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Radiomics and its emerging role in lung cancer research, imaging biomarkers and clinical management: State of the art

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ABSTRACT

With the development of functional imaging modalities we now have the ability to study the microenvironment of lung cancer and its genomic instability. *Radiomics* is defined as the use of automated or semi-automated post-processing and analysis of large amounts of quantitative imaging features that can be derived from medical images. The automated generation of these analytical features helps to quantify a number of variables in the imaging assessment of lung malignancy. These imaging features include: tumor spatial complexity, elucidation of the tumor genomic heterogeneity and composition, subregional identification in terms of tumor viability or aggressiveness, and response to chemotherapy and/or radiation. Therefore, a radiomic approach can help to reveal unique information about tumor behavior. Currently available radiomic features can be divided into four major classes: (a) morphological, (b) statistical, (c) regional, and (d) model-based. Each category yields quantitative parameters that reflect specific aspects of a tumor. The major challenge is to integrate radiomic data with clinical, pathological, and genomic information to decode the different types of tissue biology. There are many currently available radiomic studies on lung cancer for which there is a need to summarize the current state of the art.

1. Introduction

Lung cancer is the leading cause of cancer death in the world. Up to recently, the only current cure has been surgical removal of early stage disease. The results of the National lung cancer screening trial (NLST) showed a clear survival benefit for low dose computed tomography in current and former smokers [1]. This result prompted the Center for Medicare and Medicaid Services (CMS) to cover lung cancer screening in the United States for those subjects meeting the screening criteria. Meanwhile, the five year survival for this disease has slightly improved over the last fifty years. One of the bright spots in lung cancer research has been the introduction of patient-centered chemotherapy based on that patient's specific tumor cell mutations in advanced stage [2].

Imaging such as computed tomography (CT), positron emission tomography (PET), or magnetic resonance imaging (MRI) is vital in the diagnosis, staging, treatment planning, postoperative surveillance, and response evaluation in the routine management of lung cancer. Although these conventional modalities provide important information on lung cancer phenotypes, yet a great deal of genetic and prognostic information remains unrevealed. Recently, several studies have shown that functional imaging methods, such

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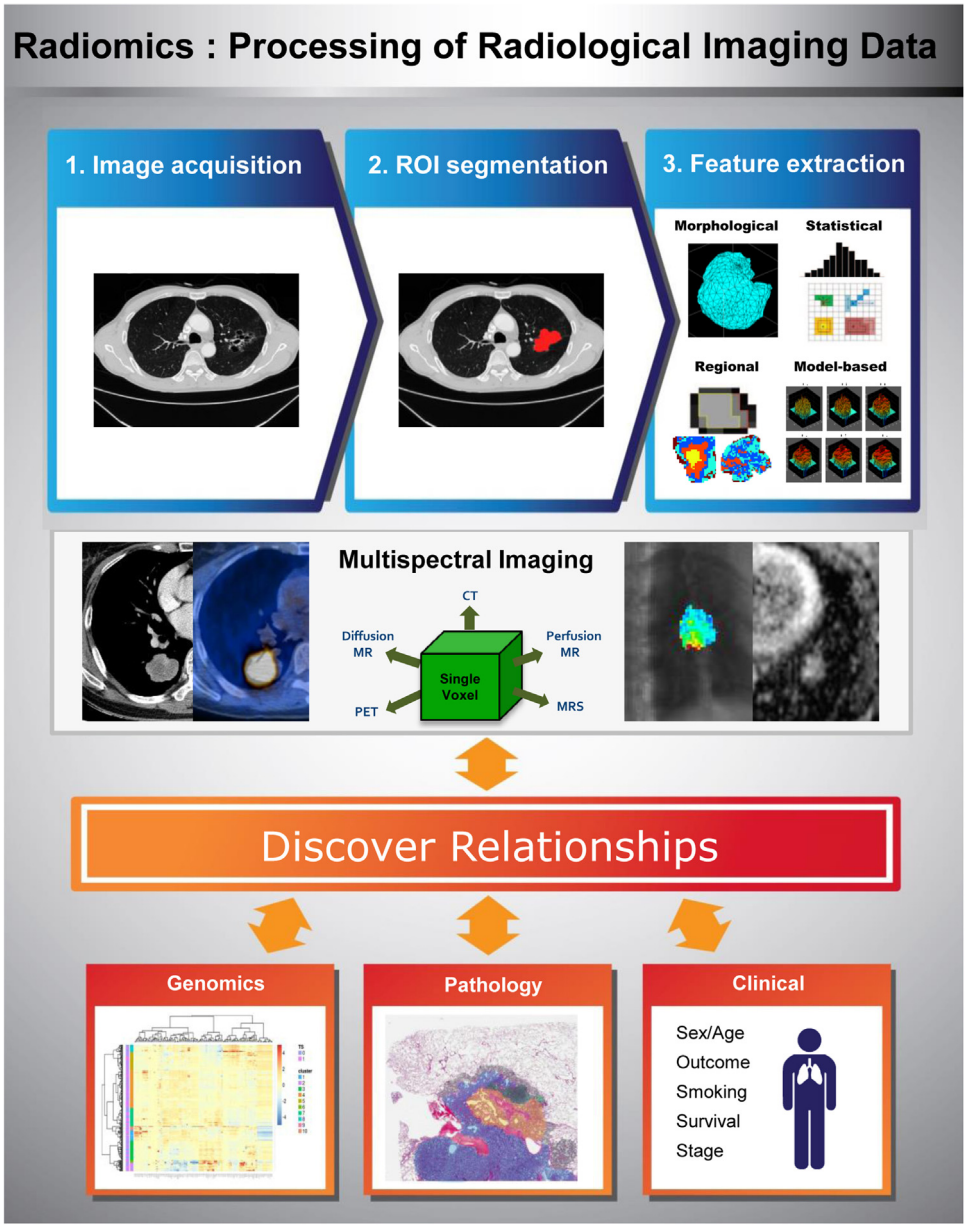

Fig. 1. Overview of radiomics, the processing of radiological imaging data.
Regions of interest are segmented for the whole tumor, and multiple quantitative features are extracted. Combining information from multiple imaging modalities provides a multispectral view of the tumor and allows improved tumor characterization. Discovering relationships among the radiomic features and genomic, pathology, and clinical data is a challenging but important step.

as diffusion-weighted MRI, perfusion techniques, PET and their combinations, allow the in-vivo depiction of physiologically and biologically important tumor processes and can even play a surrogate role in finding specific gene signatures by their characteristic imaging phenotypic expression pattern [3–9]. On the other hand, employing radiomics and radiogenomics have been found to be useful in quantifying overall tumor spatial complexity and identifying the tumor subregions that drive disease transformation, progression, and drug resistance [10–14]. These new methods will help drive further improvements in the personalization of gene-based lung cancer therapy. The purpose in this review is to consider the current state-of-the art in radiomics and radiogenomics and to offer concrete tools to implement these two approaches in thoracic oncology imaging.

1.1. What is radiomics

In the era of big data analytics, researchers have strived to discover the fundamental prognostic data embedded in medical and pathological images. Quantitative image features as well as traditional qualitative (semantic) features have shown some potential for precision medicine in oncology, and these features are continuously being refined and developed with evolving research [15–17]. With the recent availability of automated pipeline systems, quantitative computational features have gained attraction due to improved efficiency, reproducibility, and consistency [18,19]. *Radiomics* is a field of study in which high-throughput data is extracted and large amounts of advanced quantitative imaging features are analyzed from medical images (Fig. 1). The first step in radiomics requires the identification of the volumes of inter-

