



Radiomics applied to lung cancer: a review

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Abstract: Lung cancers exhibit strong phenotypic differences that can be visualized noninvasively by medical imaging. Radiomics, a concept introduced in 2012, refers to the comprehensive quantification of tumor phenotypes by applying a large number of quantitative image features (watch the animation: <https://youtu.be/Tq980GEVP0Y> and the website www.radiomics.org). Here, we review the literature related to radiomics for lung cancer. We found 11 papers related to computed tomography (CT) radiomics, 3 to radiomics or texture analysis with positron emission tomography (PET) and 8 relating to PET/CT radiomics. There are two main applications of radiomics, the classification of lung nodules (diagnostic) or prognostication of established lung cancer (theragnostic). There are quite a few methodological issues in most of the reviewed papers. Only 5 studies, out of the 22, were externally validated. Overall, it is clear that radiomics offers great potential in improving diagnosis and patient stratification in lung cancer. It may also have a real clinical impact, as imaging is routinely used in clinical practice, providing an unprecedented opportunity to improve decision support in lung cancer treatment at low cost.

Keywords: Lung cancer; imaging; radiomics; theragnostic

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Introduction

Globally, lung cancer is the most frequent cause of death in men and the second most frequent cause amongst women in the USA (1). Past smoking patterns strongly influence actual cancer rates amongst both men and women and vary considerably due to geographical location, age, race, and socioeconomic status. There is a broad consensus that it is necessary to develop better biomarkers predicting treatment response or survival, in order to identify subgroups that would benefit from individualized treatment to improve the patient's outcome.

Most tumours do not represent a homogenous entity; they are composed of multiple clonal sub-populations of cancer cells. This heterogeneous complex needs to be analysed in order to tailor the cancer care to the patient and their tumour. One way of characterizing the tumour is by extracting tumour tissue in a tumour biopsy, the tissue is then characterised using genomics based approaches. Although these approaches have successfully been used in clinical oncology, there are intrinsic limitations; repeated tumour biopsies increase the risk of complications for the patients, in particular in lung cancer and the results may vary depending on which part of the tumour is biopsied.

