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REVIEW ARTICLE

# Clinical applications of textural analysis in non-small cell lung cancer

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## ABSTRACT

Lung cancer is the leading cause of cancer mortality worldwide. Treatment pathways include regular cross-sectional imaging, generating large data sets which present intriguing possibilities for exploitation beyond standard visual interpretation. This additional data mining has been termed "radiomics" and includes semantic and agnostic approaches. Textural analysis (TA) is an example of the latter, and uses a range of mathematically derived features to describe an image or region of an image. Often TA is used to describe a suspected or known tumour. TA is an attractive tool as large existing image sets can be submitted to diverse techniques for data processing, presentation, interpretation and hypothesis testing with annotated clinical outcomes. There is a growing anthology of published data using different TA techniques to differentiate between benign and malignant lung nodules, differentiate tissue subtypes of lung cancer, prognosticate and predict outcome and treatment response, as well as predict treatment side effects and potentially aid radiotherapy planning. The aim of this systematic review is to summarize the current published data and understand the potential future role of TA in managing lung cancer.

## INTRODUCTION

Lung cancer is the second commonest cancer diagnosed in the UK after prostate cancer in males and breast cancer in females. It has a very poor prognosis.[1,2] Patients undergo regular cross-section imaging to diagnose, stage, assess response and undertake surveillance after treatment for lung cancer, which leads to a pool of imaging data that potentially has significant value beyond accurate staging of the patient. CT is a central tool in managing lung cancer. It is relatively inexpensive, quick and widely available. [$^{18}$F]–2-fluoro-2-deoxy-D-glucose positron emission tomography/computed tomography (FDG PET-CT) superposes a functional assessment of tumour metabolism. It can greatly aid in, *e.g.* the identification of malignant lung nodules with a sensitivity of 95% and specificity of 82%,[3] but is less widely available and considerably more expensive. Value-based care provides incentives to maximize information from standard investigations. Radiomics aims to extract and analyse large amounts of advanced quantitative data from medical imaging.[4] Textural analysis (TA) is a subtype of radiomics, an example of an agnostic, rather than semantic, approach within this field, based on mathematical derivations rather than prior clinical concepts.[5]

TA can be used on existing data sets with no further dedicated or specialist imaging required. A considerable body of literature has accumulated in this field. TA has the potential to differentiate between benign and malignant lung nodules[6–15] prognosticate outcome,[16–28] aid improved radiotherapy planning,[29] predicting radiotherapy side effects[30] and give a greater understanding of response assessment.[31–40] The aim of this review is to explain how different TA methods have been investigated in non-small cell lung cancer (NSCLC), and to describe their current applicability and future potential.[41]

## METHODS AND MATERIALS

PubMed, Medline and Web of Science were searched using the search terms "textural analysis", "texture analysis" and "radiomics" with MeSH terms "lung neoplasms", "non-small cell lung cancer" and "small cell lung cancer". The search period was January 2010 to December 2016.

341 papers were identified, which were filtered using the terms oncology and English. Papers discussing other primary cancers and duplicates were excluded. This left 104 papers.

## What is textural analysis (TA)?

TA uses a range of mathematically calculated features to describe an image or region of an image. Often TA is used to describe a suspected or known tumour. The complexity of the analysis depends on the feature being described. Although different textural features have been generated from a wide range of sources, they can be broadly divided into three categories: first-order (least complex), second-order and higher-order (most complex). Different subcategories of TA are summarized in Table 1. First-order features are often calculated as a single figure describing the texture of the whole volume being analysed. Second-order features describe the relationship between two points, such as two pixels or voxels within the same image. Higher-order features describe the relationship between a pixel and more than one other pixel, *i.e.* a minimum of three points in space.

First-order textural features use a range of basic statistical methods to express a single measure, including: energy, kurtosis, maximum and minimum intensity, average intensity (median and mean), range of intensities, skewness, SD, uniformity, entropy (irregularity of intensity value distribution) and variance. SD, variance and mean absolute deviation express how the range of intensities are distributed. Skewness measures how much histogram asymmetry there is around the mean. Kurtosis measures the sharpness of the histogram. Randomness can be computed using uniformity and entropy. Entropy is a measure of disorder. The higher the entropy the greater the disorder or heterogeneity. The lower the entropy, the higher the homogeneity. First-order features do not take account of any spatial relationship between different points in an image. Much of the published TA work, particularly related to lung nodules focuses on first-order features of TA.[43–48]

Second-order textural features describe a relationship between two points within the same region of interest. It can describe the three-dimensional size and shape and a range of values within a tumour. By deriving a region of interest, measurements can be taken of variations across the tumour volume, including entropy, compactness, sphericity, surface area and surface to volume ratio. Describing higher-order textural features is more complex than first- or second-order features, as it involves identifying the relationship between 3 or more points.

TA often requires complex interpretation. It is common to compare clinical interpretation with clinical interpretation

Table 1. Categories of textural analysis. Adapted from Alobaidli et al[42]

| Feature | Name of feature | Definition |
|---|---|---|
| First-order | Mean | Average intensity of values of an image |
| | Variance | Spread or variation around the mean |
| | Skewness | Symmetry of intensity values in an image. Skewness = 0 if histogram is symmetrical |
| | Kurtosis | Indication of histogram flatness, Leptokurtic curves are steeper and platykurtic curves are flatter/less peaked |
| | Energy | Uniformity of intensity values |
| Second-order local | Contrast | Measures amount of local variation in intensity values |
| | Angular second moment (energy or uniformity) | Measures homogeneity of intensity value distribution in an image |
| | Homogeneity (inverse difference moment) | Measures the homogeneity of the intensity values of the pixel pair |
| | Correlation | Measures the linear dependencies of intensity values in an image |
| | Entropy | Measure of randomness of intensity values in an image |
| | Sum of first-order features (squares, average, entropy, variance) | |
| Higher-order (local) | Complexity | Measures amount of information in texture |
| | Busyness | Measures the rate of change in intensity values |
| | Contrast | Measures the variation of intensity values in an image |
| | Coarseness | Measures the density of edges in an image |
| | Texture Strength | Measures how definable (distinguishable) primitive texture is |
| High-order (regional) | Grey-level non-uniformity: | Represents the similarity of intensity values in an image |
| | Run length non-uniformity: | Measures the run length similarity |
| | Run percentage | Ratio of total number of runs to the total number of possible runs, measuring the homogeneity of runs. For images with most linear structure, the value of run percentage is lowest. |

combined with TA. The impact of TA can be assessed by various tools including receiver operating characteristic area under the curve (ROC-AUC) and concordance index (CI). ROC-AUC is an explanation of the "usefulness" of a test assessing sensitivity and specificity, assuming a test can be defined in a binary way, *i.e.* "positive" or "negative". ROC-AUC gives a test four outcomes: true negative, true positive, false negative and false positive. The ROC-AUC analyses the true positive rate against the false positive rate, deriving values between 0.5 and 1.0. 0.5 shows a poor test as true positives = false positives, 1 is a perfect test with no false positives. Generally 0.6–0.7 = poor test, 0.7–0.8 = a fair test, 0.8–0.9 = a good test, >0.9 = an excellent test. A second measure is CI, which measures how well a prognostic test distinguishes individuals from a population with or without a particular outcome. Values range from 0.5 (no discrimination) to 1.0 (perfect discrimination).[49] To be significant, a CI measurement should exclude 0.5 from its confidence interval.

## Pre-treatment textural analysis (TA)

A wide range of studies have used TA to attempt to define different aspects of lung lesions seen on pre-treatment imaging. TA has been used to differentiate benign or minimally invasive lesions from malignant tissue (particularly lung nodules) using CT,[6,8–10,12–15,50,51] FDG PET-CT[52] ultrasound[53] and different types of tumour histology,[54–56] to aid assessment of the tumour and aid treatment decisions. These features can be combined to predict the likelihood of a nodule being malignant.