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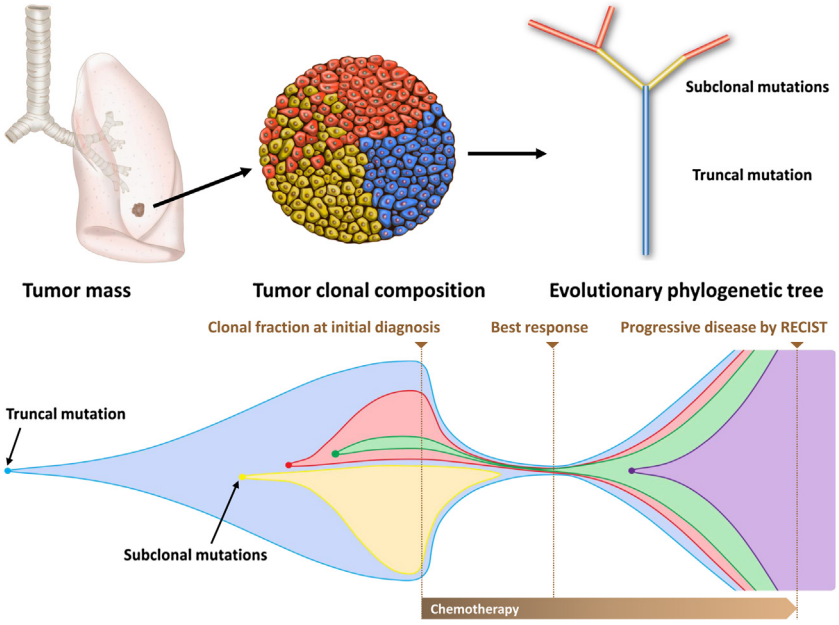

Fig. 2. Evolutionary trajectory of tumor through phylogenetic tree analysis.
Primary lung cancer comprises multiple subclones, which are represented by different colors within the tumor mass. The most recent common ancestor (truncal event) is represented by the blue trunk and blue cells in the tumor. Later in tumor evolution, several subclonal mutations (branched events) occur and are represented by yellow and red branches. Such intra-tumor heterogeneity means that metastases with distinct subclones (orange, green, and purple) could develop at multiple sites.

est in a tumor. Automated or semi-automated methods have been reported to be superior to manual methods for segmenting the tumor [20,21]. Next, multiple quantitative features are generated from the raw imaging data over the given region of interest (ROI). Finally, using radiomics features alone or in combination with clinical and pathological data to develop models that predict tumor characteristics, such as tumor response or survival, is a challenging but important step.

1.2. *Insight into tumor heterogeneity and clonal evolution*

Lung cancer is a genetic disease that develops due to the accumulation of multiple genetic mutations and epigenetic alterations that ultimately result in unchecked cell proliferation and survival. Accordingly, two fundamental principles that underlie the concept of patient-centered cancer therapy in lung cancer, namely precision medicine, are that significant genomic heterogeneity exists among and even within tumors and that those differences can play an important role in determining the likelihood of a clinical response to treatment with particular agents. The genomic expression of most lung adenocarcinomas has a mixed-subtype, i.e., polyclonal-composed of two or more different pathologic subtypes [22,23]. Research has shown that the histopathologic diversity within a tumor, (i.e., regions demarcated by various degrees of differentiation, proliferation, vascularity, inflammation, or invasiveness) reflects the degree of genetic (or clonal) heterogeneity [24].

In addition to well-known inter-patient or inter-tumor heterogeneity [25], recent next-generation sequencing and bioinformatics have demonstrated the existence of intra-tumor heterogeneity, which is the presence of multiple subclones within a tumor, resulting in heterogeneity among tumor cells [26]. High-throughput sequencing of multiple site biopsies from multiple lung cancer patients and integrative analysis has revealed the spatial composition and evolutionary trajectory of tumor subclones [25,27,28]. The clonal and subclonal composition of each tumor was used to construct distance-based phylogenetic trees (Fig. 2), wherein clonal mutations (present in all tumor regions) occur early in tumorigenesis and represent the most recent common ancestor (truncal events on the evolutionary tree) and subclonal mutations (present in only a subset of regions or cells within a single biopsy), which occur later in tumorigenesis (branched events on the evolutionary tree) [29]. Researchers have also found that intra-tumor genetic heterogeneity was universally associated with prognosis, but this relationship was nonlinear [30].

The idea that human tumors are composed of evolving clones predicts certain features, such as the existence of clonal genotypes (i.e., not all mutations occur in all cells identically) and the expansion and decline of clonal populations over time [31]. More practically, phenomena such as partial tumor responses to therapy and the emergence of drug-resistant malignant cells or the seeding of metastatic cells could be explained by the emergence of genomically distinct minor subclones of malignant cells [32–34]. Indeed, several observations have demonstrated that the presence of minor subclones itself influences tumor progression [35–37], which suggests the need to identify subclonal drivers of branched evolution, as well as challenges for therapies that have traditionally focused on genomic alterations in the dominant clone.

1.3. ***Precision medicine in thoracic oncology*** *and radiology's* ***potential role***

Recently published large databases characterizing the molecular features of human tumors have transformed the determination of each cancer type from histopathological classification to a new classification based on genetic identity [38–41]. Successful personalized medicine will require a clear understanding of each patient's tumoral heterogeneity (genomic stratification) and individual situation. However, taking multiple tumor biopsies to truly determine the clonal composition of tumors is not a simple or practical solution outside the context of clinical studies. Furthermore, given the evidence for spatial intra-tumor heterogeneity and the evolution of tumor subclones over time and in response to cancer therapies, the potential sampling bias involved in a single tumor biopsy limits oncologists' ability to identify and qualify biomarkers for clinical use and can lead to rapid treatment resistance [42–45].

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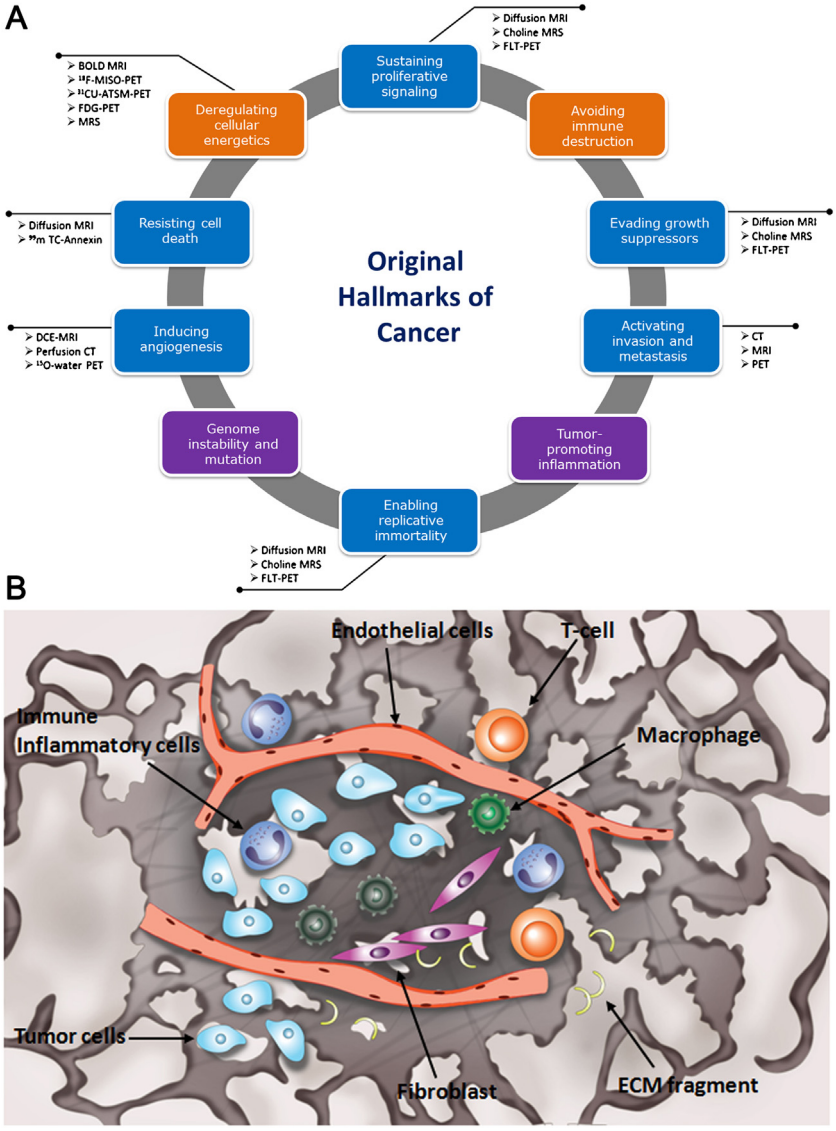

Fig. 3. Cancer hallmarks and corresponding functional imaging techniques.
A. Cancer's acquired functional capabilities are defined as the original *hallmarks of cancer*, represented here by blue boxes. Current imaging modalities have been reported to depict those original cancer hallmarks in various aspects. In addition, the microenvironment and genomic instability could be involved in the pathogenesis of cancers. Thus, two new emerging hallmarks (orange) and two enabling characteristics (purple) have been added to the concept of cancer hallmarks. Recently investigated radiomic approaches have been reported to reflect the tumor microenvironment and genomic instability.
B. Lung cancer is a complex mixture of interacting cells and extracellular components, including tumor cells, endothelium, fibroblasts, T-cells, macrophages, and extracellular matrix fragments. The assemblage of those cells creates a tumor's microenvironment, which enables tumor growth and progression.

