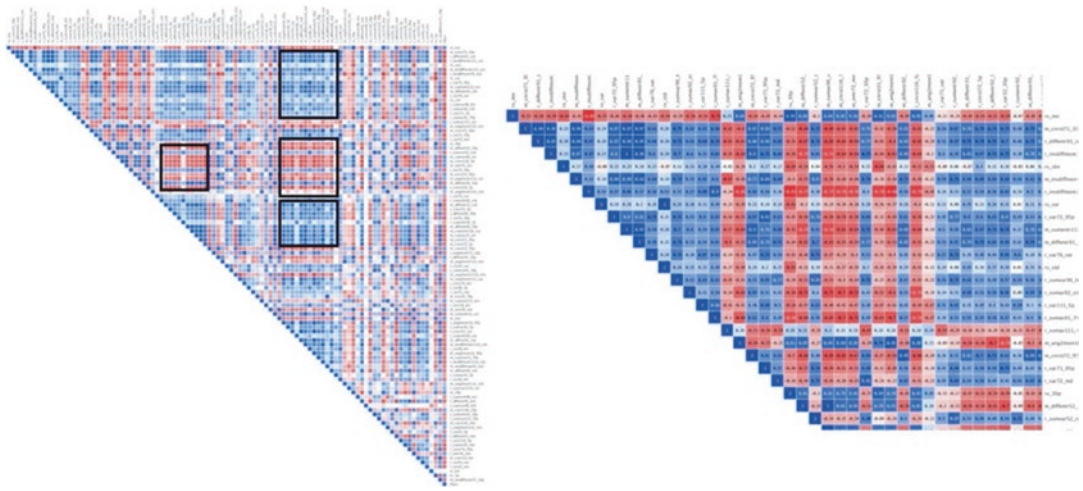

Fig. 2.2 Correlation analysis heatmap showing blocks of highly correlated radiomic features (black frames on the left and positive with red color or negative correlation with blue color on the right). When identifying such groups of highly correlated features, all but the one with the highest variance are removed from further analysis. In this case, the correlation coefficient was set to 95%. (Used under the creative commons license from Papanikolaou N, Matos C, Koh DM. How to develop a meaningful radiomic signature for clinical use in oncologic patients. Cancer Imaging. 2020;20:33.)

using computational techniques that can involve machine learning approaches, such as random forest (RF) or support vector machine (SVM). In scenarios with complex data (from radiomics and other non-radiological sources), more complex techniques, such as convolutional neural network (CNN) or deep learning neural network (DLNN), may be employed to derive insights for important go/no-go decisions or predict/assess therapy response [9]. These algorithms need to have high accuracy rates when tested using a test set. The true "test" of a radiomic model is the assessment of its performance across various centers in a clinical trial or practice. While radiomic models cannot be fully transferable to all types of populations and disease subtypes, it should have reasonable applicability in similar clinical settings, using similar equipment and protocols, and in relatable cohorts.

2.3 Clinical Application of Radiomics Using SPECT

2.3.1 Oncologic SPECT Radiomics

While still niche, the most salient application of SPECT radiomics has been in the field of oncology. This trend follows the momentum seen in the realm of PET radiomics. As SPECT plays an important role in the clinical management of a number of malignant diseases, radiomics-based studies have been performed with encouraging results in this space. The main areas of potential application of SPECT radiomics in oncology would be:

- Disease detection and classification.
- Clinical course prediction and prognostication.
- Therapy response prediction/assessment.
- Complimenting or as an alternative to nonimaging biomarkers.
- Pharmacokinetic and pharmacodynamic assessment for the clinical development of novel therapeutics.

Technetium-99 m albumin nanoparticle studies are performed for the evaluation of primary and secondary hepatic malignancies in clinical practice. Radiomic analysis of these scans has been performed that yielded signatures consisting of skewness, kurtosis, and distribution histograms to study the intra-tumoral tissue heterogeneity [10] (see Fig. 2.3). This enables qualitative and quantitative assessment of pathophysiologic processes, such as fibrosis, necrosis, metaplasia, and vasculogenesis. This, in turn, allows for quantification of the extent of cirrhosis, metastatic potential, or response to therapy. The hepatic tissue density changes detected through radiomic analysis can prove to be a harbinger of liver tumors that would be otherwise detected at a later stage through conventional imaging methods. In small animal studies, radiomic approaches have been used to study the varying patterns of radiotracer distribution, which can help distinguish between healthy and tumoral livers, which can be helpful to assess the extent of invisible tumor burden in a patient [10]. Other related approaches in this domain include the radiomic analysis of Tc-99 m sulfur colloid SPECT to predict the Child-Pugh class in hepatocellular carcinoma (HCC) patients [11, 12].