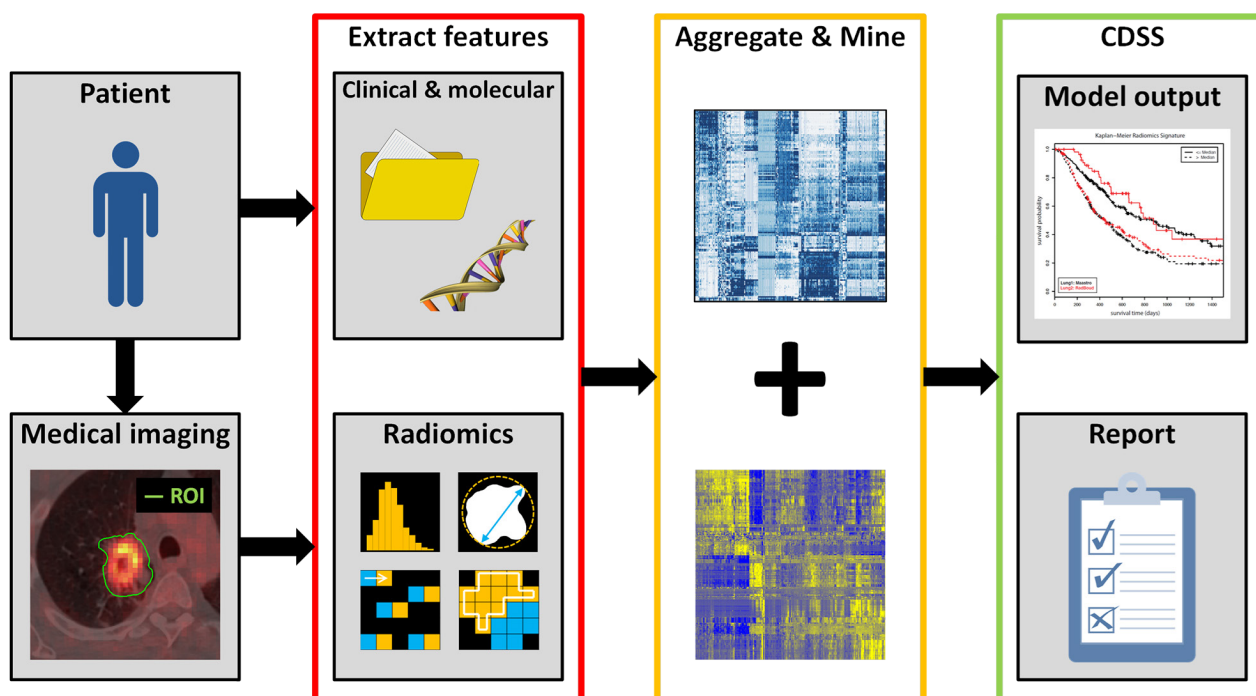


Figure 1 Overview of methodological processes in radiomics: data discovery, collection and preparation, model(s) development/validation and implementation, assessment of clinical utility.

These challenges can be addressed by medical imaging. Medical imaging is an important part of cancer care, it is essential to cancer staging and diagnosis. Unlike biopsies, it is noninvasive, three dimensional and provides information regarding the entire tumour.

Radiomics, first introduced by Lambin *et al.* (2) in 2012 and summarized in a two minute animation (<http://youtu.be/Tq980GEVP0Y>), is a process that converts standard of care images into minable high-dimensional data. The radiomics process can extract quantitative features from digital medical images, which can then be used to build descriptive and predictive models, linking the image features to the tumour's gene-protein signatures or the tumour's phenotype. As shown in recent studies, quantitative imaging features have a prognostic value and potential in predicting clinical outcomes or treatment monitoring in different cancer types (3-7). The aim of radiomics is to use these models, which can include biological or medical data, to help provide valuable diagnostic, prognostic or predictive information. radiomics aims to utilise the full potential of medical imaging by extracting and analysing large amounts of advanced quantitative imaging features, with high throughput from digital medical images, obtained

with computed tomography (CT), positron emission tomography (PET) or magnetic resonance imaging (MRI). This in turn provides a more detailed quantification of tumour phenotypic characteristics describing its intensity, shape, texture, intra-tumour heterogeneity and in doing so it effectively converts medical images into a high dimensional minable feature space.

Precision oncology is the customization of cancer care where therapies and/or practices are being tailored to individual patients, with all of the information about the tumour characteristics that radiomics provides; it presents numerous new opportunities for precision medicine.

In this paper we will review the literature and discuss the potential advantages and pitfalls of radiomics in lung cancer.

Work flow of radiomics

The radiomics process consists of three steps: (I) image acquisition and volume segmentation; (II) feature extraction and storage; (III) signature development and validation on one or several datasets (*Figure 1*) (2,8,9). Each of these three steps poses unique challenges, which will be introduced below. Once a signature has been developed and is applied on a specific patient, the process is the same except that

in step 3 the validated signature is used to determine the prognosis of the patient.

Image acquisition

Modern CT, PET and MRI scanners allow acquisition and reconstruction settings in a large range. Although this facilitates the subjective needs of the human expert, when the images are intended to be objectively characterized by a machine, these variations may create a bias that masks the true underlying biological characteristics. This phenomenon is well recognized in the field of radiomics and consequently, efforts are being made to standardize acquisition and reconstruction protocols. This advance in quantitative imaging is being led by several organizations or consortia such as the European Association of Nuclear Medicine (EANM), the QuIC-ConCePT project from the Innovative Medicine Initiative Joint Undertaking (IMIJU).