TA has also been employed to help classify histological images. An automatic classifier of squamous cell and adenocarcinoma helped aid tissue classification[57] and TA of nucleus features has been shown to predict early recurrence of NSCLC.[58]

### *Lung nodules*

TA has been used to differentiate between different tissues and determine the risk of malignancy of small pulmonary nodules. Pulmonary nodules are focal opacities appearing on imaging that are defined as less than 3 cm in axial diameter; they can be solid, semi-solid or non-solid in appearance.[59] CT density [measured in Hounsfield units (HU)] and morphology can be used to assess pulmonary nodules. Solid cancer, non-solid lepidic adenocarcinoma, blood and inactive fibrous tissue all have different HU measurements.[60] However, it is still difficult to predict with certainty the pathology of small lung lesions, because up to 39% of lung nodules with a benign CT morphological appearance can be malignant.[61]

As the use of medical imaging increases, more lung nodules are likely to be identified. Lung cancer screening using low-dose CT has a relative risk reduction of 20% for lung cancer specific survival, when compared with chest radiography in a high risk population. In each of the 3 years of screening, identification of a nodule occurred in 27.3%, 27.9% and 16.8% of the trial population in years 1–3, respectively. Individuals in whom a nodule was identified in years 1 and 2 were not automatically excluded from continuing with screening, but more than 95% of these nodules would be benign.[62] TA may aid risk stratification of these lung nodules. This has significant potential to improve the predictivity of screening and reduce the morbidities rendered by biopsy and surgical resection

As stated, lung nodules can be broadly divided into solid, semi-solid and non-solid. Several studies have aimed to help classify lung nodules into broad categories before further analysis.[44, 63] Ground glass nodules (GGNs) are non-solid and can be difficult to extract from an image accurately.[45, 64] Three studies suggest TA can convincingly determine malignant from non-malignant nodules. The first study capitalized on potential differences in heterogeneity between the nodule edge and centre. The difference was much greater in malignant nodules when compared with inflammatory nodules with ROC-AUC of 0.836.[65] In a second study, computer-aided diagnosis of whether a lesion was benign or malignant achieved 94% accuracy in correctly identifying all non-cancerous lesions as benign using a single image slice.[66] These results were achieved using all slices of the abnormal lesion.[48]

In a cohort of 55 patients, CT TA improved specificity from 38.5 to 100% when compared with a FDG PET-CT-CT in differentiating primary lung tumours from granulomatous lung lesions.[47] Sensitivity was similar in both groups (75% using five TA features *vs* 79 with FDG PET-CT %). High entropy (high level of disorder) was more common in primary NSCLCs. Interestingly in this study, using a combination of three textural features generated from a contrast-enhanced CT scan rather than a non-contrast CT scan reduced the sensitivity from 88 to 38%. The reason for this is not clear, but the presence of contrast may obscure the texture of the region of interest. Contrast could potentially act as a marker of vascularity, but as this study suggests, it could obscure textural information. The effect of contrast is not necessarily binary, as the results using contrast could depend on contrast-related factors such as speed of infusion, contrast agent used, amount of infusion given; image-related factors such as delay between contrast and image acquisition and patient-related factors such as cardiac output and body habitus. These factors may require standardization so that they do not unduly influence the TA.

GGNs have a higher malignant probability than solid nodules, while a combination of GGN and solid nodule have an even higher malignant potential (62.5–89.6%),[67] although at least half (49–70%) of these partial solid ground glass nodules disappear within 3 months. Analysis was performed aiming to identify textural features that may predict persistent *vs* transient partial solid ground glass nodules. When textural features were combined with clinical and CT features, differentiating performance significantly increased from 79 to 92.9% ($p < 0.05$). As with the previous study, Wang et al[68] showed that TA can improve diagnostic certainty. In contrast to the previous study, this study analysed the whole tumour, instead of a single image slice. This technique improved sensitivity and specificity from 0.82 and 0.47 to 0.95 and 0.71, respectively.[68] 3D TA has also been used to differentiate between pre malignant adenocarcinomas and early invasive adenocarcinomas.[56] It is not currently clear how large a region of interest needs to be analysed. There are three possible approaches, 2D analysis of a single slice, 2D analysis of multiple slices or 3D analysis of the whole region of interest. If a single slice is being used, then often this is the largest slice, but cross-sectional area does not definitely correlate with the greatest amount of extractable information. Han et al showed

that generating 2D textural features on multiple slices from 3D data was better than generating them from a single 2D slice. Although 3D data did not improve on multiple 2D slices, it can potentially analyse extra features not available in a 2D analysis. 2D analysis on a single plan on a single slice would not detect differences in other planes, *e.g.* if the axial plane was used, data regarding the coronal or sagittal plane of the tumour could not be generated. Analysing multiple 2D slices may help identify the most representative 2D slice, but does not overcome the limitations regarding information in 3D.

FDG PET-CT is another type of imaging used to assess lung nodules. In many institutions worldwide FDG PET-CT is less available than CT, but is a very useful tool in identifying malignant lung nodules, with a sensitivity of 95% and specificity of 82%.[3] Tracer uptake can be heterogeneous within a tumour because of areas of necrosis, differences in blood flow, cellular activity, microvessel density or hypoxia. Whilst this review focuses on the exploitable TA features of standard CT scans, where PET-CT data sets are available, additional value can be extracted from these scans. Fractal analysis is a TA modality that has been studied in this setting. Morphological fractal dimension and density fractal dimension can be generated from CT and PET images of pulmonary images. Combining morphological fractal dimensions and FDG PET-CT or density fractal dimensions improves diagnostic accuracy to above 90% when comparing benign nodules with a primary NSCLC[69] using FDG-PET alone.

MRI is not routinely used to assess lung tumours before treatment. However, a small single institution series suggests that entropy derived from dynamic contrast enhanced MRI may predict progression free survival (PFS).[70]

### *Pre-treatment textural analysis (TA) of primary lung tumours using CT*

TA has been shown to have potential as an imaging biomarker to identify the histological subtype of NSCLC. Although many of these studies are relatively small, CT TA radio-genomics is a rapidly expanding field. CT TA has helped to differentiate *KRAS* oncogene-mutated tumours from pan-wild type tumours,[71] epidermal growth factor receptor (*EGFR*) mutant tumours from wild type tumours,[72,73] *EGFR*-mutated tumours from anaplastic lymphoma kinase (*ALK*) () rearranged tumours,[74] lepidic adenocarcinomas from non-lepidic adenocarcinomas[75] and *ALK* rearranged tumours from unrearranged tumours.[76,77] Work in progress has identified a correlation between kurtosis (a first-order textural feature) in NSCLC and the expression of a gene coding for a protein that regulates mucin production, Mucin5AC. The expression of this gene is considered a marker of the activation of the MAP kinase signalling pathway. Increased presence of mucin produces lower attenuation with X-rays than soft tissue. This begins to demonstrate the potential for radio-pathological correlation through advanced imaging analysis.[78]

Conventional predictors of outcome in NSCLC include TNM staging, AJCC stage, age, sex, histology, comorbidities and performance status. The use of a biomarker from CT imaging to prognosticate patients' outcomes, risk of distant metastases and overall survival (OS) is attractive. CT texture features have been correlated with PET-CT SUVmax, tumour staging and degree of tumour hypoxia.[16,79] A combination of TA features have been identified that predict recurrence in surgical patients[17] and overall survival in patients with adenocarcinoma.[80]

TA can assess many different features and this presents a challengingly large experimental space. In 98 patients with stage I-III NSCLC receiving radical radiotherapy, the 15 most predictive textural features were chosen from over 600 features, from pre-treatment CT scans.[19] Risk of distant metastases were divided into high risk and low risk with a CI of 0.62. Use of simple radiomic features were able to predict risk of distant metastases in a discovery and validation set of patients. In a similar study in Stage 3 patients, receiving chemo-radiotherapy, textural features extracted from the gross tumour volume, patients could be divided into high and low risk based on traditional prognostic factors such as staging and features from TA,[20] with a CI of 0.89 and 0.91 for overall survival and locoregional control, respectively. Grove et al showed that morphologically similar tumours could be divided into better and worse prognosis groups and validated this at a separate institution, using convexity and central tumour entropy. More irregular tumours conferred a worse prognosis.[21]