These approaches have yielded promising results in animal models and can be potentially translated for clinical use eventually. In humans, a biomarker that quantifies hidden tumor burden in the liver can be a tremendously useful endpoint for patients with HCC as well as metastatic liver disease. Skewness is a direct imaging-based parameter that correlates with the inhomogeneous distribution of macrophage cells and can be quantified to show the altered tissue function even before the visual manifestation of liver tumor foci on standard imaging. This can be developed as a prognostic biomarker of malignant disease progression in HCC patients [10, 11].

Novel AI approaches have been introduced that use SPECT data in oncologic imaging interpretation. One such example is that of PSMA-AI that uses DLNN to anaylze and interpret PSMA-targeted Tc99m-MIP-1404 SPECT/CT images [13]. The results shows that PSMA-AI generated reproducible results and could compliment

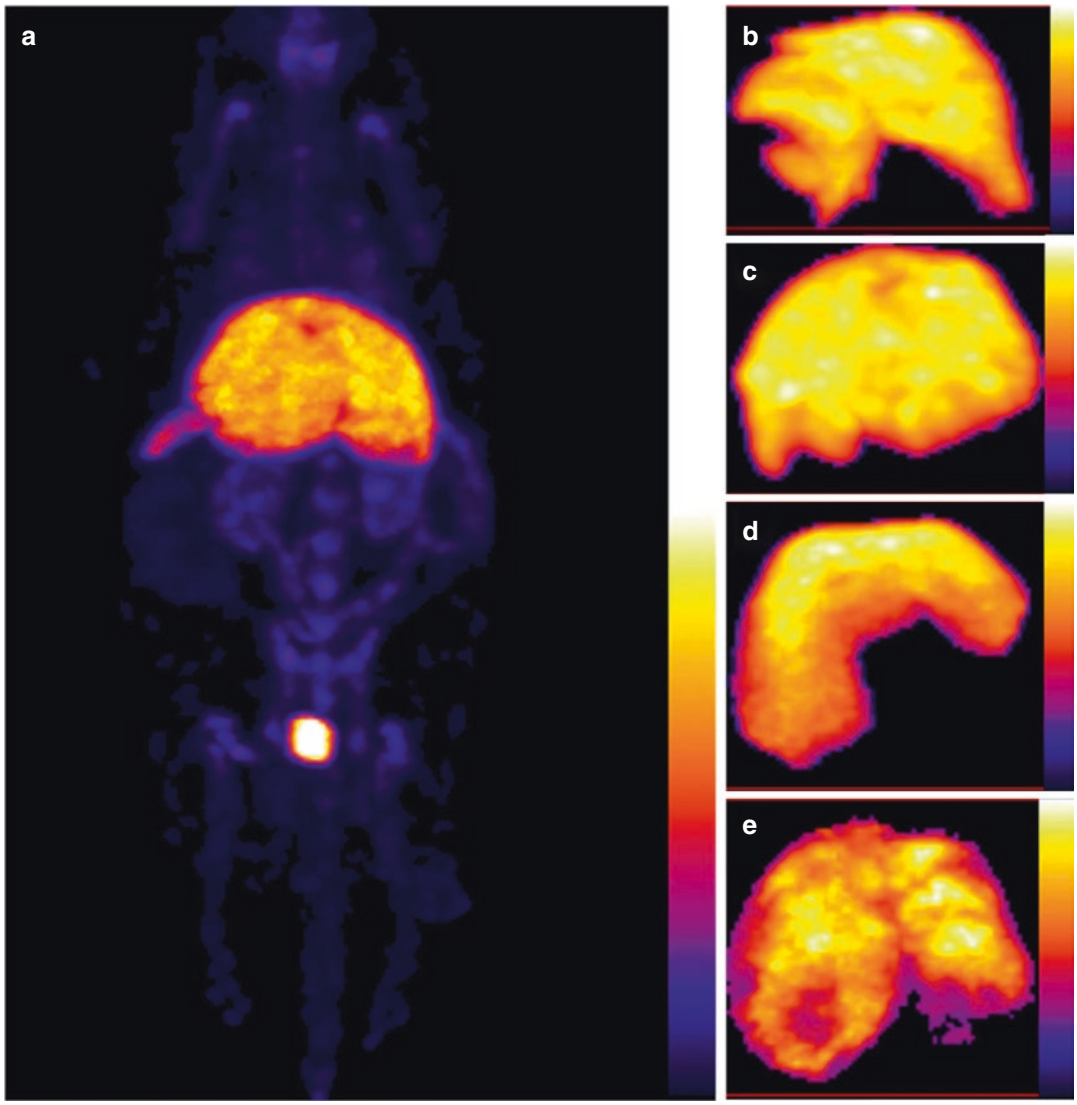

Fig. 2.3 The result of 99mTc-protein nanoparticle whole-body SPECT scan. b–e Selected projections of the segmented liver in control, obese, metastatic, and primary tumor groups, respectively, from top to bot (Used under Creative Commons license from Veres DS, Máthé D, Hegedűs N. et al. Radiomic detection of microscopic tumorous lesions in small animal liver SPECT imaging. EJNMMI Res. 2019;9:67.)

human interpretation. Radiomic analysis can be added in this approach as an additional layer of rich data generation that the PSMA-AI can use to improve its predictive values as compared to human interpretation.