Volumes of interest

One of the central processes of radiomics is to identify one or several volumes of interest (the primary tumour, nodules, etc.) on diagnostic imaging. However, predictive value may lie in the detailed analysis of subvolumes within the tumour, also known as habitats. The heterogeneity within the tumour is due to particular combinations of blood flow, oedema, necrosis, and cell density, which creates a unique pathophysiology. Using radiomics, important additional information from these habitats as well as information from a normal healthy lung, can be extracted.

Segmentation

Segmentation or delineation plays a crucial role within radiomics, because the features that are generated depend on the segmented volumes. However, many tumours, as well as subvolumes, have ambiguous borders. This can lead to a significant inter-reader bias and low reproducibility when these volumes are manually delineated. Unfortunately, there is no universal automatic segmentation algorithm that can work for all medical images (10,11). Consequently, the consensus that emerges out of this debate is that the optimum reproducible segmentation can be obtained via semi-automatic segmentation, which consists of automatic segmentation followed by, if necessary, manual curation (12). The different image modalities have also their own segmentation methods. For CT, the region of interest (ROI)

represents for example the gross tumor volume (GTV), while for PET the metabolic target volume (MTV) is segmented as ROI. The segmentation method also depends on the endpoint of the study. Cheebsumon *et al.* (13) showed that CT-based delineation was overestimated compared to pathology while PET-based tumour delineation methods provided maximum diameters in closer agreement with pathology. They also showed that for example the contrast-oriented methods seem to best suited for assessing tumour size, while an adaptive 70% threshold-based method is better for response monitoring (13).

Feature extraction

The essential part of radiomics is the high throughput extraction of quantitative image features that characterize the volumes of interest. The number of features is enormous, more than 1,000, and complex, and this leads to the risk of overfitting. Overfitting exists when a model is specifically and exclusively optimized for the training dataset and consequently performs poorly on new data. To avoid overfitting, the ratio of the number of evaluated features to the number of outcome events must be kept as low as possible. To offset this risk, there is a key process of feature reduction and ranking. In order to do so, one approach consists in looking at robustness and reproducibility of features in test-retest datasets. The information extracted from two datasets of images acquired within a small period of time (few minutes to few days) from a single patient cohort is called test-retest data and is highly advantageous for ranking features thanks to their reproducibility and stability. Therefore, when coupled with robust segmentation, test-retest data should be exploited whenever possible. Another complementary approach consists of identifying features that may be redundant, if they are for example highly correlated with one another. Groups of highly correlated features can in turn be reduced to one archetypal feature.

Model development and validation

Developing a model based on the calculated radiomics features can be data-driven or hypothesis driven. The data-driven approach makes no assumption about the meaning of individual features, therefore all features are treated with equal weight during model development, whereas the hypothesis-driven approach treats cluster features according to predefined information content and a clinical context.

The best models start with a well-defined end-point, such as overall survival (OS), and ideally can accommodate non-radiomics features. Covariates that need to be taken into account include clinical, treatment and genomic data [age, histology, tumour-node-metastasis (TNM) stage, serum markers, chemotherapy, radiotherapy, dose, fractionation, treatment time, gene expression, mutation status, gene polymorphisms...]. This information is occasionally missing for some patients; therefore models should accommodate sparse data. It is necessary that the models be adequately validated with an external dataset, preferably from an external institute. If data from an external institute is not available, the available data must be split into a model training dataset and a validation dataset.

Model performance is often measured in terms of calibration and discrimination. Accurate models correctly discriminate between patients. This can be measured using the c-index or the area under the curve (AUC) of receiver operating characteristic (ROC) for censored data (14). On the other hand, the calibration is the association between observed outcomes and model prediction.

Analysis of the literature

Reviewing all the literature about radiomics in lung cancer has shown that radiomics can be useful in many fields, such as in the classification of nodules, in the description of the tumour, and it has already been shown to be a tool that can assess patient prognosis (3,15). All of the articles published to date, to the best of our knowledge, about radiomics in lung cancer have been placed in *Table 1*.