TA in combination with machine learning has been shown to predict recurrence with a high degree of accuracy (CI 0.81)[41] and OS,[81] using the pre-treatment image of a single CT slice of 101 patients who underwent resection of Stage I primary lung adenocarcinoma. The TA used a second-order feature called Riesz wavelets, which were chosen to differentiate between solid component and ground glass opacities. Support vector machine (SVM, a form of machine learning) has been used to classify high risk and low risk lesions, as well as risk of recurrence.[23,24] The benefit is that SVM can separate non-linear data; it can separate data into two groups that are not obviously distinct when plotted, when methods such as logistic regression are less useful. The more round the tumour (spherical disproportionality) and the greater the tumour heterogeneity, the less likely the response, in patients undergoing neo-adjuvant chemo-radiotherapy for NSCLC. The strength of this study was that treatment effect was assessed by pathological assessment of the surgically resected specimen. In a separate study, CT TA measures were able to predict tumour shrinkage after radical radiotherapy.[25]

A range of TA studies have been performed with broadly similar methodology. A patient cohort with a known outcome measure is identified. A single slice or whole tumour is segmented out from the rest of the scan. A range of first-, second- and higher-order textural features can then be extracted. In many cases, a large number of TA features can be calculated. Features are chosen that correlate with outcome. The difficulty is that different TA features are significant in different studies, using different methods of analyses. An association between TA features and outcome could be statistically significant by chance, if very large numbers of parameters are analysed. Some TA features are dependent on preprocessing of the image before TA is performed, whereas others are independent,[26] which means the independent features were more likely to be robust, as they are not prone to

variations in preprocessing. These concerns limit the reproducibility of many studies and their applicability as a practical clinical tool. Large robust data sets may help to overcome some of these limitations. For example, Palmar et al were able to analyse lung tumours and head and neck tumours in 878 patients with training and validation sets for both tumour types. In this study, radiomic parameters were correlated with stage and prognosis.[82] Reproducibility is a key element in using such a biomarker more widely.

TA can potentially increase the accuracy of nodal staging as lymph nodes can be auto-mapped and identified.[83] TA has been shown to predict whether a lymph node is malignant or not in biopsy proven nodes, with a sensitivity of 81% and specificity of 80% (AUC = 0.87, $p < 0.0001$). This was achieved using a combination of three textural features: entropy, grey level non-uniformity and run length non-uniformity with three features of shape, which assessed the degree to which a lymph node was circular. Using this combination, 84% of malignant nodes and 71% of benign nodes were correctly classified on a non-contrast CT.[84] However, only half the patients (22 of 43 patients) received a staging PET-CT scan. PET imaging shows a small improvement in diagnostic efficacy when compared with measuring nodal dimensions alone. A published study using commercially available software called TexRAD has shown that it is possible to differentiate malignant nodes from benign nodes with a low sensitivity of 53%, but much improved specificity of 97%, with an ROC-AUC of 83%.[85] TA based on endobronchial ultrasound has been shown to differentiate between benign and malignant nodes using fractal dimension.[53]

### *Pre-treatment textural analysis (TA) of primary lung tumours using PET-CT*

FDG PET-CT is used as standard to stage patients potentially suitable for radical treatment for NSCLC. It is becoming increasingly used in managing treatment in NSCLC. Using simple PET metrics such as mean and maximum SUV would not be defined as TA, but analysing tracer uptake can identify heterogeneity across the tumour.

Extracting texture features is dependent on the size and FDG uptake seen on FDG PET-CT imaging.[86–88] FDG-PET texture features have been found to be prognostic[20,89–93] and provides more accurate prognostication than CT TA alone.[94,95] Simple measures such as SUVmax and metabolically active tumour volume have been associated with OS after radiotherapy and response rates after palliative chemotherapy in metastatic lung cancer.[88,96–98] In one study, these metabolic measures have also been found to correlate with first-order textural features,[99] however additional work has suggested that only second-order features correlate with OS.[100] FDG PET-CT-CT has high test-retest and high interobserver stability. In contrast, Cook et al[101] showed that FDG PET parameters (such as SUVmax) did not predict the outcome.FDG PET-CT studies have also been shown to aid the diagnosis of mediastinal lymph nodes.[102,103]Although FDG is the commonest tracer used in clinical practice, other tracers such as F-fluromisonidazole, a marker of tumour hypoxia, are available. F-fluromisonidazole uptake can vary across tumours and therefore, it is possible to assess tracer uptake heterogeneity and to use TA to generate textural features.[104,105] FDG images take 15–20 min to acquire. As a result, tumour movement caused by respiration during image acquisition appears to affect some, but not all textural measures,[106] *e.g.* busyness (a measure of intensity change between a voxel and those around it) was 20% higher in the 4D scan, suggesting that as possibly expected blurring means these measures are sensitive to motion. Fried et al identified that a combination of histogram features, co-occurrence matrices (using 2D relationships), shape and volume correlated with OS and locoregional control, but was not externally validated. Further studies have shown that SUVmax and mean, total lesional glycolysis (TLG) and metabolic tumour volume correlated positively with entropy. Energy and contrast had an inverse relationship[107] and that the FDG PET and CT heterogeneity assessments can separately predict OS.

In a pilot study, Wu et al[29] segmented subregions of tumour based on similarity of appearance, using CT and FDG PET-CT. Each tumour was over-segmented into multiple super pixels using K clustering of the FDG PET and CT images. The volume of the metabolically active subregion predicted OS in this patient cohort, with a CI 0.67 and hazard ratio of 2.79 (log rank $p = 0.004$). These regions appear to be robust against a degree of misregistration, but the PET data does not appear to account for tumour movement. In supporting the use of TA in radiotherapy planning, some CT texture features are robust enough to be identified on linear accelerator based cone beam CT scans from on treatment imaging during radiotherapy.[108] Image quality and the ability to quantify an image is likely to improve as cone beam CT technology quality improves.

The majority of these studies are retrospective. Many studies also use a lot of clinical data alongside to stratify outcome, adding in TA then slightly improves prediction of outcome compared with clinical data alone, rather than the tumour textural features alone predicting outcome. These studies are heterogeneous. They utilize different standards, measurements, equipment and techniques. For this reason, it is difficult to achieve accurate reproducibility. Some studies have heterogeneous cohorts receiving different treatment, either combining tumours that received radiotherapy alone with chemo-radiotherapy or different radiotherapy schedules. Accurate localization and segmentation of tumours on CT imaging is easier to overcome using appropriate windowing, than differences on FDG PET-CT, particularly if 3D PET is used. Some studies have specifically looked at reproducibility and this is an important area of further research.[109,110] At present, it is unlikely that TA assessment is sufficiently robust to act as a biomarker.

## Assessing treatment response

Follow-up CT and PET-CT scans both provide additional opportunities for assessment of treatment response beyond simple visual interpretation. SUV intensity on FDG PET-CT imaging may give a faster response than decrease in tumour volume.[111] Early prediction of response to chemo-radiotherapy has been made using PET heterogeneity. In a study by Dong et al, patients undergoing an on treatment FDG PET-CT scan (after receiving approximately two-thirds of total radiation dose), certain textural features

indicated response to treatment with a higher sensitivity (92 *vs* 73%) and specificity (84 *vs* 80%) than baseline PET features.[112]

Identifying early recurrence after radical radiotherapy can be complex, particularly after stereotactic ablative body radiotherapy (SABR).[113] SABR describes a battery of methods that facilitate the highly targeted delivery of a high dose of radiotherapy in fewer larger doses to an early stage lung tumour. The centre of the tumour often receives two or three times the biological equivalent dose compared with standard radiotherapy. Pre-treatment textural features can improve prediction of outcome, compared with SUVmax alone.[28] Compared with other treatment response assessments, the evidence base for using radiomics and textural features in SABR response assessment is relatively advanced. Treatment-related toxicity is also amenable to assessment by TA. Radiation induced lung injury (RILI) consolidation commonly occur after SABR.[114] Differentiating RILI and tumour recurrence is difficult. When comparing areas of ground glass opacity and consolidation, recurrences were denser and had different textural features than areas of RILI and early response could be predicted.[31–33] FDG PET SUV >5 or SUV higher than the diagnostic FDG PET-CT suggest recurrence.[113] Radiomic features have been extracted, which predict early recurrence and are able to improve sensitivity when compared with physician assessment (AUC 0.85, false negative rate 23% *vs* 99%).[33] Another study has suggested that perfusion characteristics of RILI and recurrence are different, with the areas of recurrence exhibiting changes in perfusion termed as wash-in and wash out phenomenon, not seen in areas of RILI.[34] Lung CT TA changes can be identified in patients receiving radical radiotherapy to the oesophagus, this technique not only identified patients who did, and did not, develop radiation pneumonitis, it also quantified it.[115] It achieved this by comparing randomly generated regions of interest in both pre and post treatment imaging.