Tc99m-Sestamibi SPECT/CT has been used to differentiate between oncocytomas (hot lesions) and renal cell carcinoma (cold lesions). Radiomic analysis of these cold spots has been performed in an attempt to differentiate between various subtypes of RCC [14]. While there were challenges related to mis-segmentation and high variation, this approach highlights the potential of radiomics for clinically performed SPECT studies.

SPECT imaging plays a critical role in the successful planning and monitoring of antibody-targeted radionuclide imaging and therapy (radioimmunotherapy). ^{111}In-ibritumomab tiuxetan is a SPECT agent that is used prior to the administra-

tion of ^{90}Y-ibritumomab tiuxetan radioimmunotherapy to determine eligibility for its treatment by determining whether there is sufficient and uniform antibody retention within the tumor. Features extracted using radiomic texture analysis that describe the relationships between gray-level intensity and position of pixels from these images can help assess the underlying biological complexity and tissue heterogeneity.

Longitudinal SPECT imaging is also used to monitor antibody biodistribution and dosimetry in patients. This has been performed in patients receiving anti-carcinoembryonic antigen (CEA) ^{131}I-A5B7 antibody in combination with the vascular disrupting agent (VDA), combretastatin A4-phosphate for gastrointestinal carcinoma [15]. Performing texture analysis on these SPECT images would allow the quantification of the heterogeneity of antigen distribution noninvasively, before and after therapy. This strategy can be useful in the clinical trials as it can speak to the resistance of some tumors to antigen-targeted therapy. It has been demonstrated in animal studies that texture analysis (using gray-level co-occurrence matrix feature extraction) of ^{125}I-A5B7 SPECT can show spatial heterogeneity variations of antibody distribution between well- and poorly differentiated liver metastases before antivascular treatment [16].

For radionuclide therapies of cancer, the concept of intra-tumoral heterogeneity is important as it can determine the treatment response to radionuclide therapy, especially when the bystander effect is required to kill neighboring cells that do not express the target. In a study using preclinical colon tumor models that express carcinoembryonic antigen (CEA), treatment response to ^{131}I-labeled anti-CEA antibody has been shown to depend on the vascular supply and CEA distribution [17].

2.3.2 Neurologic SPECT Radiomics

SPECT imaging has a number of applications in the management of neurologic diseases. For the radiomic analysis of neurologic SPECT images, the lesion identification and segmentation are performed on the MR images co-registered with the SPECT images.

Imaging of the dopaminergic system with ^{123}I-ioflupane-dopamine transporter (DAT) is a widely used SPECT study in the clinical workup for Parkinson's disease. DAT SPECT images are typically assessed visually; however, adding radiomics can provide a new set of information that can help predict clinical outcomes (see Fig. 2.4) [18]. Such a noninvasive biomarker could be useful for the purposes of prognostic assessment and would be crucial in designing clinical trials [19]. Radiomic models can provide a more accurate and objective alternative to the clinical metrics, such as (i) the UPDRS (part III—motor) score, disease duration as measured from (ii) time of diagnosis (DD-diag.) and (iii) time of appearance of symptoms (DD-sympt.), or (iv) the Montreal Cognitive Assessment (MoCA) score [19]. However, in order to do that, the radiomic models will require reference regions for normalization.

The radiomic features extracted from the caudate, putamen, and ventral striatum of DaTscan images at different timepoints of disease evolution could serve to quantify heterogeneity and texture in radiotracer uptake [20]. Quantifying feature eccentricity from the more affected ventral striatum may provide a useful predictor [20]. Thus, a combined approach involving standard SPECT interpretation and radiomic analysis performed on DAT SPECT imaging can improve the overall prediction of clinical outcomes.

Radiomics-based Haralick texture metrics extracted from striatal DAT SPECT have been shown to have a greater sensitivity to PD symptoms as compared to the routine mean uptake analysis [21]. These metrics may serve as a noninvasive imaging biomarker for disease progression.

These efforts in DAT SPECT radiomics are consistent with the aims of the Parkinson's Progressive Marker Initiative (PPMI), which emphasizes on the promotion of quantitative measurement and analysis of imaging used in the management of Parkinson's disease.