Consequently, sophisticated radio-phenotyping needs to be able to more accurately stratify lung cancer patients to promote the success of precision oncology, inasmuch as imaging can quantify the spatial and temporal variations in tumoral architecture and function through which intra-tumoral evolution might be determined. Imaging would thus be an effective approach to understanding how tumors evolve during disease progression and in response to treatment.

Meanwhile, the clonal evolution of human cancers underpins their successive acquisition of the *hallmarks of cancer*, defined as the acquired functional capabilities that allow cancer cells to survive, proliferate, and disseminate [24]. Conceptual progress in the past decade has added two emerging cancer hallmarks and two other enabling characteristics to the six original capabilities (Fig. 3A). Current imaging modalities closely reflect the nature of a tumor in various aspects. In terms of the two remaining factors (tumor microenvironment (Fig. 3B) and genomic instability), which have not been manifested by current functional imaging, a radiomic approach could be a solution.

2. Dimensions of radiomics features

2.1. Single parameter read-out

In practice, CT and PET-CT are the most commonly performed modalities for response monitoring and observation of patients diagnosed with lung cancer. The advantage of a single parameter read-out is that the features extracted from serial scans in a single modality can be compared longitudinally for a patient.

2.2. Multispectral across different modalities

Given the increasing number and complexity of diagnostic imaging methods, multispectral analysis has substantial poten-

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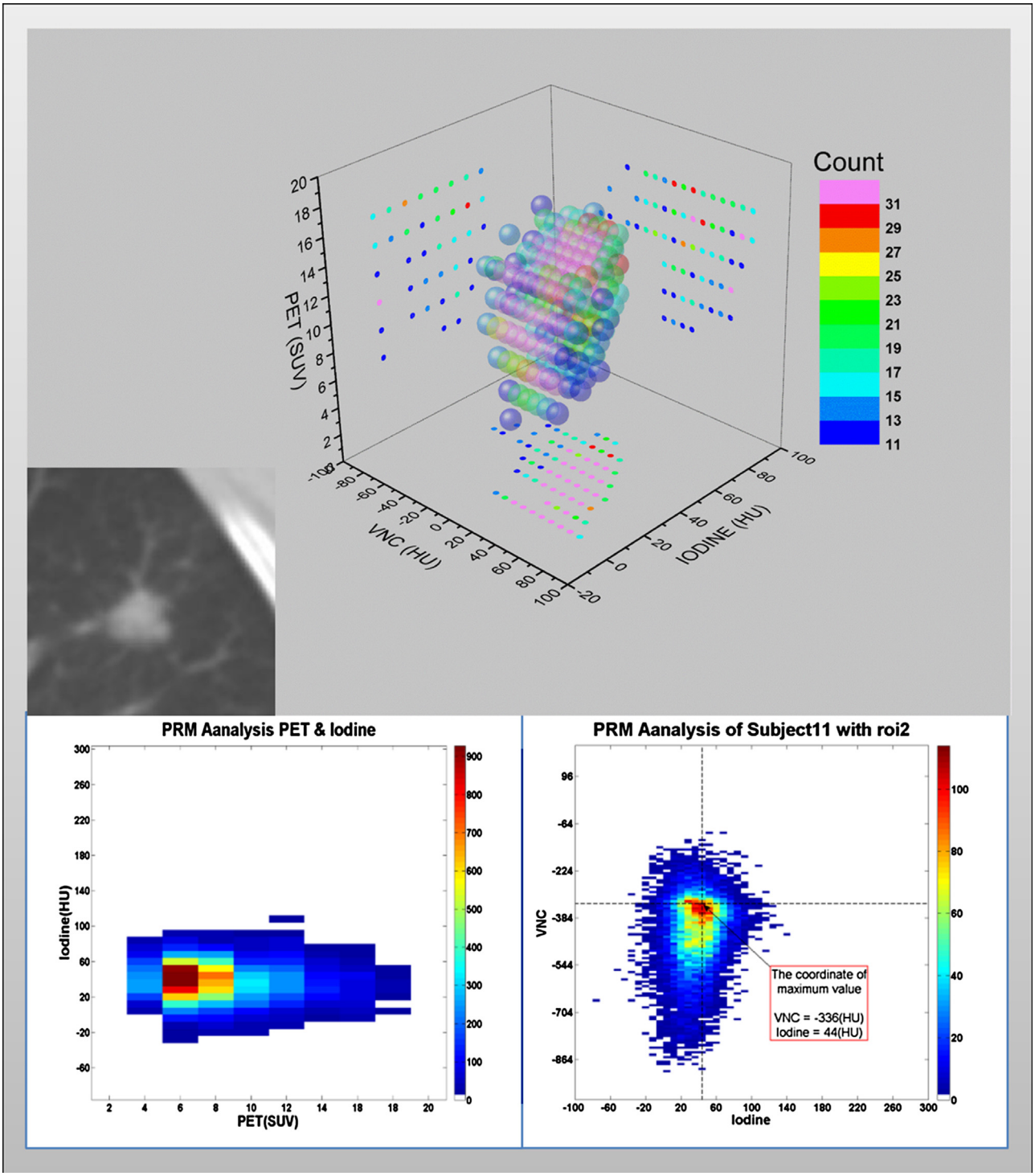

Fig. 4. Multispectral analysis.
Voxel-by-voxel correlations of virtual non-contrast images, iodine from contrast-enhanced CT scans, and maximum standard uptake value (SUVmax) from PET scans are shown for invasive adenocarcinoma.

tial for elucidating the molecular characteristics in lung cancer. By combining anatomic, metabolic, and functional data, noninvasive phenotyping of tumor biology could provide valuable information for tumor diagnosis, classification, prognosis stratification, and early response evaluation in patients with lung cancer (Fig. 4). However, a drawback of multispectral analysis is the possibility of misregistration and measurement errors in medical images from different modalities obtained at different times. Furthermore, not all modalities are available for all patients, nor is it necessarily desirable from a workflow point of view, which could mean sparse data for individuals.

More important, there are no standardized protocols or methods for clustering multispectral analyses. Challenging investigations using tumor hypoxia, glucose metabolism, and tumor perfusion have been published, facilitating the search for the best set of modalities to characterize lung cancer [5,46,47].

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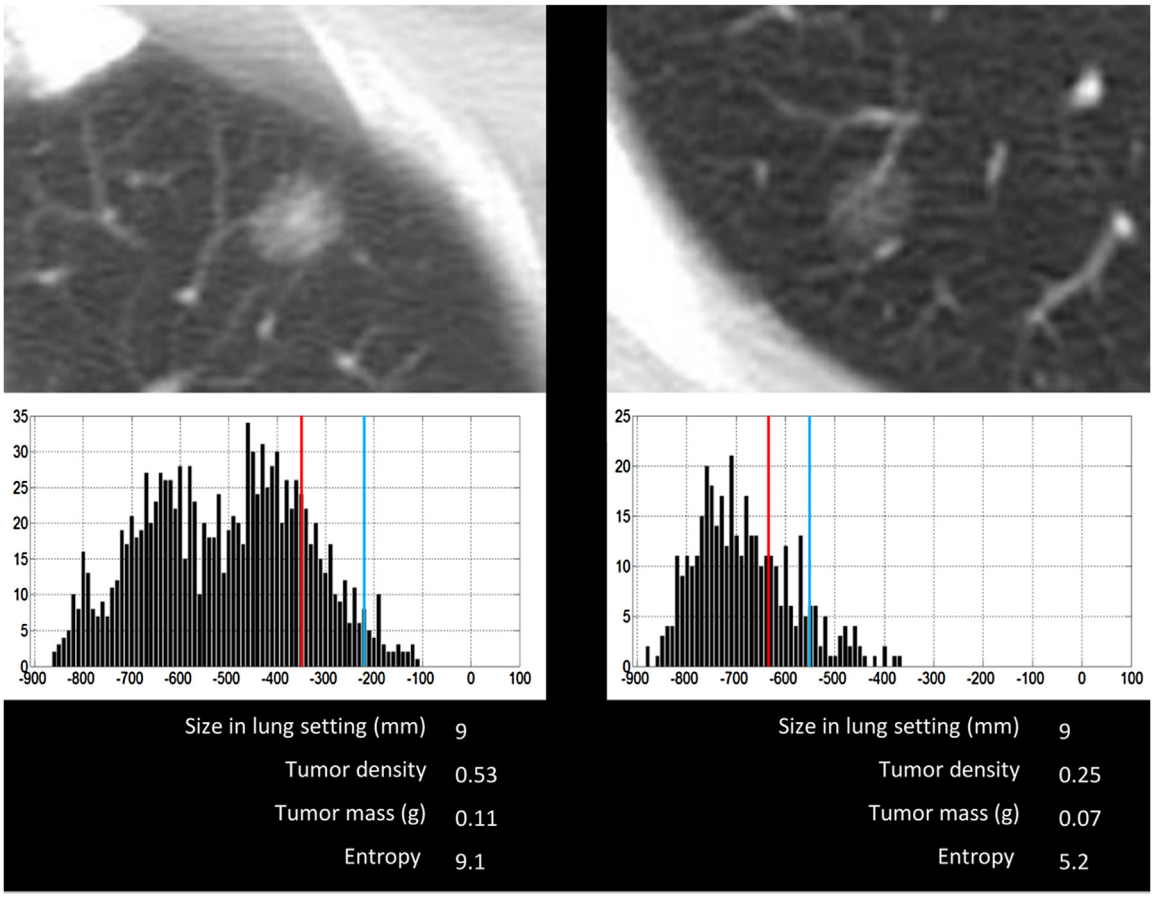