First of all, 16 articles in the table assess the prognostic value of texture analysis from standard of care CT and FDG-PET images, which can predict treatment outcome in some ways.

Certain methodological aspects of radiomics have been studied, for example, in order to find a way of reducing redundancy and comparing the prognostic characteristics of radiomics features across cancer types. Parmar *et al.* (27), investigated cancer-specific radiomics feature clusters in his study published in 2015. This study concluded that consensus clustering could provide robust radiomics feature clusters and therefore could reduce feature redundancy. Another study, published by Leijenaar *et al.* (28) analysed the test-retest and inter-observer variability of radiomics features in FDG-PET images. The study concluded that the majority of assessed features had both a high test-retest (71%) and inter-observer (91%) stability, and that overall,

features that were more stable in repeated PET imaging were also found to be more robust against inter-observer variability.

One of the first studies showing the potential of CT texture analysis as independent marker of survival for patients with non-small cell lung cancer (NSCLC) is the study of Ganeshan *et al.* from 2012 (24). They showed that patients with heterogeneous tumours with low uniformity values demonstrated poorer survival and that CT texture and PET stage were significant independent predictors of survival. Another study of Balagurunathan *et al.* (8) showed that a large value of run length calculated on CT images (one of the reproducible features) indicated a more homogeneous tumour, and that this was related to a longer survival. The largest, the most comprehensive and rigorous study is from Aerts *et al.*, (15) who worked on radiomics to decode the tumour phenotype, found that a large number of radiomics features have prognostic power in independent datasets of lung and head and neck cancer patients, many of which were previously not identified as significant. After a very strict features reduction process, using test-retest datasets and multiple delineations datasets, they created a signature consisting of “only” four features quantifying tumour heterogeneity, consistently with their initial hypothesis. Combining this radiomics signature with TNM staging showed a significant improvement in all datasets, compared with TNM staging alone, considered as gold standard. Remarkably, the same signature was working on lung and head and neck cancer suggesting that radiomics identifies a general prognostic phenotype existing in both lung and head and neck cancer. They also showed in a series of operated patients, having had standardized CT imaging and gene expression array, the so-called “radiogenomic approach”, that the four feature prognostic radiomics signature, capturing intratumour heterogeneity, is associated with underlying gene-expression patterns linked to tumour proliferation (32). Overall, this study convincingly validate the signature on three external datasets and recently in a fourth one (33).

Next to the studies describing radiomics alone to stratify patients, there are also some studies describing the value of adding radiomics features to conventional prognostic factors alone. A study of Desseroit *et al.* (18) described the development of a nomogram combining clinical staging with PET/CT image features stage I-III NSCLC patients. The nomogram had a higher stratification power than the clinical staging alone. Patients with stage III disease, with a large tumour volume, low CT heterogeneity although a