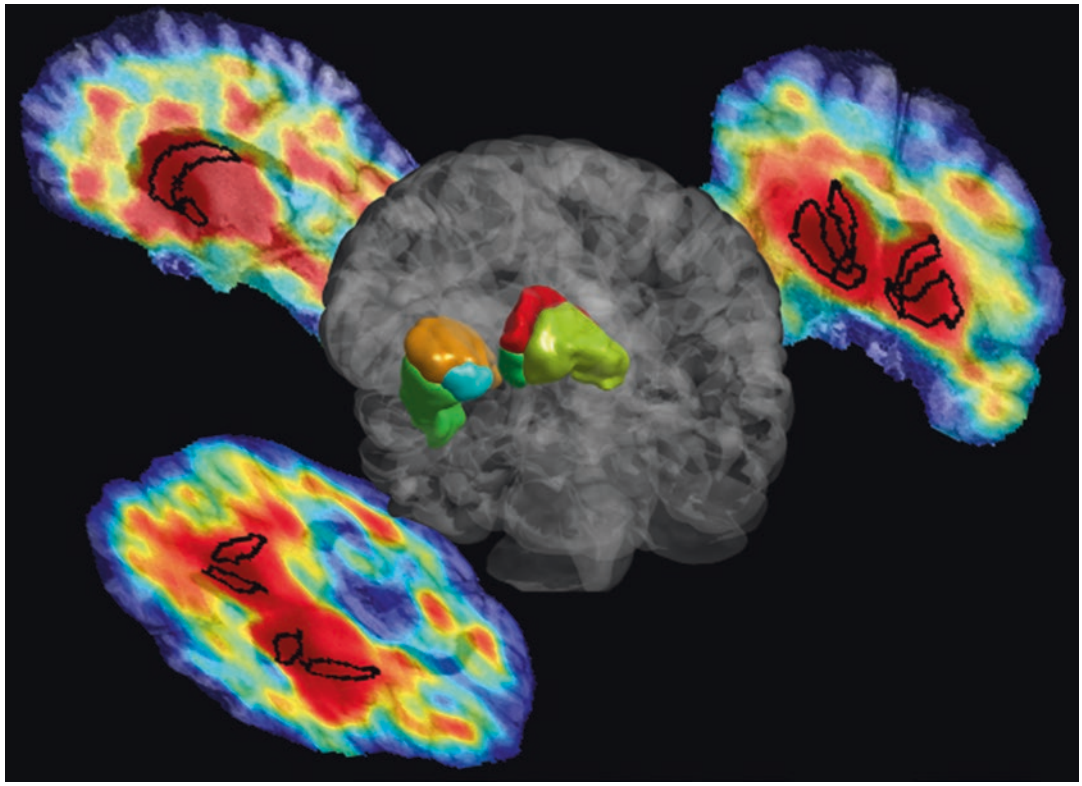

Fig. 2.4 3D volume rendering of six segmentations (caudate, putamen and VS; both right and left) for a typical study, as well as trans axial, coronal, and sagittal slices through the DAT SPECT image with superimposed segmentations. (Used under the Creative commons license from Rahmim A, Huang P, Shenkov N, Fotouhi S, Davoodi-Bojd E, Lu L, Mari Z, Soltanian-Zadeh, H, Sossi V. Improved prediction of outcome in Parkinson's disease using radiomics analysis of longitudinal DAT SPECT images. NeuroImage: Clinical. 2017 Jan 1;16:539–44.)

2.3.3 Cardiac SPECT Radiomics

Myocardial perfusion imaging (MPI) using SPECT is an established diagnostic test for patients suspected with coronary artery disease (CAD). 99mTc-Sestamibi is one of the preferred radiotracers used for this indication. Clinically, these studies are analyzed and interpreted manually with some support from a computer-aided diagnosis (CAD) program. Radiomics has the potential to improve the diagnostic and prognostic yield of MPI SPECT by way of providing biomarkers that correlate with perfusion heterogeneity [22].

In a standard MPI SPECT study, most features are not reproducible due to the low resolution. In studies where radiomic analysis was performed on MPI SPECT, it was observed that the most significant features were the intensity skewness and GLCM cluster shade for the right coronary artery (RCA), and intensity at 90% volume histogram for left circumflex artery (LCX). It has also been shown that left anterior descending artery (LAD) and RCA extracted from the vascular plot had more significant correlation than bull's eye plot, while LCX from the latter plot was noted to be more significant [23].

Radiomic analysis, regardless of the modality and indication, is highly sensitive to these factors, which impact the results even more profoundly in case of MPI SPECT. It is critically important to assess the robustness of cardiac SPECT radiomics features against variations in image acquisition and reconstruction parameters. For this purpose, the coefficient of variation (COV), which is a widely adopted metric, needs

to be measured for each of the radiomic features for all imaging settings. It has been noted that the repeatability and reproducibility of SPECT/CT cardiac radiomic features under different imaging settings are feature-dependent. The radiomic features that exhibited low COV against changes in all imaging settings included the Inverse Difference Moment Normalized (IDMN) and Inverse Difference Normalized (IDN) features from the Gray Level Co-occurrence Matrix (GLCM), Run Percentage (RP) from the Gray Level Co-occurrence Matrix (GLRLM), Zone Entropy (ZE) from the Gray Level Size Zone Matrix (GLSZM), and Dependence Entropy (DE) from the Gray Level Dependence Matrix (GLDM) [24]. Of these image acquisition parameters, matrix size has been found to have the largest impact on feature variability [24].