Fig. 5. Histogram analysis of ground-glass opacity nodules.
Histogram-based features such as entropy and a 75th percentile CT (red vertical line) attenuation value reportedly enable differentiation of invasive adenocarcinoma (left) and adenocarcinoma in situ (right).

3. Types of radiomics features

Currently available radiomics features can be divided into four major classes: (a) morphological, (b) statistical, (c) regional, and (d) model-based (Fig. 1). Morphological features are the most basic and provide information about the shape and physical characteristics of a tumor. Statistical features, which are calculated using statistical methods, can be further classified into 1st-order statistical (histogram) features and higher-order statistical (texture) features. Regional features can quantify beyond the immediate neighborhood and represent intra-tumor clonal heterogeneity through subregional clustering. Model-based features are extracted using mathematical approaches, such as the fractal model. We summarize the representative features of each class below and provide clinical applications for which the methods have been shown to be successful.

3.1. Morphological features

Morphological features define the physical characteristics of a tumor in terms of shape and volume, such as surface area and surface-to-volume ratio. Surface area is calculated by triangulation, which is a procedure for generating a net of triangles that completely covers the tumor surface. In terms of the surface-to-volume ratio, a larger ratio indicates a more spiculated and irregular tumor, whereas a lower ratio indicates a smoother and rounder tumor. Spherical disproportion, sphericity, and discrete compactness are assessed to determine how spherical (round) a tumor is. Among those features, discrete compactness, which is proportional to the circularity of a tumor, has been reported to correlate with invasion beyond the tumor [48].

The Laplacian of Gaussian approach is a two-step process to detect regions that differ in properties from surrounding regions, in other words from the edges of a ROI. Through this approach, quantitative analysis regarding tumor margin characterization (ill-defined or well-defined) is embodied, and this information indicates the relationship between tumor and surrounding normal tissue which is another element of the tumor microenvironment. In addition, a Gaussian smoothing filter is most often applied to reduce sensitivity to noise, and then a Laplacian filter, an isotropic calculation of the second spatial derivative of a pixel, is applied. Although this is a well-known method in medical image processing, only a few investigators have applied both a Laplacian filter and a Gaussian filter for CT in thoracic radiology. To date, satisfactory results for automated nodule location and size estimation has been achieved using this method [49,50].

As for tumor volume, a large amount of literature has concluded that volumetric measurement is a key parameter in lung cancer, with a shorter volume doubling time reflecting greater histological tumor aggressiveness and suggesting a poor prognosis [51,52]. However, the most widely used method includes the assumption that the tumor is a sphere with a diameter averaged from the length and width measured on CT scans. In practice, tumors are irregular, far from a complete sphere. In radiomics, tumor volume is determined by counting the number of voxels in the tumor ROI and multiplying by the voxel volume. Thus, radiomics features provide more accurate and reproducible measurements of a tumor's physical features than previously known methods. Further-

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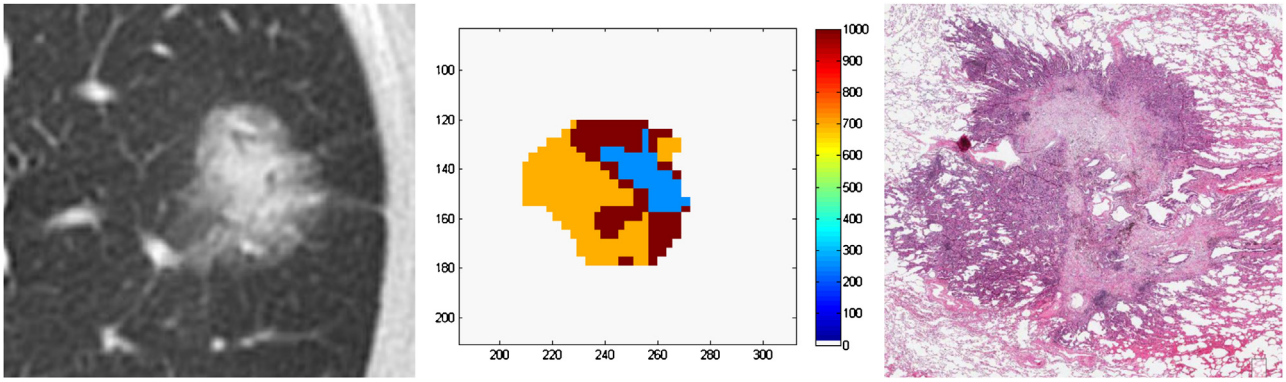

Fig. 6. Quantifying tumor subregions. Subregional partitioning provides quantification of multiple clusters that reflect pathologic intra-tumor heterogeneity.

more, volumetric measurements have been reported to evaluate treatment response better than conventional methods, which miss morphologic changes in tumors that show no change in diameter [53–56].

In addition, tumor mass, a parameter that integrates volume and density, is an important feature of lung cancers that can be accurately measured by radiomic methods. Given that a wide spectrum of lung adenocarcinomas manifest as sub-solid nodules, including ground glass opacity (GGO) proportion, tumor mass measurement enables the detection of growth earlier than conventional measurements [22,57].

3.2. Statistical features

3.2.1. (1st order) Histogram features

A histogram is a simple plot of tumor pixel attenuation along one axis versus the frequency of pixels at each attenuation value along the other axis; thus, a histogram displays the range and frequency of pixel values within the defined lesion ROI [58]. Multiple first order statistics (i.e., mean, median, standard deviation, kurtosis, skewness, energy, entropy, uniformity, and variance) can be generated from a histogram, and most features appear to be reproducible [59]. One report suggested that histogram features are useful for differentiating between benign and malignant lung nodules [60]. In addition, tumor response evaluation is traditionally assessed mainly by changes in tumor size. However, recently introduced targeted chemotherapies can cause tumor necrosis, hemorrhage, or cavitation, which do not necessarily correspond to tumor shrinkage right away. In other words, tumor size might be insufficient to reflect the morphological, functional, and metabolic changes of a tumor after treatment [61]. Radiomic features from histogram analysis and texture are thus promising predictors of pathologic response in patients with lung cancer undergoing concurrent chemoradiation therapy [13].

Many lung cancer studies using histogram analysis have been reported because it is an easily performed analysis of medical imaging that provides many descriptors to reflect the distribution of pixel values. Thus, the greatest advantage of histogram analysis is extracting hidden spectral information at the voxel level, which has greatly facilitated the objective assessment and detection of very subtle changes in lung cancers. On the other hand, the major limitation of histogram analysis remains the loss of spatial information about each voxel.