In advanced NSCLC tumours, neither volumetric measurements on CT nor RECIST criteria predicted OS.[35] PET SUVmax has been associated with response to chemotherapy and TKIs,[36,37] but not with OS.[38,97] TA could identify response of adenocarcinomas in the metastatic setting but could not identify response in non-adenocarcinomas..[38] Different textural features have been identified in assessing response to chemo-radiotherapy (found tumour volume, mass, kurtosis and skewness) or an EGFR tyrosine kinase inhibitor (heterogeneity).[39] 11 C erlotinib PET requires further investigation but has been shown to potentially identify TKI responders and non-responders in a murine model.[40] Kurtosis after neoadjuvant chemotherapy and intensity variability after tyrosine kinase Inhibitor therapy have been shown to independently predict pathological response.[39] Having a predictor of response is useful as non-responders could potentially avoid a toxic treatment, which would not benefit them and reduce costs of futile therapy.

## Future perspective

The use of TA and radiomics is rapidly evolving. It is attractive as it uses existing imaging data to gain greater information about a tumour or disease state. There has been sufficient work to establish that certain textural features can act as biomarkers. Indeed tumour kurtosis and entropy are entering real-world clinical evaluation as markers of poor prognosis.[78] However, to become more widespread a range of obstacles require attention. It is important to consider standardization of each step in the process including: acquisition, segmentation (ideally auto-segmentation), analysis and interpretation of the data. TA techniques often require an expert to accurately delineate the tumour. TA requires a significant degree of computing power to generate the analysis, it is not currently integrated into current assessment of imaging in diagnosis and response assessment and TA potentially makes workflow with a radiology department more complex.

Some of these challenges can be overcome. For example, extracting textural features automatically reduces or eliminates interobserver error,[116] using an automated technique to delineate tumour volume is more robust than manual delineation[117] and commercialization and user interface optimization may facilitate the incorporation of TA into radiology department workflows. Many studies have analysed the primary tumour and so at present are more likely to be useful for pre-treatment prognostication, rather than post treatment assessment.

To gain the full benefit of textural features, identification and classification of features need to be sufficiently robust to overcome variables such as patient factors (including positioning, respiration phase and motion management and effects or lack of IV contrast), acquisition and processing variables such as image acquisition power, image slice thickness, image reconstruction algorithms, use of segmentation software and operator variability in tumour delineation. Some texture features are reproducible, while others are highly variable and do not generate the same results with repeat testing.[118,119] To minimize these variables and identify the changes related to tumours alone many studies standardize their image acquisition process.[110] Useful biomarkers need to overcome these features or have to be standardized to ensure accurate interpretation of this information.

TA of routine imaging is likely to have a range of uses in the future both within and outside of oncology. With more robust measures of texture it may be helpful in differentiating between benign and malignant lesions, identifying subtypes of malignancy. It will aid surgical and radiotherapy planning and hopefully provide more accurate response assessment. Response assessment is becoming more important as treatment becomes increasingly complex. Standard RECIST size criteria are not adequate for assessing response in immunotherapy as standard RECIST criteria underestimate benefit.[120] Texture could potentially have a role in assessing how a lesion changes rather than just using size assessment. Assessing response after stereotactic radiotherapy is difficult because of the localized radiotherapy change induced by the treatment. Differentiating between inflammation and tumour is difficult, particularly if a biopsy is inconclusive.

Outside of oncology, TA has already been used to assess hepatic and pulmonary fibrosis[121] and to see if different lung pathologies can be diagnosed on imaging alone. It can potentially have a role in differentiating tissue anywhere in the body, potentially preventing the need for more invasive tests.

For these reasons, being able to extract more information for standard imaging is an attractive way of getting more "value" from investigations and is likely to be more routinely introduced into clinical practice in the coming years.