123-iodine meta-iodobenzylguanidine (^{123}I-mMIBG) SPECT imaging is a study performed clinically in the management of cardiomyopathy, and its interpretation is largely manual. However, texture analysis performed to study regional washout from non-infarcted tissue can improve the predictive capability of cardiac events using multivariate analysis of regional washout associated with territories adjacent to myocardial infarction [25]. In a study by Currie et al., artificial neural network (ANN)-based analysis was performed on the ^{123}I-MIBG images, and the calculated planar global washout of >30% was shown to be the best indicator for risk of cardiac event when accompanied by a decline in left ventricular ejection fraction of >10% [25]. This is encouraging for new ML-driven efforts (such as radiomics) for automated feature extraction from raw image datasets in nuclear cardiology.

2.3.4 Other Applications of SPECT Radiomics

Preclinical studies have demonstrated that changes in opacity in SPECT/CT with Tc-99 m-MDP can be used for the assessment of bone remodeling. One such study compared the increase of bone opacity and decrease of Tc-99 m-MDP activity variables [26]. Radiomics can be applied here to study bone healing, bone grafting, and bone replacement, which can improve the prognostic value of these studies (see Fig. 2.5).

Theranostics is a molecular imaging technique that involves specific molecular targeting for the purposes of diagnostics and therapy [27]. One example of a theranostic approach using ^{111}In/^{90}Y-ibritumomab tiuxetan has been described above (in the oncologic SPECT radiomics section). Visualization of the potential target for a specific therapeutic is a tremendously powerful tool that minimizes untoward effects and improves therapeutic efficacy. Radiomics approaches can increase the range of information revealing the tissue processes that can guide treatment and those that reflect changes secondary to treatment. This way, radiomics can impact both the diagnostic and therapeutic arms of theranostics, respectively. Texture analysis-based radiomic features can identify and target activity of the theranostic agents and study the cellular- and tissue-level changes induced by their action. Quantification of involved processes such as T-cell recruitment and resulting apoptosis/necrosis as features extracted from the SPECT study performed as a part of the theranostics can be highly useful in patient selection and therapy response assessment in clinical studies [28]. When using radiomics for such sophisticated approaches, which may involve multimodal imaging, it is important to implement image-quality harmonization and perform optimal integrative analysis (by choosing the right ML methods) [29].

2.4 Challenges and Opportunities of SPECT Radiomics

While reviewing the current landscape of radiomics-related work using SPECT, it becomes quite apparent that the field of SPECT radiomics is still in its infancy. Most of the studies are preclinical, using animal models. Furthermore, only a few indications within each specialty have been