In the spectrum of lung adenocarcinomas, the thickening of the alveolar septa and increased cellularity are of particular importance because they signify the presence and degree of pathological invasiveness [62,63]. Although approximately half of pure GGO nodules have been reported to have a pathologically invasive component, discrimination between the invasive and non-invasive proportions remains challenging in pure GGO lesions because of limited visual perception and subjective analysis of conventional CT scans [64,65]. Several investigators have demonstrated that quantification and feature extraction of GGO lesions (using numerical values) can find small pathologically invasive components, which are reflected at the medical imaging voxel level and otherwise not visually detectable [16,66,67]. Entropy or a high attenuation value, such as the 75th percentile CT attenuation value from histograms, has been reported as a significant differentiation factor for invasive adenocarcinomas [67]. Furthermore, the 97.5th percentile CT attenuation value and the slope of CT attenuation values have been suggested as predictors for future CT attenuation changes and the growth rate of pure GGO lesions [68]. Overall, lung cancer–specific (GGO-related) radiomic features could provide additional information about tumor invasiveness and progression from other indolent or non-invasive lesions and even predict tumor growth (Fig. 5).

3.2.2. (Higher order) Texture features

Unlike histogram features, higher order statistics can retain spatial information among pixels, thus reflecting the textural characteristics of tumors. The most commonly used gray level co-occurrence matrix (GLCM) is constructed using the number, distance, and angle of a combination of gray levels that occur in the image. Representative features extracted from GLCM include correlation, cluster, contrast, energy, and entropy. The gray level run length matrix (GLRL) considers continuous pixels with the same gray level in any direction. Therefore, 13 different GLRL matrices can be constructed for three-dimensional studies. Representative features extracted from GLRL include short run emphasis, long run emphasis, gray level non-uniformity, run length non-uniformity, and run percentage. The neighborhood gray-tone difference matrix (NGTDM) uses the intensity values of a neighborhood instead of one pixel to represent how similar or dissimilar pixel intensities are within a neighborhood. Features extracted from NGTDM include busyness, complexity, and texture strength.

Texture features obtained from the different matrices have been applied extensively to CT and PET in the field of thoracic oncology. In a study with a large cohort, the authors found that CT texture features from GLCM and GLRL showed strong correlations with gene expression [15]. Furthermore, texture features extracted from NGTDM significantly predicted survival in patients with non-small cell lung cancer undergoing concurrent chemoradiation therapy [69]. Texture obtained from pre-treatment ^{18}F-FDG PET-CT has also been reported as an independent factor for disease-specific survival in early stage non-small cell lung cancer patients [70].

Overall, many studies have shown that textural features are associated with tumor stage, metastasis, response, survival, and metagenes in lung cancer [6,69,71–74], thereby providing evidence

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that textural features show substantial promise as prognostic indicators in thoracic oncology.

3.3. Regional features

Regional features are based on computation of variation intensity between regions. In other words, regional features demonstrate how many subregions and how often certain subregions occur within a tumor. Therefore, in contrast to textural features, regional features are expected to ultimately quantify subclonal heterogeneity beyond the immediate neighborhood. Methods of subregional partitioning include data-driven segmentation and the use of threshold values [11,75,76]. Data-driven segmentation groups voxels with similar intensity into clusters, and threshold values also group voxels into clusters.

Two recent investigations support the importance of intratumor subregional partitioning using multiparametric images [11,76]. In one study, researchers successfully divided a tumor into necrotic regions and viable regions by incorporating ^{18}F-FDG PET and diffusion-weighted MRI, which showed good agreement with histology [11]. In the other study, researchers identified clinically relevant, high-risk subregions in lung cancer using intra-tumor partitioning of ^{18}F FDG-PET and CT images [76].

Although numerous microenvironmental factors, including histologic subtype, anatomic location, glucose metabolism, hypoxia and angiogenesis, are involved in phenotype determination in tumor regions, subregions with genetically identical tumor cells can exhibit similar phenotypes due to their basic molecular structural similarity. In that context, regional features obtained through radiomics can efficiently reflect intra-tumor heterogeneity (Fig. 6) [11,77]. Moreover, intra-tumor heterogeneity is recognized as one of the most promising prognostic factors predicting patient survival, and regional features have been reported to correlate with prognosis [74,78,79].

3.4. Model-based features

Fractal alteration characterizes the shape complexity of an object over a range of scales. Based on this concept, the fractal dimension is a mathematical measurement that reflects the intrinsic shape of an object. Over the years, many researchers have tried to apply the fractal dimension to thoracic radiology, and some investigators successfully used it to differentiate between aggressive and nonaggressive lung cancers [71,80]. Advantages of the fractal dimension are that it is relatively stable, less susceptible to noise than other features, and can be used for longitudinal assessment in a single patient [81]. In addition, the recently developed fractal signature dissimilarity method has been suggested as a novel image texture analysis technique [82]. In that study, the fractal signature dissimilarity method quantitatively evaluated contrast agent uptake heterogeneity dynamics, thus suggesting a promising role in monitoring early response to anti-angiogenesis treatment [82].

4. Radiogenomics: discovering genomic information through radiomic phenotypes

While radiomics is defined as the post-processing and analysis of large amounts of quantitative imaging features which can be derived from medical images, radiogenomics is focused on defining relationships between the radiomics phenotypes and genomic information [83]. For lung cancers, significant genomic heterogeneity components that affect the likelihood of metastasis and predict response to therapy have been established [84,85]. Furthermore, genomic analysis is now essential for appropriate therapeutic planning in this era of precision medicine for advanced lung cancers with distinct tumor subregions. Accordingly, there have been several attempts to explore tumor genomics by applying a radiomic approach. Nevertheless, radiogenomics, the link between genomics and radiomic phenotyping in lung cancer, is still poorly understood.

Preliminary data have associated radiomic features from CT and PET scans in non-small cell lung cancer with each other to predict metagenes with an acceptable accuracy of 65–86%, among which tumor size, edge shape, and sharpness ranked highest for prognostic significance [6]. In one study, the authors performed a detailed analysis of features from 18F-FDG PET in patients with early-stage lung cancer [86]. Multiple features of PET tracer uptake correlated with signatures associated with major oncogenomic alterations in lung cancer [86,87]. According to another recent study, the combination of radiomic features and clinical information successfully predicted oncogenic fusion genes in lung cancer [88]. In general, researchers have shown promising results in using radiomics to identify radiographic tumor phenotypes that favored specific genetic expressions [6,15,86,88,89].

Radiogenomics in lung cancer is still in its very early stages, and many problems remain to be solved, emphasizing the need for larger data studies. One current concern is the integration of medical imaging, genomics, and clinical data, which can provide different insights about a single tumor. However, we speculate that data from these different sources are not just different ways of measuring the same biological processes; rather, data from each source may represent different processes in an inter-related biological pathway. Ultimately, efforts to harmonize phenotypes and genomes should create a whole new world of multidisciplinary strategies for advancing personalized medicine.

5. Outlook

Many hurdles remain before defining a role for radiomics in the field of thoracic oncology. First, despite a recent series of publications on the value and potential of quantitative radiographic image features to link tumor phenotypes with prognosis or genotypes, the findings were mostly based on retrospective analysis of imaging data and used a wide variety of scanning techniques and parameters [90]. Any identification of reliable and meaningful quantitative imaging biomarkers for tumors must be reproducible [90–92]. Therefore, efforts should be made to standardize dose administration, image acquisition, image reconstruction, and value normalization. Second, the methodology used to determine various radiomic features is also subject to variability [91,93,94]. Standardization is therefore needed in selecting features and determining which predictive modeling method to apply. Because it is essentially high-throughput data-mining, radiomics must incorporate appropriate feature selection strategies that enhance the performance of its predictive models while minimizing the overfitting of those models to increase generalizability [95,96]. In addition, predictive and prognostic models with high accuracy, reliability, and efficiency are vital factors driving the success of radiomics. Various computational methods, *machine-learning*, are available to generate such models, and they should be compared in terms of predictive performance [95]. Third, in terms of MR image, special consideration is required to apply radiomics due to MR specific characteristics, intensity inhomogeneity which can significantly affect radiomic feature extraction [97,98]. Thus, before registration of MR images, the necessity of bias field correction by convolving the images with a Gaussian low-pass filter, resulting in uniform intensities across the volume should be inquired [99]. Fourth, promising data must be replicated in other institutions, and biomarkers must be validated independently to reliably generalize the results [75,100]. Fifth, various cancer “omics” has recently shown potential in precision oncology as well, thus, future stud-

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ies integrating radiomics data with additional "omics" profiling are warranted [101].