Table 1 Overview of the literature

Name	Description	Year	N	Imaging	Endpoint	AUC or CI, P value, HR	External validation
Prognostic							
Coroller et al. (16)	Predictive Radiomic features for pathological response, in patients with locally advanced non-small cell lung cancer after neoadjuvant chemoradiation	2016	127	CT	Pathological response	Seven features were predictive for pathologic gross residual disease AUC >0.6, P value <0.05	No
Fried et al. (17)	Prognostic value of FDG PET quantitative imaging features combined with clinical prognostic factors in stage III NSCLC	2016	195	PET	OS	Quantitative imaging features and conventional prognostic factors P=0.18 concordance index 0.62 vs. conventional prognostic factors alone P=0.0001 concordance index 0.58	No
Desseroit et al. (18)	Combining clinical staging with 18F-FDG PET/CT image features in NSCLC stage I-III	2016	116	PET/CT	Nomogram stratification	Stage I vs. II HR 4.7, stage I vs. III HR 6.6	No
Carvalho et al. (19)	Early variation of FDG-PET radiomics features in NSCLC is related to OS: the "delta-radiomics" concept	2016	54±32±26	PET	OS	Model CI 0.66; external validation 0.61; 0.58	Yes
Lovinfosse et al. (20)	Outcome prediction of NSCLC patients treated by stereotactic radiation therapy outcome using ¹⁸ F-FDG uptake intensity, volume or heterogeneity	2016	63	PET	OS, DSS, PFS	OS: not significant; DSS: HR 0.822, P value 0.037; DFS: HR 0.834, P value <0.01	No
Coroller et al. (3)	Prediction of distant metastasis in lung adenocarcinoma using CT-based radiomics signature	2015	98±84	CT	Distant metastasis	P value (radiomics only: 1.79×10 ⁻¹⁷); (radiomics + clinical: 1.56×10 ⁻¹¹)	Yes
Mattonen et al. (21)	Radiomics in the detection of local cancer recurrence after stereotactic ablative radiation therapy	2015	45	CT	Best way of identifying recurrence	AUC =0.85	No
Mattonen et al. (22)	Automated prediction of lung cancer recurrence after stereotactic radiotherapy using imaging texture analysis	2015	22	CT	Best segmentation method	AUC semiautomatic segmentation vs. manual: 0.7–0.73 vs. 0.64	No
Cook et al. (6)	Association of ¹⁸ F-FDG uptake at PET with treatment response and prognosis of NSCLC treated with erlotinib	2015	47	PET/CT	Response to erlotinib	P values: 0.001–0.03	No
Aerts et al. (15)	Using a radiomics approach to decode tumour phenotype	2014	1,019	CT	OS	CI =0.65 Lung2; CI =0.69 H&N1; CI =0.69 H&N2	Yes
Cunliffe et al. (23)	Correlation of radiomics-based features with radiation therapy dose and radiation pneumonitis development	2015	106	CT	Dose pneumonitis	AUC: 0.59–0.84	No
Balagurunathan et al. (8)	Reproducibility and prognosis of quantitative features	2014	32±59	CT	OS	P<0.046	Yes

Table 1 (continued)

Table 1 (continued)

Name	Description	Year	N	Imaging	Endpoint	AUC or CI, P value, HR	External validation
Fried <i>et al.</i> (4)	Prognostic value and reproducibility of CT texture features	2014	91	CE-CT + 4D CT	OS, LRC, FFDM	CPF: P=0.046; LRC: P=0.01; FFDM: P=0.005	No
Cook <i>et al.</i> (7)	Association of ¹⁸ F-FDG PET tumor textural features in NSCLC with response and survival after chemoradiotherapy	2013	53	PET	OS, PFS, LPFS	OS: P value 0.007, 0.02; PFS: P value 0.003, 0.02, 0.02; LPFS: P value 0.01, 0.06; AUC: 0.54-0.82	No
Carvalho <i>et al.</i> (5)	Prognostic value of metabolic metrics extracted from PET images in NSCLC	2013	220	PET	OS	P value 0.05	No
Ganeshan <i>et al.</i> (24)	Assessing tumor heterogeneity in NSCLC by texture analysis, a potential marker of survival	2012	54	PET/CT	OS	PET stage OR: 3.85; CTTA OR: 56.4	No
Identification of suspicious lung nodules							
Dhara <i>et al.</i> (25)	Classification of pulmonary nodules in lung CT using shape and texture features	2016	891 nodules	CT	Nodule classification	AUC configuration 1: 0.951; configuration 2: 0.882; configuration 3: 0.849	No
Dilger <i>et al.</i> (26)	Pulmonary nodule classification utilizing lung parenchyma features	2015	50 nodules	CT	Nodule classification	AUC nodule only including nodule size 0.918; excluding nodule size 0.872; including parenchyma 0.938; including global 0.932	No
Methodology							
Parmar <i>et al.</i> (27)	Radiomics feature clusters and prognostic signatures	2015	878	CT	Histology stage	Lung histology AUC 0.56±0.03, Lung stage AUC 0.61±0.01	Yes
Leijenaar <i>et al.</i> (28)	Analysis of test-retest and inter-observer variability	2013	11±23	PET/CT	Feature stability	Considering all features: $\rho_s=0.665$, $P\leq 0.001$	No
Imaging							
Oliver <i>et al.</i> (29)	Variability of image features from conventional and respiratory gated PET/CT	2015	23	PET/CT	Best imaging protocol (3D or RG PET/CT)	3D PET and RG PET: P value <0.05; 3D CT and RG CT: P value <0.05	No
Yip <i>et al.</i> (30)	Texture features derived from static and respiratory-gated PET images in NSCLC	2014	26	PET/CT	Best imaging protocol (3D or RG PET/CT)	Difference between 3D and 4D PET: P value ≤ 0.01	No
Tumor description							
Yoon <i>et al.</i> (31)	Identification of ALK, ROS1, and RET fusions using a radiomics approach	2015	539	CT and PET	Mutation status (ALK, ROS1, and RET fusions)	Tumor stage P=0.042; central location P=0.017; SUV _{max} P=0.005; homogeneity on 1-voxel P=0.030; 2-voxel P=0.023; 3-voxel P=0.028 sum mean on 2-voxel distance, P=0.049	No