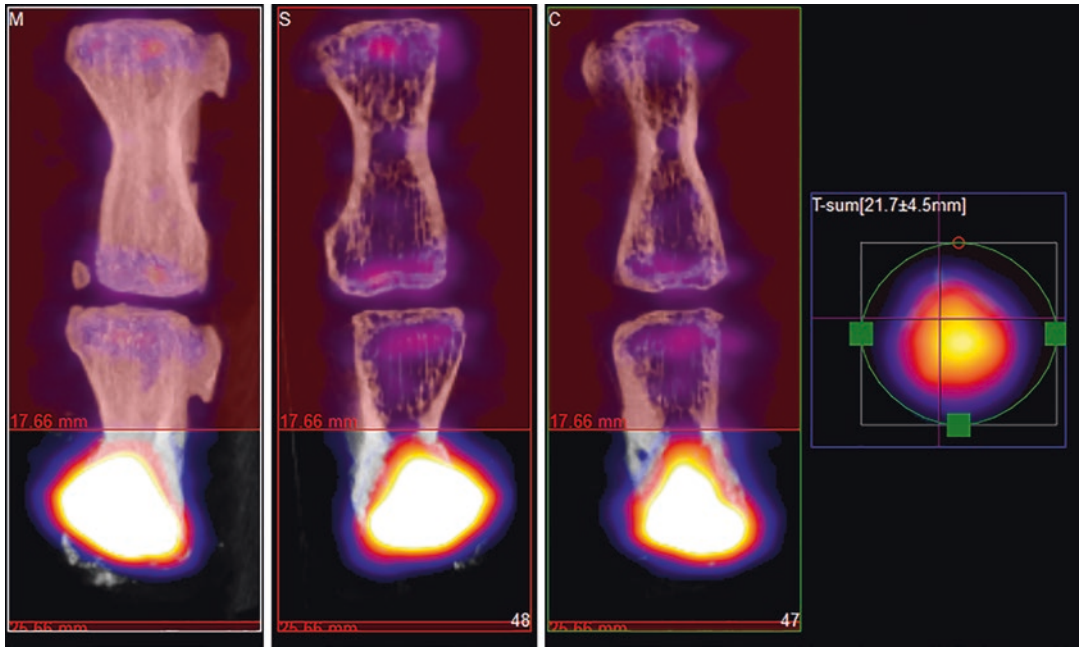

Fig. 2.5 Tc-99m-MDP activity in *caudal vertebrae* of treated rats after 8 weeks. The C5 *vertebrae* (down) were treated and filled with a bone graft which was selected as VOI in SPECT at 8 weeks after surgery. The color intensity shows the activity of Tc-99 m-MDP in the last region of *vertebra*. The upper bones are C4 control *vertebrae*. (Used under the creative commons license from Budán F, Szigeti K, Weszl M, et al. Novel radiomics evaluation of bone formation utilizing multimodal (SPECT/X-ray CT) in vivo imaging. PLoS One. 2018;13(9):e0204423. Published 2018 Sep 25. doi: https://doi.org/10.1371/journal.pone.0204423.)

the focus of such efforts. Having said that, the initial results are encouraging. Learning from the experience with PET radiomics, one can expect an expansion of the breadth and scope of such studies, both in terms of indications and technical advancements that will make SPECT radiomics ready for prime time in human studies and eventual clinical practice.

The main challenges in this path include the availability of high-quality data to develop such models. SPECT is not as ubiquitous in clinical use the way CT or even PET is. This poses a limitation in the development of ML-based radiomic models that require large training and validation sets. Another major challenge, which has been alluded to above, is that of the robustness of SPECT models being affected by the variations in the imaging parameters (related to acquisition protocol, scanner types, patient preparation, and other factors). This limits the way radiomics could be applied as a reproducible and reliable methodology across multiple centers with reasonably similar imaging parameters and patient populations. One way to address this problem is to design large-scale studies in which all variables are represented. This goes back to our initial challenge of data paucity for SPECT studies. However, smarter trial designs, multicenter collaborations, improved data liquidity and availability, and leveraging the power of AI can help overcome this challenge. Furthermore, designing radiomic models that address multimodal imaging (SPECT/CT, SPECT/MR) and other -omics (genomics, transcriptomics, metabolomics, pathomics, etc.) will improve the specificity and predictive values of these methods.

Having a well-articulated clinical question based on a real-world need and designing a radiomic methodology that attempts to answer thst question by using a rich data set is critical to the success of a radiomics-based application. Optimizing each step of the workflow, including