The last thing that needs to be considered is how to deal with traditional qualitative (semantic) features. A large effort is being made by expert radiologists to define descriptive and unstandardized terms to establish a uniform lexicon for semantic annotation which "RadLex" is correspond to in case of lung cancer [102]. The advantage of developing a standardized semantic lexicon is that it builds on the experience of expert radiologists [103]. Furthermore, expert human readers can handle even imaging data with lower qualities like low resolution or artifacts [103]. Therefore, complementary use of semantic features have also been suggested [103].

In conclusion, a potential role for radiomics is the ability to perform image genotyping and sophisticated image phenotyping on a whole-tumor basis in vivo and longitudinally. This would create a new multidisciplinary strategy for advancing personalized medicine by focusing on phenotype and genome together, rather than the genome in isolation. A radiomic approach for image genotyping has the potential to allow clinicians to make informed therapeutic choices and treat patients with drugs tailored to their tumor profile generating improved patient outcomes for lung cancer.

Conflict of interest

None.

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References

[1] D.R. Aberle, S. DeMello, C.D. Berg, et al., Results of the two incidence screenings in the National Lung Screening Trial, N. Engl. J. Med. 369 (2013) 920–931.
[2] W.L. Tan, A. Jain, A. Takano, et al., Novel therapeutic targets on the horizon for lung cancer, Lancet Oncol. 17 (2016) e347–362.
[3] J.T. Chi, D.E. Thrall, C. Jiang, et al., Comparison of genomics and functional imaging from canine sarcomas treated with thermoradiotherapy predicts therapeutic response and identifies combination therapeutics, Clin. Cancer Res. 17 (2011) 2549–2560.
[4] C.M. Zegers, W. van Elmpt, B. Reymen, et al., In vivo quantification of hypoxic and metabolic status of NSCLC tumors using [18F]HX4 and [18F]FDG-PET/CT imaging, Clin. Cancer Res. 20 (2014) 6389–6397.
[5] W. van Elmpt, C.M. Zegers, B. Reymen, et al., Multiparametric imaging of patient and tumour heterogeneity in non-small-cell lung cancer: quantification of tumour hypoxia, metabolism and perfusion, Eur. J. Nucl. Med. Mol. Imaging 43 (2016) 240–248.
[6] O. Gevaert, J. Xu, C.D. Hoang, et al., Non-small cell lung cancer: identifying prognostic imaging biomarkers by leveraging public gene expression microarray data–methods and preliminary results, Radiology 264 (2012) 387–396.
[7] Y.N. Kim, H.Y. Lee, K.S. Lee, et al., Dual-energy CT in patients treated with anti-angiogenic agents for non-small cell lung cancer: new method of monitoring tumor response, Korean J. Radiol. 13 (2012) 702–710.
[8] H.Y. Lee, J.Y. Jeong, K.S. Lee, et al., Histopathology of lung adenocarcinoma based on new IASLC/ATS/ERS classification: prognostic stratification with functional and metabolic imaging biomarkers, J. Magn. Reson. Imaging 38 (2013) 905–913.
[9] H.Y. Lee, N. Kim, J.M. Goo, E.K. Chie, H.J. Song, Perfusion parameters as potential imaging biomarkers for the early prediction of radiotherapy response in a rat tumor model, Diagn. Interv. Radiol. 22 (2016) 231–240.
[10] C. Messiou, M. Orton, J.E. Ang, et al., Advanced solid tumors treated with cediranib: comparison of dynamic contrast-enhanced MR imaging and CT as markers of vascular activity, Radiology 265 (2012) 426–436.
[11] M.R. Divine, P. Katiyar, U. Kohlhofer, L. Quintanilla-Martinez, B.J. Pichler, J.A. Disselhorst, A population-based Gaussian Mixture Model Incorporating 18F-FDG PET and diffusion-weighted MRI Quantifies Tumor Tissue Classes, J. Nuclear Med. 57 (2016) 473–479.
[12] L. Chen, P.L. Choyke, T.H. Chan, C.Y. Chi, G. Wang, Y. Wang, Tissue-specific compartmental analysis for dynamic contrast-enhanced MR imaging of complex tumors, IEEE Trans. Med. Imaging 30 (2011) 2044–2058.
[13] Y. Chong, J.H. Kim, H.Y. Lee, et al., Quantitative CT variables enabling response prediction in neoadjuvant therapy with EGFR-TKIs: are they different from those in neoadjuvant concurrent chemoradiotherapy? PLoS One 9 (2014) e88598.
[14] J.Y. Son, H.Y. Lee, J.H. Kim, et al., Quantitative CT analysis of pulmonary ground-glass opacity nodules for distinguishing invasive adenocarcinoma from non-invasive or minimally invasive adenocarcinoma: the added value of using iodine mapping, Eur. Radiol. 26 (2016) 43–54.
[15] H.J. Aerts, E.R. Velazquez, R.T. Leijenaar, et al., Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach, Nat. Commun. 5 (2014) 4006.
[16] J.P. Ko, J. Suh, O. Ibidapo, et al., Lung adenocarcinoma: correlation of quantitative CT findings with pathologic findings, Radiology 280 (2016) 931–939.
[17] J. Park, Y. Kobayashi, K.Y. Urayama, H. Yamaura, Y. Yatabe, T. Hida, Imaging characteristics of driver mutations in EGFR, KRAS, and ALK among treatment-naive patients with advanced lung adenocarcinoma, PLoS One 11 (2016) e0161081.
[18] S. Kothari, J.H. Phan, T.H. Stokes, M.D. Wang, Pathology imaging informatics for quantitative analysis of whole-slide images, J. Am. Med. Inform. Assoc. 20 (2013) 1099–1108.
[19] K.H. Yu, C. Zhang, G.J. Berry, et al., Predicting non-small cell lung cancer prognosis by fully automated microscopic pathology image features, Nat. Commun. 7 (2016) 12474.
[20] T. Heye, E.M. Merkle, C.S. Reiner, et al., Reproducibility of dynamic contrast-enhanced MR imaging. Part II. Comparison of intra- and interobserver variability with manual region of interest placement versus semiautomatic lesion segmentation and histogram analysis, Radiology 266 (2013) 812–821.
[21] E. Rios Velazquez, H.J. Aerts, Y. Gu, et al., A semiautomatic CT-based ensemble segmentation of lung tumors: comparison with oncologists' delineations and with the surgical specimen, Radiother. Oncol. 105 (2012) 167–173.
[22] H.Y. Lee, J.Y. Jeong, K.S. Lee, et al., Solitary pulmonary nodular lung adenocarcinoma: correlation of histopathologic scoring and patient survival with imaging biomarkers, Radiology 264 (2012) 884–893.
[23] N. Motoi, J. Szoke, G.J. Riely, et al., Lung adenocarcinoma: modification of the 2004 WHO mixed subtype to include the major histologic subtype suggests correlations between papillary and micropapillary adenocarcinoma subtypes, EGFR mutations and gene expression analysis, Am. J. Surg. Pathol. 32 (2008) 810–827.
[24] D. Hanahan, R.A. Weinberg, Hallmarks of cancer: the next generation, Cell 144 (2011) 646–674.
[25] M. Jamal-Hanjani, S.A. Quezada, J. Larkin, C. Swanton, Translational implications of tumor heterogeneity, Clin. Cancer Res. 21 (2015) 1258–1266.
[26] R.A. Burrell, N. McGranahan, J. Bartek, C. Swanton, The causes and consequences of genetic heterogeneity in cancer evolution, Nature 501 (2013) 338–345.
[27] C. Swanton, Intratumor heterogeneity: evolution through space and time, Cancer Res. 72 (2012) 4875–4882.
[28] M. Greaves, C.C. Maley, Clonal evolution in cancer, Nature 481 (2012) 306–313.
[29] E.C. de Bruin, N. McGranahan, R. Mitter, et al., Spatial and temporal diversity in genomic instability processes defines lung cancer evolution, Science 346 (2014) 251–256.
[30] D. Killock, Genetics: intratumour heterogeneity—a game of snakes and ladders, Nat. Rev. Clin. Oncol. 13 (2016) 1.
[31] S. Aparicio, C. Caldas, The implications of clonal genome evolution for cancer medicine, N. Engl. J. Med. 368 (2013) 842–851.
[32] S.E. Baldus, K.L. Schaefer, R. Engers, D. Hartleb, N.H. Stoecklein, H.E. Gabbert, Prevalence and heterogeneity of KRAS BRAF, and PIK3CA mutations in primary colorectal adenocarcinomas and their corresponding metastases, Clin. Cancer Res. 16 (2010) 790–799.
[33] E.A. Kidd, P.W. Grigsby, Intratumoral metabolic heterogeneity of cervical cancer, Clin. Cancer Res. 14 (2008) 5236–5241.
[34] V. Huyge, C. Garcia, J. Alexiou, et al., Heterogeneity of metabolic response to systemic therapy in metastatic breast cancer patients, Clin. Oncol. (R. Coll. Radiol.) 22 (2010) 818–827.
[35] J.A. Engelman, J. Settleman, Acquired resistance to tyrosine kinase inhibitors during cancer therapy, Curr. Opin. Genet. Dev. 18 (2008) 73–79.
[36] T. Kosaka, Y. Yatabe, H. Endoh, et al., Analysis of epidermal growth factor receptor gene mutation in patients with non-small cell lung cancer and acquired resistance to gefitinib, Clin. Cancer Res. 12 (2006) 5764–5769.
[37] A.B. Turke, K. Zejnullahu, Y.L. Wu, et al., Preexistence and clonal selection of MET amplification in EGFR mutant NSCLC, Cancer Cell 17 (2010) 77–88.
[38] C. Curtis, S.P. Shah, S.F. Chin, et al., The genomic and transcriptomic architecture of 2,000 breast tumours reveals novel subgroups, Nature 486 (2012) 346–352.
[39] R.S. Heist, J.A. Engelman, SnapShot: non-small cell lung cancer, Cancer Cell 21 (2012), 448, e442.
[40] The Cancer Genome Atlas Research Network, Comprehensive genomic characterization of squamous cell lung cancers, Nature 489 (2012) 519–525.
[41] The Cancer Genome Atlas Research Network, Comprehensive molecular profiling of lung adenocarcinoma, Nature 511 (2014) 543–550.