## REFERENCES


1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2012. *CA Cancer J Clin* 2012; **62**: 10–29; **62**: 10–29. doi: https://doi.org/10.3322/caac.20138
2. UK CR. Lung cancer survival statistics. 2015. Available from: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/lung [cited November 2015]
3. Cronin P, Dwamena BA, Kelly AM, Carlos RC. Solitary pulmonary nodules: meta-analytic comparison of cross-sectional imaging modalities for diagnosis of malignancy. *Radiology* 2008; **246**: 772–82. doi: https://doi.org/10.1148/radiol.2463062148
4. Gillies RJ, Kinahan PE, Hricak H. Radiomics: images are more than pictures, they are data. *Radiology* 2016; **278**: 563–77. doi: https://doi.org/10.1148/radiol.2015151169
5. Materka A, Strzelecki M. Texture analysis methods – a review: Technical University of Lodz, Institute of Electronics. 1998.
6. Devan L, Santosham R, Hariharan R. Automated texture-based characterization of fibrosis and carcinoma using low-dose lung CT images. *Int J Imaging Syst Technol* 2014; **24**: 39–44.
7. Dilger SK, Judisch A, Uthoff J, Hammond E, Newell JD, Jr, Sieren JC. Improved pulmonary nodule classification utilizing lung parenchyma texture features. In: Hadjiiski LM, Tourassi GD, eds. *Medical imaging 2015: computer-aided diagnosis*. Proceedings of SPIE. 94142015. Bellingham, Washington, USA: SPIE; 2015.
8. Froz BR, de Carvalho Filho AO, Silva AC, de Paiva AC, Nunes RA, Gattass M. Lung nodule classification using artificial crawlers, directional texture and support vector machine. *Expert Syst Appl* 2017; **69**: 176–88.
9. Lin P-L, Huang P-W, Lee C-H, M-T W. Automatic classification for solitary pulmonary nodule in CT image by fractal analysis based on fractional Brownian motion model. *Pattern Recog* 2013; **46**: 3279–87.
10. Hwang IP, Park CM, Park SJ, Lee SM, McAdams HP, Jeon YK, et al. Persistent pure ground-glass nodules larger than 5 mm: differentiation of invasive pulmonary adenocarcinomas from preinvasive lesions or minimally invasive adenocarcinomas using texture analysis. *Invest Radiol* 2015; **50**: 798–804. doi: https://doi.org/10.1097/RLI.0000000000000186
11. Padma A, Sukanesh R. Combined texture feature analysis of segmentation and classification of benign and malignant tumour CT slices. *J Med Eng Technol* 2013; **37**: 1–9. doi: https://doi.org/10.3109/03091902.2012.712199
12. Pires A, Rusinek H, Suh J, Naidich DP, Pass H, Ko JP. Clustering of lung adenocarcinomas classes using automated texture analysis on CT images. In: Ourselin S, Haynor DR, eds. *Medical imaging 2013: image processing*. Proceedings of SPIE. 86692013. Florida, FL: Springer-Verlag; 2013.
13. Sun T, Zhang R, Wang J, Li X, Guo X. Computer-aided diagnosis for early-stage lung cancer based on longitudinal and balanced data. *PLoS ONE* 2013; **8**: e63559. doi: https://doi.org/10.1371/journal.pone.0063559
14. Orozco HM, Villegas OOV, Sanchez VGC, Domnguez HDO, Alfaro MDN. Automated system for lung nodules classification based on wavelet feature descriptor and support vector machine. *Biomed Eng Online* 2015; **14**: 9. doi: https://doi.org/10.1186/s12938-015-0003-y
15. Son JY, Lee HY, Lee KS, Kim JH, Han J, Jeong JY, 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* 2014; **9**.
16. Ganeshan B, Abaleke S, Young RC, Chatwin CR, Miles KA. 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* 2010; **10**: 137–43. doi: https://doi.org/10.1102/1470-7330.2010.0021
17. Emaminejad N, Qian W, Kang Y, Guan YB, Lure F, Zheng B. Exploring new quantitative CT image features to improve assessment of lung cancer prognosis. In: Hadjiiski LM, Tourassi GD, eds. *Medical Imaging 2015: Computer-Aided Diagnosis*. Proceedings of SPIE. 94142015. Bellingham, Washington, USA: SPIE; 2015.
18. Hawkins SH, Korecki JN, Balagurunathan Y, Gu Y, Kumar V, Basu S, et al. Predicting outcomes of nonsmall cell lung cancer using CT image features. *IEEE Access* 2014; **2**: 1418–26.
19. Coroller TP, Grossmann P, Hou Y, Rios Velazquez E, Leijenaar RT, Hermann G, et al. CT-based radiomic signature predicts distant metastasis in lung adenocarcinoma. *Radiother Oncol* 2015; **114**: 345–50. doi: https://doi.org/10.1016/j.radonc.2015.02.015
20. Fried DV, Tucker SL, Zhou S, Liao Z, Mawlawi O, Ibbott G, 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* 2014; **90**: 834–42. doi: https://doi.org/10.1016/j.ijrobp.2014.07.020
21. Grove O, Berglund AE, Schabath MB, Aerts HJ, Dekker A, Wang H, et al. Quantitative computed tomographic descriptors associate tumor shape complexity and intratumor heterogeneity with prognosis in lung adenocarcinoma. *PLoS One* 2015; **10**: e0118261: . doi: https://doi.org/10.1371/journal.pone.0118261
22. Song J, Dong D, Huang Y, Liu Z, Tian J I. Association between tumor heterogeneity and overall survival in patients with non-small cell lung cancer. In: *IEEE 13th International Symposium on Biomedical Imaging*; 2016. pp. 1249–52.
23. Kang J, Schwartz R, Flickinger J, Beriwal S. Machine learning approaches for predicting radiation therapy outcomes: a clinician's perspective. *Int J Radiat Oncol Biol Phys* 2015; **93**: 1127–35. doi: https://doi.org/10.1016/j.ijrobp.2015.07.2286
24. Cirujeda P, Cid Y, Muller H, Rubin D, Aguilera T, Loo B, et al. A 3-D riesz-covariance texture model for prediction of nodule recurrence in lung CT. *IEEE Trans Med Imaging* 2016;. doi: https://doi.org/10.1109/TMI.2016.2591921
25. Hunter LA, Chen YP, Zhang L, Matney JE, Choi H, Kry SF, et al. NSCLC tumor shrinkage prediction using quantitative image features. *Comput Med Imaging Graph* 2016; **49**: 29–36. doi: https://doi.org/10.1016/j.compmedimag.2015.11.004
26. Fave X, Zhang L, Yang J, Mackin D, Balter P, Gomez D, et al. Impact of image preprocessing on the volume dependence and prognostic potential of radiomics

features in non-small cell lung cancer. *Transl Cancer Res* 2016; **5**: 349–63.
27. Parmar C, Leijenaar RT, Grossmann P, Rios Velazquez E, Bussink J, Rietveld D, et al. Radiomic feature clusters and prognostic signatures specific for lung and head & neck cancer. *Sci Rep* 2015; **5**: : 11044. doi: https://doi.org/10.1038/srep11044
28. Kohutek Z, Oh J, Apte AP, Folkert M, Foster A, Wu A, et al. Predictive modeling of outcomes following SBRT for non-small cell lung cancer using FDG-PET image statistical and texture characteristics. *Int J RadiatPhys* 2014; **90**: S24–S5.