OS, overall survival; DSS, disease specific survival; DFS, disease free survival; PFS, progression free survival; LRC, loco-regional control; LPFS, local progression free survival; AUC, area-under the curve; CI, C-Index; HR, Hazard Ratio, CTTA, CT texture analysis; CPF, conventional prognostic factors; FFDM, freedom from distant metastases.

high PET heterogeneity had the poorest prognosis. A study of Fried *et al.* (4) also showed that models using textural features and conventional prognostic factors improved stratification power compared to models using conventional prognostic factors alone.

In addition, it was found that radiomics features can reflect different biologic mechanisms, such as gene-expression patterns or cell cycling pathways. A study of Yoon *et al.* (31) also made the link with gene-expression and showed that quantitative imaging using radiomics can capture distinct phenotypic differences between tumours. They showed that ALK/ROS1/RET fusion positive lung adenocarcinomas possesses certain imaging features next to clinical features that enable good discrimination between fusion positive and fusion negative tumours.

Three articles studied the imaging texture analysis of lung cancer in patients treated by stereotactic radiotherapy (20-22). Two studies by Mattonen *et al.* (21,22) investigated the use of imaging texture analysis in a decision support system in order to support earlier salvage for patients with recurrence and fewer investigations of benign radiation-induced lung injury. They found that Radiomic features, extracted from CT images using an automated method, are able to predict recurrence with better performance than physicians. The study of Lovinfosse *et al.* (20) used radiomics along with clinical features, using univariate and multivariate analysis for OS, disease-specific survival (DSS) and disease-free survival (DFS) in order to assess the predictive value of the radiomics features. They concluded that the textural feature 'dissimilarity' measured on the baseline ^{18}F -FDG PET/CT appears to be a strong independent predictor of the outcome in patients with NSCLC treated by stereotactic body radiation therapy.

Prognostic value of metabolic metrics extracted from baseline PET images in NSCLC is studied in three separate articles using OS to assess the prognostic value (5,7,17). The study from 2013 by Carvalho *et al.* (5) examined the prognostic value of metabolic PET descriptors on OS for NSCLC patients and they showed that only one metric, relative volume above 80% SUV, was significantly related to OS ($P=0.05$). The study from 2013 Cook *et al.* (7) investigated the relation of radiomics features to response and survival after chemoradiotherapy for 53 NSCLC patients. This study concluded that three textural features were able to differentiate between responders and non-responders to chemoradiotherapy (determined using RECIST) and were independent predictors of OS.