Please cite this article in press as: G. Lee, et al., Radiomics and its emerging role in lung cancer research, imaging biomarkers and clinical management: State of the art, Eur J Radiol (2016), http://dx.doi.org/10.1016/j.ejrad.2016.09.005

[42] H. Bai, Z. Wang, K. Chen, et al., Influence of chemotherapy on EGFR mutation status among patients with non-small-cell lung cancer, J. Clin. Oncol. 30 (2012) 3077–3083.
[43] M. Gerlinger, A.J. Rowan, S. Horswell, et al., Intratumor heterogeneity and branched evolution revealed by multiregion sequencing, N. Engl. J. Med. 366 (2012) 883–892.
[44] M.W. Schmitt, L.A. Loeb, J.J. Salk, The influence of subclonal resistance mutations on targeted cancer therapy, Nat. Rev. Clin. Oncol. 13 (2016) 335–347.
[45] H.J. Yoon, H.Y. Lee, K.S. Lee, et al., Repeat biopsy for mutational analysis of non-small cell lung cancers resistant to previous chemotherapy: adequacy and complications, Radiology 265 (2012) 939–948.
[46] R. Iqbal, G.M. Kramer, E.E. Verwer, et al., Multiparametric analysis of the relationship between tumor hypoxia and perfusion with 18F-fluoroazomycin arabinoside and 15O-H2O PET, J. Nucl. Med. 57 (2016) 530–535.
[47] Y. Ohno, H. Koyama, H.Y. Lee, T. Yoshikawa, K. Sugimura, Magnetic resonance imaging (MRI) and positron emission tomography (PET)/MRI for lung cancer staging, J. Thorac. Imaging 31 (2016) 215–227.
[48] J. Einenkel, U.D. Braumann, L.C. Horn, et al., Evaluation of the invasion front pattern of squamous cell cervical carcinoma by measuring classical and discrete compactness, Comput. Med. Imaging Graph 31 (2007) 428–435.
[49] S. Diciotti, S. Lombardo, G. Coppini, L. Grassi, M. Falchini, M. Mascalchi, The LoG characteristic scale: a consistent measurement of lung nodule size in CT imaging, IEEE Trans. Med. Imaging 29 (2010) 397–409.
[50] A.C. Jirapatnakul, S.V. Fotin, A.P. Reeves, A.M. Biancardi, D.F. Yankelevitz, C.I. Henschke, Automated nodule location and size estimation using a multi-scale Laplacian of Gaussian filtering approach, Conf. Proc. IEEE Eng. Med. Biol. Soc. 2009 (2009) 1028–1031.
[51] F.C. Detterbeck, C.J. Gibson, Turning gray: the natural history of lung cancer over time, J. Thorac. Oncol. 3 (2008) 781–792.
[52] B.B. Tan, K.R. Flaherty, E.A. Kazerooni, M.D. Iannettoni, The solitary pulmonary nodule, Chest 123 (2003) 89S–96S.
[53] Z.E. Labby, S.G. Armato 3rd, J.J. Dignam, C. Straus, H.L. Kindler, A.K. Nowak, Lung volume measurements as a surrogate marker for patient response in malignant pleural mesothelioma, J. Thorac. Oncol. 8 (2013) 478–486.
[54] Z.E. Labby, C. Straus, P. Caligiuri, et al., Variability of tumor area measurements for response assessment in malignant pleural mesothelioma, Med. Phys. 40 (2013) 081916.
[55] H.Y. Lee, S.H. Hyun, K.S. Lee, et al., Volume-based parameter of 18)F-FDG PET/CT in malignant pleural mesothelioma: prediction of therapeutic response and prognostic implications, Ann. Surg. Oncol. 17 (2010) 2787–2794.
[56] J.H. Lee, H.Y. Lee, M.J. Ahn, et al., Volume-based growth tumor kinetics as a prognostic biomarker for patients with EGFR mutant lung adenocarcinoma undergoing EGFR tyrosine kinase inhibitor therapy: a case control study, Cancer Imaging 16 (2016) 5.
[57] B. de Hoop, H. Gietema, S. van de Vorst, K. Murphy, R.J. van Klaveren, M. Prokop, Pulmonary ground-glass nodules: increase in mass as an early indicator of growth, Radiology 255 (2010) 199–206.
[58] K.T. Bae, P. Fuangtharnthip, S.R. Prasad, B.N. Joe, J.P. Heiken, Adrenal masses: CT characterization with histogram analysis method, Radiology 228 (2003) 735–742.
[59] J. Yang, L. Zhang, X.J. Fave, et al., Uncertainty analysis of quantitative imaging features extracted from contrast-enhanced CT in lung tumors, Comput. Med. Imaging Graph 48 (2016) 1–8.
[60] A. Kamiya, S. Murayama, H. Kamiya, T. Yamashiro, Y. Oshiro, N. Tanaka, Kurtosis and skewness assessments of solid lung nodule density histograms: differentiating malignant from benign nodules on CT, Jpn. J. Radiol. 32 (2014) 14–21.
[61] H. Kang, H.Y. Lee, K.S. Lee, J.H. Kim, Imaging-based tumor treatment response evaluation: review of conventional new, and emerging concepts, Korean J. Radiol. 13 (2012) 371–390.
[62] H.Y. Lee, K.S. Lee, Ground-glass opacity nodules: histopathology imaging evaluation, and clinical implications, J. Thorac. Imaging 26 (2011) 106–118.
[63] J.H. Min, H.Y. Lee, K.S. Lee, et al., Stepwise evolution from a focal pure pulmonary ground-glass opacity nodule into an invasive lung adenocarcinoma: an observation for more than 10 years, Lung Cancer 69 (2010) 123–126.
[64] T. Eguchi, A. Yoshizawa, S. Kawakami, et al., Tumor size and computed tomography attenuation of pulmonary pure ground-glass nodules are useful for predicting pathological invasiveness, PLoS One 9 (2014) e97867.
[65] H.Y. Lee, Y.L. Choi, K.S. Lee, et al., Pure ground-glass opacity neoplastic lung nodules: histopathology imaging, and management, AJR Am. J. Roentgenol. 202 (2014) W224–233.
[66] K. Ikeda, K. Awai, T. Mori, K. Kawanaka, Y. Yamashita, H. Nomori, Differential diagnosis of ground-glass opacity nodules: CT number analysis by three-dimensional computerized quantification, Chest 132 (2007) 984–990.
[67] J.Y. Son, H.Y. Lee, K.S. Lee, et al., Quantitative CT analysis of pulmonary ground-glass opacity nodules for the distinction of invasive adenocarcinoma from pre-invasive or minimally invasive adenocarcinoma, PLoS One 9 (2014) e104066.
[68] S.H. Bak, H.Y. Lee, J.H. Kim, et al., Quantitative CT scanning analysis of pure ground-glass opacity nodules predicts further CT scanning change, Chest 149 (2016) 180–191.
[69] G.J. Cook, C. Yip, M. Siddique, et al., Are pretreatment 18F-FDG PET tumor textural features in non-small cell lung cancer associated with response and survival after chemoradiotherapy, J. Nucl. Med. 54 (2013) 19–26.
[70] T. Pyka, R.A. Bundschuh, N. Andratschke, et al., Textural features in pre-treatment [F18]-FDG-PET/CT are correlated with risk of local recurrence and disease-specific survival in early stage NSCLC patients receiving primary stereotactic radiation therapy, Radiat. Oncol. 10 (2015) 100.
[71] O.S. Al-Kadi, D. Watson, Texture analysis of aggressive and nonaggressive lung tumor CE CT images, IEEE Trans. Biomed. Eng. 55 (2008) 1822–1830.