29. Wu J, Gensheimer MF, Dong X, Rubin DL, Napel S, Diehn M, et al. Robust intratumor partitioning to identify high-risk subregions in lung cancer: a pilot study. *Int J Radiat Oncol Biol Phys* 2016; **95**: 1504–12. doi: https://doi.org/10.1016/j.ijrobp.2016.03.018
30. Cunliffe AR, Armato SG, Fei XM, Tuohy RE, Al-Hallaq HA. Lung texture in serial thoracic CT scans: registration-based methods to compare anatomically matched regions. *Med Phys* 2013; **40**: 061906. doi: https://doi.org/10.1118/1.4805110
31. Mattonen SA, Palma DA, Haasbeek CJ, Senan S, Ward AD. Early prediction of tumor recurrence based on CT texture changes after stereotactic ablative radiotherapy (SABR) for lung cancer. *Med Phys* 2014; **41**: 033502. doi: https://doi.org/10.1118/1.4866219
32. Mattonen SA, Tetar S, Palma DA, Senan S, Ward AD. Automated texture analysis for prediction of recurrence after stereotactic ablative radiation therapy for lung cancer. *Int J Radiat BiolPhys* 2015; **93**: S5–S6.
33. Mattonen SA, Palma DA, Johnson C, Louie AV, Landis M, Rodrigues G, et al. Detection of local cancer recurrence after stereotactic ablative radiation therapy for lung cancer: physician performance versus radiomic assessment. *Int J Radiat Oncol Biol Phys* 2016; **94**: 1121: 8.
34. Moore W, Chaya Y, Chaudhry A, Depasquale B, Glass S, Lee S, et al. Computed tomography assessment of ablation zone enhancement in patients with early-stage lung cancer after stereotactic ablative radiotherapy. *J Comput Assist Tomogr* 2015; **39**: 804–9. doi: https://doi.org/10.1097/RCT.0000000000000262
35. Knollmann FD, Kumthekar R, Fetzer D, Socinski MA. Assessing response to treatment in non--small-cell lung cancer: role of tumor volume evaluated by computed tomography. *Clin Lung Cancer* 2014; **15**: 103–9. doi: https://doi.org/10.1016/j.cllc.2013.11.001
36. Cook GJ, O'Brien ME, Siddique M, Chicklore S, Loi HY, Sharma B, et al. Non-small cell lung cancer treated with erlotinib: heterogeneity of (18)F-FDG uptake at PET-association with treatment response and prognosis. *Radiology* 2015; **276**: 883–93. doi: https://doi.org/10.1148/radiol.2015141309
37. van Gool MH, Aukema TS, Sinaasappel M, Valdés Olmos RA, Klomp HM. Tumor heterogeneity on $^{18}$F-FDG-PET/CT for response monitoring in non-small cell lung cancer treated with erlotinib. *J Thorac Dis* 2016; **8**: E200–E3. doi: https://doi.org/10.21037/jtd.2016.02.10
38. Ravanelli M, Farina D, Morassi M, Roca E, Cavalleri G, Tassi G, et al. Texture analysis of advanced non-small cell lung cancer (NSCLC) on contrast-enhanced computed tomography: prediction of the response to the first-line chemotherapy. *Eur Radiol* 2013; **23**: 3450–5. doi: https://doi.org/10.1007/s00330-013-2965-0
39. Chong Y, Kim JH, Lee HY, Ahn YC, Lee KS, Ahn MJ, 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* 2014; **9**: e88598: : . doi: https://doi.org/10.1371/journal.pone.0088598
40. Petrulli J, Contessa J, Morris E. Texture analysis based stratification of non-small cell lung cancer type using 11C-erlotinib PET. *J Nuclear Med* 2015; **56**.
41. Depeursinge A, Yanagawa M, Leung AN, Rubin DL. Predicting adenocarcinoma recurrence using computational texture models of nodule components in lung CT. *Med Phys* 2015; **42**: 2054–63. doi: https://doi.org/10.1118/1.4916088
42. Alobaidli S, McQuaid S, South C, Prakash V, Evans P, Nisbet A. The role of texture analysis in imaging as an outcome predictor and potential tool in radiotherapy treatment planning. *Br J Radiol* 2014; **87**. doi: https://doi.org/10.1259/bjr.20140369
43. Jacobs C, van Rikxoort EM, Scholten ET, de Jong PA, Prokop M, Schaefer-Prokop C, et al. Solid, part-solid, or non-solid?: classification of pulmonary nodules in low-dose chest computed tomography by a computer-aided diagnosis system. *Invest Radiol* 2015; **50**: 168–73. doi: https://doi.org/10.1097/RLI.0000000000000121
44. Park S, Kim B, Lee J, Goo JM, Shin YG. GGO nodule volume-preserving nonrigid lung registration using GLCM texture analysis. *IEEE Trans Biomed Eng* 2011; **58**: 2885–94. doi: https://doi.org/10.1109/TBME.2011.2162330
45. Elizabeth DS, Nehemiah HK, CSR R, Kannan A. Computer-aided diagnosis of lung cancer based on analysis of the significant slice of chest computed tomography image. *IET Image Process* 2012; **6**: 697–705.
46. Dennie C, Thornhill R, Sethi-Virmani V, Souza CA, Bayanati H, Gupta A, et al. Role of quantitative computed tomography texture analysis in the differentiation of primary lung cancer and granulomatous nodules. *Quant Imaging Med Surg* 2016; **6**: 6–15. doi: https://doi.org/10.3978/j.issn.2223-4292.2016.02.01
47. Han F, Wang H, Zhang G, Han H, Song B, Li L, , et al. Texture feature analysis for computer-aided diagnosis on pulmonary nodules. *J Digit Imaging* 2015; **28**: 99–115. doi: https://doi.org/10.1007/s10278-014-9718-8
48. Lee SH, Lee SM, Goo JM, Kim KG, Kim YJ, Park CM. Usefulness of texture analysis in differentiating transient from persistent part-solid nodules(PSNs):a retrospective study. *PLoS ONE* 2014; **9**.
49. Tripepi G, Jager KJ, Dekker FW, Zoccali C. Statistical methods for the assessment of prognostic biomarkers (Part I): discrimination. *Nephrol Dial Transplant* 2010; **25**: 1399–401. doi: https://doi.org/10.1093/ndt/gfq018
50. Dilger SK, Uthoff J, Judisch A, Hammond E, Mott SL, Smith BJ, et al. Improved pulmonary nodule classification utilizing quantitative lung parenchyma features. *J Med Imaging* 2015; **2**. doi: https://doi.org/10.1117/1.JMI.2.4.041004
51. Padma A, Sukanesh R. Combined texture feature analysis of segmentation and classification of benign and malignant tumour CT slices. *J Med EngTechnol* 2013; **37**: 1–9.
52. Orlhac F, Soussan M, Chouahnia K, Martinod E, Buvat I. 18F-FDG PET-derived textural indices reflect tissue-specific uptake pattern in non-small cell lung cancer. *PLoS ONE* 2015; **10**: e0145063. doi: https://doi.org/10.1371/journal.pone.0145063
53. Nguyen P, Bashirzadeh F, Hundloe J, Salvado O, Dowson N, Ware R, et al. Grey scale texture analysis of endobronchial ultrasound mini probe images for prediction of benign or malignant aetiology. *Respirology* 2015; **20**: 960–6. doi: https://doi.org/10.1111/resp.12577
54. Basu S. In: Hall L. O, Goldgof D, Sarkar S, eds. *Developing Predictive Models for Lung Tumor Analysis*: ProQuest Dissertations Publishing; 2012.
55. Wu W, Parmar C, Grossmann P, Quackenbush J, Lambin P, Bussink J, et al.