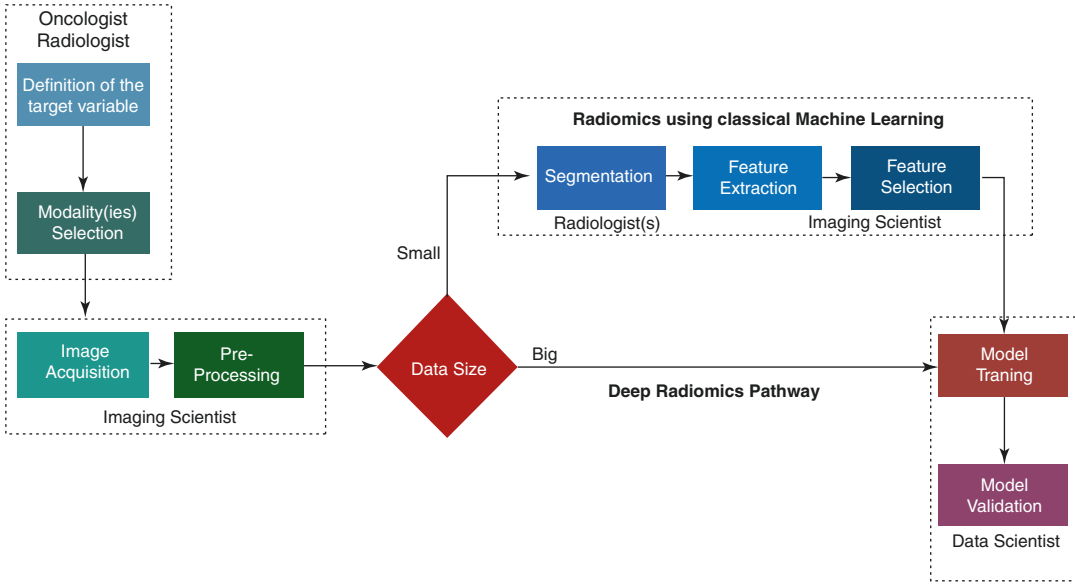

Fig. 2.6 A multidisciplinary radiomics workflow. Initially a group of clinicians should define the clinical problem that the proposed model should deal with and make decisions on what kind of imaging modalities should be recruited. Imaging scientists need to make sure that acquisition protocols are optimally designed producing high-quality images, as well as for the preprocessing of the images. Then depending on the size of the available imaging studies, we need to decide which pipeline to use. In case of big data (in the order of thousands), a deep radiomics approach can be suggested avoiding tedious and time-consuming processes like tumor segmentation by multiple radiologists. In addition, deep convolutional neural networks have been proven more efficient to model complex problems compared with traditional machine learning algorithms, as long as data availability requirement is satisfied. Finally, the data sets are allocated for training, validation, and testing purposes. (Used under the creative commons license from Papanikolaou N, Matos C, Koh DM. How to develop a meaningful radiomic signature for clinical use in oncologic patients. Cancer Imaging. 2020;20:33.)

preprocessing the data prior to analysis and applying the most suitable statistical/ML strategies, will render high accuracy rates (see Fig. 2.6) [30]. Testing these models in real-world is another key step that ensures that a radiomic model is ready for clinical use.

This is an exciting time to be involved in the fields of functional/molecular imaging and informatics, as recent and ongoing advancements have enabled us to merge these fields to devise advanced quantitative image analysis approaches that make help revive and promote modalities, such as SPECT in the era of precision medicine.

References

1. Zwanenburg A. Radiomics in nuclear medicine: robustness, reproducibility, standardization, and how to avoid data analysis traps and replication crisis. Eur J Nucl Med Mol Imaging. 2019;46(13):2638–55.
2. Aktolun C. Artificial intelligence and radiomics in nuclear medicine: potentials and challenges. Eur J Nucl Med Mol Imaging. 2019;46:2731–6.
3. Larue RT, Defraene G, De Ruysscher D, Lambin P, Van Elmpt W. Quantitative radiomics studies for tissue characterization: a review of technology and methodological procedures. Br J Radiol. 2017;90(1070):20160665.
4. Ibrahim A, Vallieres M, Woodruff H, Primakov S, Beheshti M, Keek S, Sanduleanu S, Walsh S, Morin O, Lambin P, Hustinx R. Radiomics analysis for clinical decision support in nuclear medicine. In: Seminars in nuclear medicine. WB Saunders; 2019.
5. Parmar C, Velazquez ER, Leijenaar R, Jermoumi M, Carvalho S, Mak RH, Mitra S, Shankar BU, Kikinis R, Haibe-Kains B, Lambin P. Robust radiomics feature quantification using semiautomatic volumetric segmentation. PLoS One. 2014;9(7):e102107.
6. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. Radiology. 2016;278(2):563–77.
7. Kumar V, Gu Y, Basu S, Berglund A, Eschrich SA, Schabath MB, Forster K, Aerts HJ, Dekker A, Fenstermacher D, Goldgof DB. Radiomics: the process and the challenges. Magn Resonance Imaging. 2012;30(9):1234–48.