A study by Cook *et al.* (6) showed that the response

to erlotinib is associated with reduced heterogeneity at ^{18}F -FDG PET and that changes in first-order entropy are independently associated with OS and treatment response. And the 2016 study by Fried *et al.* (17) showed that pretreatment PET features were associated with OS in 195 patients with stage III NSCLC. In this study, predictors of OS generated with both quantitative imaging features and conventional prognostic factors demonstrated improved risk stratification compared with those generated with conventional prognostic factors.

Another study investigating the prognostic value of PET features by van Gómez López *et al.* (34) showed that textural analyses of ^{18}F -FDG PET images to assess tumour heterogeneity were related to global metabolic parameters (e.g., SUV_{max} , SUV_{mean} , MTV and TLG) and pathologic staging.

In addition, the study by Coroller *et al.* (16) identified predictive Radiomic features for pathological response in 127 patients with locally advanced NSCLC after neoadjuvant chemoradiation. This study demonstrated that radiomics can provide valuable clinical information, and perform better than conventional imaging.

Furthermore, one study published in 2015 used radiomics to predict tumour distant metastasis, and concluded that radiomics features capture detailed information of the tumour phenotype and therefore can be used as a prognostic biomarker for clinically-relevant factors such as distant metastasis (3). However, distant metastasis is not the only clinically-relevant factor with which radiomics features can be correlated. A different study assessed the relationship between radiation dose and change of texture-based features of lung tissue in order to determine the ability of texture analysis to identify patients who develop radiation pneumonitis (RP) (23). A relationship between dose and change in a set of image-based features was observed. For 12 features, feature values were significantly related to RP development. This study demonstrated the ability of radiomics to provide a quantitative, individualized measurement of patient lung tissue reaction to radiation therapy and assess RP development.

In the field of diagnostics, radiomics can be used for the classification of nodules. A study by Dhara *et al.* (25) showed that using support vector machine nodules can be classified as benign or malignant. In addition the study by Dilger *et al.* (26) showed that this classification can be improved by including features quantified from the surrounding lung tissue.

Radiomics is usually performed using textural information



Figure 2 Fused PET/CT images obtained with optimal gating (left), 3D reconstruction (middle) and 3D reconstruction (4D), showing variations in SUV_{max} (45). PET, positron emission tomography; CT, computed tomography.

derived from the primary tumor. However, textural information derived from the lymph nodes may contain complementary information. An ongoing study on ^{18}F -FDG-PET images of 262 NSCLC patients is performing radiomics on both primary tumour and lymph nodes and is investigating the predictive performance to OS (35).

The above-mentioned studies performed radiomics on pre-treatment scans to advance the stratification of patients for therapy leading to improvements in health outcomes. Some other studies focused more on radiomics for response assessment by comparing radiomics features of a baseline scan with radiomics features of a second scan performed during treatment. Information about early changes in radiomics features can potentially increase the prognostic value of a model. Currently, percentage variations of radiomics features derived from PET images at baseline and the second week of treatment are calculated and related to OS for NSCLC patients (19). The next challenge will be to use radiomics approaches for PET biomarkers different than fluorodeoxyglucose in an attempt to extract more information (36-39).

Challenges and future prospects

Tumour motion

Standardization of image acquisition and reconstruction is one of the major challenges of radiomics (40-42). Reproducibility and stability of radiomics features is important for potential clinical utility (12,28,43). In lung cancer, breathing-induced tumour motion is one of the factors causing variability in image features, and different

methods exist to reduce the influence of breathing motion on image characteristics (44). Due to the scan duration of a 3D (free-breathing) PET scan, images are averaged over multiple breathing cycles and introduce some noise. During a respiratory correlated 4D PET acquisition, counts are binned into typically 5 to 10 phases. This gating based on respiratory motion reduces blurring, but due to the reduced acquisition time per phase an increased noise is observed. However, there are also motion correction techniques available (45-47). For CT images of lung cancer patients, the mid-ventilation phase of a respiratory-gated (4D) acquisition is commonly used, in the motion management option, for target delineation. This phase is typically used for treatment planning purposes and the GTV or MTV can also be used as the ROI for tumour quantification with radiomics. Variations in radiomics feature values may occur when a different phase or a static (3D) CT is used instead. In *Figure 2*, variations in SUV_{max} are shown using different acquisition methods.