Exploratory study to identify radiomics classifiers for lung cancer histology. *Front Oncol* 2016; **6**: 71. doi: https://doi.org/10.3389/fonc.2016.00071
56. Chae HD, Park CM, Park SJ, Lee SM, Kim KG, Goo JM. Computerized texture analysis of persistent part-solid ground-glass nodules: differentiation of preinvasive lesions from invasive pulmonary adenocarcinomas. *Radiology* 2014; **273**: 285–93. doi: https://doi.org/10.1148/radiol.14132187
57. Wang C-W, C-P Y. Automated morphological classification of lung cancer subtypes using H&E tissue images. *Mach Vision Appl* 2013; **24**: 1383–91.
58. Wang X, Janowczyk A, Zhou Y, Rakshit S, Velcheti V, Madabhushi A. Computer extracted features of nuclear morphology from digital H&E images are predictive of recurrence in stage I and II non-small cell lung cancer. *Lab Investig* 2016; **96**: 401A–2A.
59. Callister ME, Baldwin DR, Akram AR, Barnard S, Cane P, Draffan J, et al. British thoracic society guidelines for the investigation and management of pulmonary nodules. *Thorax* 2015; **70 Suppl 2**: ii1–ii54.. doi: https://doi.org/10.1136/thoraxjnl-2015-207168
60. Sieren JC, Smith AR, Thiesse J, Namati E, Hoffman EA, Kline JN, et al. Exploration of the volumetric composition of human lung cancer nodules in correlated histopathology and computed tomography. *Lung Cancer* 2011; **74**: 61–8. doi: https://doi.org/10.1016/j.lungcan.2011.01.023
61. Erasmus JJ, McAdams HP, Connolly JE. Solitary pulmonary nodules: part II. Evaluation of the indeterminate nodule. *Radiographics* 2000; **20**: 59–66. doi: https://doi.org/10.1148/radiographics.20.1.g00ja0259
62. Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, Fagerstrom RM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. *New Engl J Med* 2011; **365**: 395–409. doi: https://doi.org/10.1056/NEJMoa1102873
63. Mukhopadhyay S. A segmentation framework of pulmonary nodules in lung CT images. *J Digit Imaging* 2016; **29**: 86–103. doi: https://doi.org/10.1007/s10278-015-9801-9
64. Li B, Chen K, Peng G, Guo Y, Tian L, Ou S, et al. Segmentation of ground glass opacity pulmonary nodules using an integrated active contour model with wavelet energy-based adaptive local energy and posterior probability-based speed function. *Mater Express* 2016; **6**: 317–27.
65. Suo S, Cheng J, Cao M, Lu Q, Yin Y, Xu J, et al. Assessment of heterogeneity difference between edge and core by using texture analysis: differentiation of malignant from inflammatory pulmonary nodules and masses. *Acad Radiol* 2016; **23**: 1115–22. doi: https://doi.org/10.1016/j.acra.2016.04.009
66. Elizabeth DS, Nehemiah HK, Retmin Raj CS, Kannan A. Computer-aided diagnosis of lung cancer based on analysis of the significant slice of chest computed tomography image. *IET Image Process* 2012; **6**: 697–705.
67. Lee SH, Lee SM, Goo JM, Kim KG, Kim YJ, Park CM. Usefulness of texture analysis in differentiating transient from persistent part-solid nodules(PSNs): a retrospective study. *PLoS One* 2014; **9**: e85167: : . doi: https://doi.org/10.1371/journal.pone.0085167
68. Wang J, Sun T, Gao N, Menon DD, Luo Y, Gao Q, et al. Contourlet textual features: improving the diagnosis of solitary pulmonary nodules in two dimensional CT images. *PLoS One* 2014; **9**: e108465. doi: https://doi.org/10.1371/journal.pone.0108465
69. Miwa K, Inubushi M, Wagatsuma K, Nagao M, Murata T, Koyama M, et al. FDG uptake heterogeneity evaluated by fractal analysis improves the differential diagnosis of pulmonary nodules. *Eur J Radiol* 2014; **83**: 715–9. doi: https://doi.org/10.1016/j.ejrad.2013.12.020
70. Yoon SH, Park CM, Park SJ, Yoon JH, Hahn S, Goo JM. Tumor heterogeneity in lung cancer: assessment with dynamic contrast-enhanced MR imaging. *Radiology* 2016; **280**: 940–8. doi: https://doi.org/10.1148/radiol.2016151367
71. Weiss GJ, Ganeshan B, Miles KA, Campbell DH, Cheung PY, Frank S, et al. Noninvasive image texture analysis differentiates K-ras mutation from pan-wildtype NSCLC and is prognostic. *PLoS One* 2014; **9**: e100244: : .
72. Ozkan E, West A, Dedelow JA, Chu BF, Zhao W, Yildiz VO, et al. CT gray-level texture analysis as a quantitative imaging biomarker of epidermal growth factor receptor mutation status in adenocarcinoma of the lung. *AJR Am J Roentgenol* 2015; **205**: 1016–25. doi: https://doi.org/10.2214/AJR.14.14147
73. Rizzo S, Petrella F, Buscarino V, De Maria F, Raimondi S, Barberis M, et al. CT radiogenomic characterization of EGFR, K-RAS, and ALK mutations in non-small cell lung cancer. *Eur Radiol* 2016; **26**: 32–42. doi: https://doi.org/10.1007/s00330-015-3814-0
74. Caramella C, Bluthgen M, Rosellini S, Leduc C, Facchinetti F, Haspinger E, et al. Prognostic value of texture analysis and correlation with molecular profile in EGFR mutated/ALK rearranged advanced non-small cell lung cancer (NSCLC). *Eur J Cancer* 2015; **51**: S647–S8.
75. Wang H, Schabath MB, Liu Y, Berglund AE, Bloom GC, Kim J, et al. Semiquantitative computed tomography characteristics for lung adenocarcinoma and their association with lung cancer survival. *Clin Lung Cancer* 2015; **16**: E141–E63. doi: https://doi.org/10.1016/j.cllc.2015.05.007
76. Bluthgen M, Caramella C, Faivre L, Rosellini S, Facchinetti F, Haspinger E, et al. Prognostic value of texture analysis in advanced non-small cell lung cancer (NSCLC). *Eur J Cancer* 2015; **51**: S645–S6.
77. Yoon HJ, Sohn I, Cho JH, Lee HY, Kim JH, Choi YL, et al. Decoding tumor phenotypes for ALK, ROS1, and RET fusions in lung adenocarcinoma using a radiomics approach. *Medicine* 2015; **94**: 1–8. doi: https://doi.org/10.1097/MD.0000000000001753
78. Miles KA. How to use CT texture analysis for prognostication of non-small cell lung cancer. *Cancer Imaging* 2016; **16**: 10. doi: https://doi.org/10.1186/s40644-016-0065-5
79. Ganeshan B, Miles KA. Quantifying tumour heterogeneity with CT. *Cancer Imaging* 2013; **13**: 140–9. doi: https://doi.org/10.1102/1470-7330.2013.0015
80. Hawkins SH, Korecki JN, Balagurunathan Y, Gu Y V, Kumar S, Basu LO, et al. Predicting outcomes of nonsmall cell lung cancer using CT image features. *Access, IEEE* 2014; **2**: 1418–26.
81. Song JD, Dong D, Huang YQ, Liu ZY, Tian J. IEEE. Association between tumor heterogeneity and overall survival in patients with non-smallcell lung cancer. In: *IEEE 13th International Symposium on Biomedical Imaging*; 2016.
82. Parmar C, Leijenaar RT, Grossmann P, Rios Velazquez E, Bussink J, Rietveld D, et al. Radiomic feature clusters and prognostic signatures specific for lung and head & neck cancer. *Sci Rep* 2015; **5**: 11044. doi: https://doi.org/10.1038/srep11044
83. Liu J, Hoffman J, Zhao J, Yao J, Lu L, Kim L, et al. Mediastinal lymph node detection and station mapping on chest CT using spatial priors and random forest. *Med Phys* 2016; **43**: 4362. doi: https://doi.org/10.1118/1.4954009
84. Bayanati H, E Thornhill R, Souza CA, Sethi-Virmani V, Gupta A, Maziak D, et al. Quantitative CT texture and shape analysis: can it differentiate benign and malignant