[72] D.V. Fried, S.L. Tucker, S. Zhou, et al., Prognostic value and reproducibility of pretreatment CT texture features in stage III non-small cell lung cancer, Int. J. Radiat. Oncol. Biol. Phys. 90 (2014) 834–842.
[73] B. Ganeshan, S. Abaleke, R.C. Young, C.R. Chatwin, K.A. Miles, Texture analysis of non-small cell lung cancer on unenhanced computed tomography: initial evidence for a relationship with tumour glucose metabolism and stage, Cancer Imaging 10 (2010) 137–143.
[74] B. Ganeshan, E. Panayiotou, K. Burnand, S. Dizdarevic, K. Miles, Tumour heterogeneity in non-small cell lung carcinoma assessed by CT texture analysis: a potential marker of survival, Eur. Radiol. 22 (2012) 796–802.
[75] J.P. O'Connor, C.J. Rose, J.C. Waterton, R.A. Carano, G.J. Parker, A. Jackson, Imaging intratumor heterogeneity: role in therapy response resistance, and clinical outcome, Clin. Cancer Res. 21 (2015) 249–257.
[76] J. Wu, M.F. Gensheimer, X. Dong, et al., Robust intratumor partitioning to identify high-risk subregions in lung cancer: a pilot study, Int. J. Radiat. Oncol. Biol. Phys. 95 (2016) 1504–1512.
[77] J. Wu, M.F. Gensheimer, X. Dong, et al., Robust intratumor partitioning to identify high-risk subregions in lung cancer: a pilot study, Int. J. Radiat. Oncol. Biol. Phys. 95 (2016) 1504–1512.
[78] F. Tixier, C.C. Le Rest, M. Hatt, et al., Intratumor heterogeneity characterized by textural features on baseline 18F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer, J. Nucl. Med. 52 (2011) 369–378.
[79] T. Win, K.A. Miles, S.M. Janes, et al., Tumor heterogeneity and permeability as measured on the CT component of PET/CT predict survival in patients with non-small cell lung cancer, Clin. Cancer Res. 19 (2013) 3591–3599.
[80] S. Kido, K. Kuriyama, M. Higashiyama, T. Kasugai, C. Kuroda, Fractal analysis of internal and peripheral textures of small peripheral bronchogenic carcinomas in thin-section computed tomography: comparison of bronchioloalveolar cell carcinomas with nonbronchioloalveolar cell carcinomas, J. Comput. Assist. Tomogr. 27 (2003) 56–61.
[81] F.E. Lennon, G.C. Cianci, N.A. Cipriani, et al., Lung cancer-a fractal viewpoint, Nat. Rev. Clin. Oncol. 12 (2015) 664–675.
[82] C. Wang, E. Subashi, F.F. Yin, Z. Chang, Dynamic fractal signature dissimilarity analysis for therapeutic response assessment using dynamic contrast-enhanced MRI, Med. Phys. 43 (2016) 1335–1347.
[83] M.D. Kuo, N. Jamshidi, Behind the numbers: decoding molecular phenotypes with radiogenomics–guiding principles and technical considerations, Radiology 270 (2014) 320–325.
[84] E.L. Kwak, Y.J. Bang, D.R. Camidge, et al., Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer, N. Engl. J. Med. 363 (2010) 1693–1703.
[85] R. Pirker, M. Filipits, Personalized treatment of advanced non-small-cell lung cancer in routine clinical practice, Cancer Metastasis Rev. 35 (2016) 141–150.
[86] V.S. Nair, O. Gevaert, G. Davidzon, et al., Prognostic PET 18F-FDG uptake imaging features are associated with major oncogenomic alterations in patients with resected non-small cell lung cancer, Cancer Res. 72 (2012) 3725–3734.
[87] M.W. Dewhirst, J.T. Chi, Understanding the tumor microenvironment and radioresistance by combining functional imaging with global gene expression, Semin. Radiat. Oncol. 23 (2013) 296–305.
[88] H.J. Yoon, I. Sohn, J.H. Cho, et al., Decoding tumor phenotypes for ALK ROS1, and RET fusions in lung adenocarcinoma using a radiomics approach, Medicine (Baltim.) 94 (2015) e1753.
[89] C.J. Jeong, H.Y. Lee, J. Han, et al., Role of imaging biomarkers in predicting anaplastic lymphoma kinase-positive lung adenocarcinoma, Clin. Nucl. Med. 40 (2015) e34–39.
[90] B. Zhao, Y. Tan, W.Y. Tsai, et al., Reproducibility of radiomics for deciphering tumor phenotype with imaging, Sci. Rep. 6 (2016) 23428.
[91] R.T. Leijenaar, G. Nalbantov, S. Carvalho, et al., The effect of SUV discretization in quantitative FDG-PET radiomics: the need for standardized methodology in tumor texture analysis, Sci. Rep. 5 (2015) 11075.
[92] F.H. van Velden, G.M. Kramer, V. Frings, et al., Repeatability of radiomic features in non-small-cell lung cancer [18F]FDG-PET/CT studies: impact of reconstruction and delineation, Mol. Imaging Biol. 18 (2016) 788–795.
[93] X. Fave, D. Mackin, J. Yang, et al., Can radiomics features be reproducibly measured from CBCT images for patients with non-small cell lung cancer, Med. Phys. 42 (2015) 6784–6797.
[94] M.J. Nyflot, F. Yang, D. Byrd, S.R. Bowen, G.A. Sandison, P.E. Kinahan, Quantitative radiomics: impact of stochastic effects on textural feature analysis implies the need for standards, J. Med. Imaging (Bellingham) 2 (2015) 041002.
[95] C. Parmar, P. Grossmann, J. Bussink, P. Lambin, H.J. Aerts, Machine learning methods for quantitative radiomic biomarkers, Sci. Rep. 5 (2015) 13087.

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[96] C.C. Reyes-Aldasoro, A. Bhalerao, Volumetric texture description and discriminant feature selection for MRI, Inf. Process Med. Imaging 18 (2003) 282–293.
[97] J. Antunes, S. Viswanath, M. Rusu, et al., Radiomics analysis on FLT-PET/MRI for characterization of early treatment response in renal cell carcinoma: a proof-of-concept study, Transl. Oncol. 9 (2016) 155–162.
[98] B.R. Condon, J. Patterson, D. Wyper, A. Jenkins, D.M. Hadley, Image non-uniformity in magnetic resonance imaging: its magnitude and methods for its correction, Br. J. Radiol. 60 (1987) 83–87.
[99] U. Vovk, F. Pernus, B. Likar, A review of methods for correction of intensity inhomogeneity in MRI, IEEE Trans. Med. Imaging 26 (2007) 405–421.
[100] L. Alic, W.J. Niessen, J.F. Veenland, Quantification of heterogeneity as a biomarker in tumor imaging: a systematic review, PLoS One 9 (2014) e110300.
[101] K.H. Yu, M. Snyder, Omics profiling in precision oncology, Mol. Cell Proteom. 15 (2016) 2525–2536.
[102] P. Opulencia, D.S. Channin, D.S. Raicu, J.D. Furst, L.I.D.C. Mapping, RadLex: and lung nodule image features, J. Digit. Imaging 24 (2011) 256–270.
[103] H.J. Aerts, The potential of radiomic-based phenotyping in precision medicine: a review, JAMA Oncol. (2016), http://dx.doi.org/10.1001/jamaoncol.2016.2631 (ahead of print).

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