For generalizability and robust extraction of radiomics for lung cancer, it is important that the impact of tumour motion on the radiomics feature values is minimized, using gated acquisitions or breath-hold methods.

Two recent studies investigated the influence of motion on radiomics feature values derived from PET and CT. Relative differences in features values were calculated between 3D and 4D acquisitions. A study by Yip *et al.* (30) investigated five texture features derived from 3D PET and 4D PET for 26 lung cancer patients. In this study, 4D PET counts were binned into five phases and the differences in features values between all five phase bins were assessed.

They reported significant differences between 3D and all bins of 4D PET for three features and significant differences between 3D and 4D for four out of five bins for one feature. The textural feature 'Contrast' was not significantly different between 3D and 4D PET. Between different breathing phases, none of the five features was significantly different. A second study evaluated the influence of 56 radiomics features between 3D PET/CT and 4D PET/CT acquisitions for lung cancer patients (n=23) (29). The acquired data from the PET scan were binned into ten phases. Features were extracted from the first phase (inhale) and the fifth phase (exhale) of the respiratory-gated scan. They found that the differences in features between a 3D and 4D acquisitions varied between 0% and 193% for PET and 0% and 176% for CT, with the feature kurtosis being an outlier for both modalities. Substantial differences between radiomics features derived from 3D and 4D acquisitions were observed for both CT and PET. Respiratory-gated imaging reduces effects of motion, including blurring, rotation and deformation at the expense of a somewhat higher noise level. It is important to choose the respiratory phase-bin with robust features for quantitative tumour characterization using 4D imaging. To improve standardization in radiomics, acquisition and reconstruction protocols used to acquire quantitative image features should always be described in detail for both PET and CT.

Methodological issues

There is one major risk in radiomics studies: the selection of significant features by chance and overfitting. This issue is very similar to that in the field of genomics. Authors should clearly state in their publication, in what way the study has advanced the field of radiomics and how it has specifically identified and met an unmet need. It is also important that authors avoid making overly optimistic claims concerning robustness and generalizability as they diminish scientific and clinical impact. Furthermore, only 5 of the 22 articles were externally validated, this highlights another methodological issue. Study design, protocols, detailed quality assurance processes and standard operating procedures should be exhaustively reported in the publications. Rigorous reporting guidelines and requirements are necessary for the maturation of radiomics. While the minute technical details of radiomics and finding external validation datasets can be tedious, they potentially have a great influence on the robustness, generalizability

and confound meta-analyses.

The following points are crucial in radiomics studies:

- (I) Standardized imaging protocols allow for appropriate meta-analysis;
- (II) The effects of inter-scanner differences should be considered and minimized;
- (III) Robust segmentation, preferably automated, is advantageous for ranking features on the basis of their spatial reproducibility/stability;
- (IV) Test-retest is useful for ranking features on the basis of their temporal reproducibility/stability (28);
- (V) Independent validation datasets, preferably from another centre and multiple datasets can provide crucial information with regard to overfitting, clinical performance and generalizability.

Conclusions

There are two main applications of radiomics in lung cancer, classification of lung nodules (diagnostic) or prognostication of established lung cancer (theragnostic). Overall, it is clear that radiomics has great potential to improve diagnosis and patients stratification in lung cancer. It may also have a clinical impact as imaging is routinely used in clinical practice, providing an unprecedented opportunity to improve decision support in lung cancer for diagnosis or treatment at low cost (48-51).

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