mediastinal lymph nodes in patients with primary lung cancer? *Eur Radiol* 2015; **25**: 480–7. doi: https://doi.org/10.1007/s00330-014-3420-6

85. Andersen MB, Harders SW, Ganeshan B, Thygesen J, Torp Madsen HH, Rasmussen F. CT texture analysis can help differentiate between malignant and benign lymph nodes in the mediastinum in patients suspected for lung cancer. *Acta Radiol* 2016; **57**: 669–76. doi: https://doi.org/10.1177/0284185115598808
86. Brooks FJ, Grigsby PW. Low-order non-spatial effects dominate second-order spatial effects in the texture quantifier analysis of 18F-FDG-PET images. *PLoS One* 2015; **10**: e0116574: : . doi: https://doi.org/10.1371/journal.pone.0116574
87. Chicklore S, Goh V, Siddique M, Roy A, Marsden PK, Cook GJ. Quantifying tumour heterogeneity in $^{18}$F-FDG PET/CT imaging by texture analysis. *Eur J Nucl Med Mol Imaging* 2013; **40**: 133–40. doi: https://doi.org/10.1007/s00259-012-2247-0
88. Hatt M, Majdoub M, Vallières M, Tixier F, Le Rest CC, Groheux D, et al. 18F-FDG PET uptake characterization through texture analysis: investigating the complementary nature of heterogeneity and functional tumor volume in a multi-cancer site patient cohort. *J Nucl Med* 2015; **56**: 38–44. doi: https://doi.org/10.2967/jnumed.114.144055
89. Pyka T, Bundschuh RA, Andratschke N, Mayer B, Specht HM, Papp L, 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* 2015; **10**: 9.
90. Cheng NM, Fang YH, Tsan DL, Hsu CH, Yen TC. Respiration-averaged CT for attenuation correction of PET images - impact on PET texture features in non-small cell lung cancer patients. *PLoS ONE* 2016; **11**. doi: https://doi.org/10.1371/journal.pone.0150509
91. Fried DV, Mawlawi O, Zhang L, Fave X, Zhou S, Ibbott G, et al. Stage III non-small cell lung cancer: prognostic value of FDG PET quantitative imaging features combined with clinical prognostic factors. *Radiology* 2016; **278**: 214–22. doi: https://doi.org/10.1148/radiol.2015142920
92. Desseroit MC, Visvikis D, Tixier F, Majdoub M, Perdrisot R, Guillevin R, et al. Development of a nomogram combining clinical staging with (18)F-FDG PET/CT image features in non-small-cell lung cancer stage I-III. *Eur J Nucl Med Mol Imaging* 2016; **43**: 1477–85. doi: https://doi.org/10.1007/s00259-016-3325-5
93. Win T, Miles KA, Janes SM, Ganeshan B, Shastry M, Endozo R, 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* 2013; **19**: 3591–9. doi: https://doi.org/10.1158/1078-0432.CCR-12-1307
94. Desseroit M-C, Majdoub M, Tixier F, Visvikis D, Le Rest CC, Hatt M. Quantification of tumor heterogeneity using textural features analysis of PET and CT images provides complementary prognostic value in stage I-III NSCLC. *Journal of Nuclear Medicine* 2015; **56**.
95. Lovinfosse P, Janvary ZL, Coucke P, Jodogne S, Bernard C, Hatt M, et al. FDG PET/CT texture analysis for predicting the outcome of lung cancer treated by stereotactic body radiation therapy. *Eur J Nucl Med Mol Imaging* 2016; **43**: 1453–60. doi: https://doi.org/10.1007/s00259-016-3314-8
96. Borst GR, Belderbos JS, Boellaard R, Comans EF, De Jaeger K, Lammertsma AA, et al. Standardised FDG uptake: a prognostic factor for inoperable non-small cell lung cancer. *Eur J Cancer* 2005; **41**: 1533–41. doi: https://doi.org/10.1016/j.ejca.2005.03.026
97. Lee KH, Lee SH, Kim DW, Kang WJ, Chung JK, Im SA, , et al. High fluorodeoxyglucose uptake on positron emission tomography in patients with advanced non-small cell lung cancer on platinum-based combination chemotherapy. *Clin Cancer Res* 2006; **12**(14 Pt 1): 4232–6. doi: https://doi.org/10.1158/1078-0432.CCR-05-2710
98. Hayano K, Kulkarni NM, Duda DG, Heist RS, Sahani DV. Exploration of imaging biomarkers for predicting survival of patients with advanced non-small cell lung cancer treated with antiangiogenic chemotherapy. *AJR Am J Roentgenol* 2016; **206**: 987–93. doi: https://doi.org/10.2214/AJR.15.15528
99. van Gómez López O, García Vicente AM, Honguero Martínez AF, Soriano Castrejón AM, Jiménez Londoño GA, Udias JM. Heterogeneity in $^{18}$F fluorodeoxyglucose positron emission tomography/computed tomography of non-small cell lung carcinoma and its relationship to metabolic parameters and pathologic staging. *Molecular Imaging* 2014; **13**: 1–12.
100. Park J, Byun BH, Moon H, Choi JH, Lim I, Kim BI, et al. Prognostic value of F-18-FDG PET tumor texture analysis in non-small cell lung cancer. *J Nucl Med* 2015; **56**.
101. Cook GJ, Yip C, Siddique M, Goh V, Chicklore S, Roy A, et al. Are pretreatment $^{18}$F-FDG PET tumor textural features in non-small cell lung cancer associated with response and survival after chemoradiotherapy? *J Nucl Med* 2013; **54**: 19–26. doi: https://doi.org/10.2967/jnumed.112.107375
102. Gao X, Chu C, Li Y, Lu P, Wang W, Liu W, et al. The method and efficacy of support vector machine classifiers based on texture features and multi-resolution histogram from $^{18}$F-FDG PET-CT images for the evaluation of mediastinal lymph nodes in patients with lung cancer. *Eur J Radiol* 2015; **84**: 312–7. doi: https://doi.org/10.1016/j.ejrad.2014.11.006
103. Leijenaar RT, Carvalho S, Velazquez ER, van Elmpt WJ, Parmar C, Hoekstra OS, et al. Stability of FDG-PET radiomics features: an integrated analysis of test-retest and inter-observer variability. *Acta Oncol* 2013; **52**: 1391–7. doi: https://doi.org/10.3109/0284186X.2013.812798
104. Schwartz J, Grkovski M, Rimner A, Schöder H, Zanzonico PB, Carlin SD, et al. Pharmacokinetic analysis of dynamic $^{18}$F-fluoromisonidazole PET data in Non-small cell lung cancer. *J Nucl Med* 2017; **58**: 911–9. doi: https://doi.org/10.2967/jnumed.116.180422
105. Grkovski M, Apte A, Schwartz J, Rimner A, Schoder H, Carlin S. Reproducibility of F-18-FMISO intratumor distribution and texture features in NSCLC. *J Nuclear Med* 2015; **56**: 126–126.
106. Yip S, McCall K, Aristophanous M, Chen AB, Aerts HJ, Berbeco R. Comparison of texture features derived from static and respiratory-gated PET images in non-small cell lung cancer. *PLoS ONE* 2014; **9**: e115510. doi: https://doi.org/10.1371/journal.pone.0115510
107. Lopez OVG, Garcia Vicente AM, Honguero Martinez AF, Soriano Castrejon AM, Jimenez Londono GA, Manuel Udias J. Heterogeneity in F-18 fluorodeoxyglucose positron emission tomography/computed tomography of non-small cell lung carcinoma and its relationship to metabolic parameters and pathologic staging. *Mol Imaging* 2014; **13**.
108. Fave X, Mackin D, Yang J, Zhang J, Fried D, Balter P, et al. Can radiomics features be reproducibly measured from CBCT images for patients with non-small cell lung cancer? *Med Phys* 2015; **42**: 6784–. doi: https://doi.org/10.1118/1.4934826
109. Hunter LA, Krafft S, Stingo F, Choi H, Martel MK, Kry SF, et al. High quality machine-robust image features:

identification in nonsmall cell lung cancer computed tomography images. *Med Phys* 2013; **40**: 121916. doi: https://doi.org/10.1118/1.4829514

110. Balagurunathan Y, Kumar V, Gu Y, Kim J, Wang H, Liu Y, et al. Test–retest reproducibility analysis of lung CT image features. *J Digit Imaging* 2014; **27**: 805–23. doi: https://doi.org/10.1007/s10278-014-9716-x
111. Hicks RJ. Role of 18F-FDG PET in assessment of response in non-small cell lung cancer. *J Nuclear Med* 2009; **50**(Suppl_. 1): 31S–42. doi: https://doi.org/10.2967/jnumed.108.057216
112. Dong X, Sun X, Sun L, Maxim PG, Xing L, Huang Y, et al. Early change in metabolic tumor heterogeneity during chemoradiotherapy and its prognostic value for patients with locally advanced non-small cell Lung Cancer. *PLoS One* 2016; **11**: : e0157836: . doi: https://doi.org/10.1371/journal.pone.0157836
113. Huang K, Dahele M, Senan S, Guckenberger M, Rodrigues GB, Ward A, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR) – can we distinguish recurrence from fibrosis? A systematic review of the literature. *Radiother Oncol* 2012; **102**: 335–42. doi: https://doi.org/10.1016/j.radonc.2011.12.018
114. Dunlap NE, Yang W, McIntosh A, Sheng K, Benedict SH, Read PW, et al. Computed tomography-based anatomic assessment overestimates local tumor recurrence in patients with mass-like consolidation after stereotactic body radiotherapy for early-stage non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 2012; **84**: 1071–7.
115. Cunliffe A, Armato SG, Castillo R, Pham N, Guerrero T, Al-Hallaq HA. Lung texture in serial thoracic computed tomography scans: correlation of radiomics-based features with radiation therapy dose and radiation pneumonitis development. *IntJ Radiat Oncol Biol Phys* 2015; **91**: 1048–56.
116. Tixier F, Hatt M, Valla C, Fleury V, Lamour C, Ezzouhri S, et al. Visual versus quantitative assessment of intratumor 18F-FDG PET uptake heterogeneity: prognostic value in non-small cell lung cancer. *J Nuclear Med* 2014; **55**: 1235–41. doi: https://doi.org/10.2967/jnumed.113.133389
117. Parmar C, Rios Velazquez E, Leijenaar R, Jermoumi M, Carvalho S, Mak RH, et al. Robust radiomics feature quantification using semiautomatic volumetric segmentation. *PLoS ONE* 2014; **9**: e102107. doi: https://doi.org/10.1371/journal.pone.0102107
118. Desseroit MC, Tixier F, Weber WA, Siegel BA, Cheze Le Rest C, Visvikis D, et al. Reliability of PET/CT shape and heterogeneity features in functional and morphological components of non-small cell lung cancer tumors: a repeatability analysis in a prospective multi-center cohort. *J Nucl Med* 2017; **58**: 406–11. doi: https://doi.org/10.2967/jnumed.116.180919
119. Orlhac F, Soussan M, Maisonobe J-A, Garcia CA, Vanderlinden B, Buvat I. Tumor texture analysis in 18F-FDG PET: relationships between texture parameters, histogram indices, standardized uptake values, metabolic volumes, and total lesion glycolysis. *J Nuclear Med* 2014; **55**: 414–22. doi: https://doi.org/10.2967/jnumed.113.129858
120. Hodi FS, Hwu W-J, Kefford R, Weber JS, Daud A, Hamid O, et al. Evaluation of immune-related response criteria and RECIST v1.1 in patients with advanced melanoma treated with pembrolizumab. *JClin Oncol* 2016; **34**: 1510–7. doi: https://doi.org/10.1200/JCO.2015.64.0391
121. Alemzadeh M, Boylan C, Kamath MV. Review of texture quantification of CT images for classification of lung diseases. *Crit Rev Biomed Eng* 2015; **43**: 183–200. doi: https://doi.org/10.1615/CritRevBiomedEng.2015011026