8. Zheng B, Liu L, Zhang Z, et al. Radiomics score: a potential prognostic imaging feature for postoperative survival of solitary HCC patients. BMC Cancer. 2018;18:1148.
9. Parmar C, Grossmann P, Bussink J, Lambin P, Aerts HJ. Machine learning methods for quantitative radiomic biomarkers. Sci Rep. 2015;5:13087.
10. Veres DS, Máthé D, Hegedűs N, Horváth I, Kiss FJ, Taba G, Tóth-Bodrogi E, Kovács T, Szigeti K. Radiomic detection of microscopic tumorous lesions in small animal liver SPECT imaging. EJNMMI Res. 2019;9(1):67.
11. Schaub S, Hippe D, Bowen S, Wootton L, Chaovalitwongse W, Kinahan P, Apisarnthanarax S, Nyflot M. Radiomics of sulfur colloid SPECT/CT to predict child-pugh class in hepatocellular carcinoma patients. Med Phys. 2019;46(6):E174.
12. Bell M, Turkbey EB, Escorcia FE. Radiomics, radiogenomics, and next-generation molecular imaging to augment diagnosis of hepatocellular carcinoma. Cancer J. 2020;26(2):108–15.
13. Pouliot F, Sjöstrand K, Stambler N, Richter J, Gjertsson K, Johnsson K, Wong V, Jensen J, Edenbrandt L, Anand A. Prospective evaluation of a novel deep learning algorithm (PSMA-AI) in the assessment of 99mTc-MIP-1404 SPECT/CT in patients with low or intermediate risk prostate cancer, 2019.
14. Ashrafinia S, Jones K, Gorin MA, Rowe SP, Javadi MS, Pomper MG, Allaf ME, Rahmim A. Reproducibility of cold uptake radiomics in 99m Tc-Sestamibi SPECT imaging of renal cell carcinoma. In: 2017 IEEE Nuclear Science Symposium and Medical Imaging Conference (NSS/MIC). IEEE; 2017. p. 1–4.
15. Meyer T, Gaya AM, Dancey G, Stratford MR, Othman S, Sharma SK, Wellsted D, Taylor NJ, Stirling JJ, Poupard L, Folkes LK, Chan PS, Pedley RB, Chester KA, Owen K, Violet JA, Malaroda A, Green AJ, Buscombe J, Padhani AR, Rustin GJ, Begent RH. A phase I trial of radioimmunotherapy with 131I-A5B7 anti-CEA antibody in combination with combretastatin-A4-phosphate in advanced gastrointestinal carcinomas. Clin Cancer Res. 2009;15:4484–92.
16. Rajkumar V, Goh V, Siddique M, et al. Texture analysis of (125)I-A5B7 anti-CEA antibody SPECT differentiates metastatic colorectal cancer model phenotypes and anti-vascular therapy response. Br J Cancer. 2015;112(12):1882–7. https://doi.org/10.1038/bjc.2015.166.
17. El Emir E, Qureshi U, Dearling JL, Boxer GM, Clatworthy I, Folarin AA, et al. Predicting response to radioimmunotherapy from the tumor microenvironment of colorectal carcinomas. Cancer Res. 2007;67:11896–905.
18. Rahmim A, Huang P, Shenkov N, Fotouhi S, Davoodi-Bojd E, Lu L, Mari Z, Soltanian-Zadeh H, Sossi V. Improved prediction of outcome in Parkinson's disease using radiomics analysis of longitudinal DAT SPECT images. NeuroImage: Clin. 2017;16:539–44.
19. Adams M, Tang J. Convolutional neural network based motor score prediction using DAT SPECT imaging of Parkinson's disease. J Nucl Med. 2019;60(Suppl. 1):405.
20. Huang P, Shenkov N, Fotouhi S, Davoodi-Bojd E, Lu L, Mari Z, Soltanian-Zadeh H, Sossi V, Rahmim A. Radiomics analysis of longitudinal DaTscan images for improved progression tracking in Parkinson's disease. J Nucl Med. 2017;58(Suppl. 1):412.
21. Rahmim A, Salimpour Y, Blinder S, Klyuzhin I, Sossi V. Optimized haralick texture quantification to track Parkinson's disease progression from DAT SPECT images. J Nucl Med. 2016;57(Suppl. 2):428.
22. Ashrafinia S, Dalaie P, Yan R, Ghazi P, Marcus C, Taghipour M, Huang P, Pomper M, Schindler T, Rahmim A. Radiomics analysis of clinical myocardial perfusion SPECT to predict coronary artery calcification. J Nucl Med. 2018;59(Suppl. 1):512.
23. Ashrafinia S, Dalaie P, Yan R, Huang P, Pomper M, Schindler T, Rahmim A. Application of texture and radiomics analysis to clinical myocardial perfusion SPECT imaging. J Nucl Med. 2018;59(Suppl. 1):94.
24. Ashrafinia S, Ghazi P, Marcus CV, Taghipour M, Yan R, Valenta I, Pomper M, Schindler TH, Rahmim A. Robustness and reproducibility of radiomic features in 99mTc-Sestamibi SPECT imaging of myocardial perfusion. Med Phys. 2017;44(6)
25. Currie G, Iqbal B, Kiat H. Intelligent imaging: radiomics and artificial neural networks in heart failure. J Med Imaging Radiat Sci. 2019;50(4):571–4. https://doi.org/10.1016/j.jmir.2019.08.006.
26. Budán F, Szigeti K, Weszl M, et al. Novel radiomics evaluation of bone formation utilizing multimodal (SPECT/X-ray CT) in vivo imaging. PLoS One. 2018;13(9):e0204423. Published 2018 Sep 25. https://doi.org/10.1371/journal.pone.0204423.
27. Yordanova A, Eppard E, Kürpig S, Bundschuh RA, Schönberger S, Gonzalez-Carmona M, Feldmann G, Ahmadzadehfar H, Essler M. Theranostics in nuclear medicine practice. OncoTargets Ther. 2017;10:4821.
28. Keek SA, Leijenaar RT, Jochems A, Woodruff HC. A review on radiomics and the future of theranostics for patient selection in precision medicine. Br J Radiol. 2018;91(1091):20170926.
29. Ha S. Perspectives in radiomics for personalized medicine and theranostics. Nucl Med Mol Imaging. 2019;53:164–6. https://doi.org/10.1007/s13139-019-00578-x.
30. Papanikolaou N, Matos C, Koh DM. How to develop a meaningful radiomic signature for clinical use in oncologic patients. Cancer Imaging. 2020;20:33.