Clin Transl Imaging (2014) 2:269–276
DOI 10.1007/s40336-014-0064-0

REVIEW ARTICLE

Radiomics in PET: principles and applications

Gary J. R. Cook · Musib Siddique · Benjamin P. Taylor · Connie Yip · Sugama Chicklore · Vicky Goh

Received: 28 March 2014 / Accepted: 6 May 2014 / Published online: 3 June 2014

Abstract Radiomics is an evolving field in which the extraction of large amounts of features from diagnostic medical images may be used to predict underlying molecular and genetic characteristics, thereby improving treatment response prediction and prognostication and potentially allowing personalisation of cancer treatment. There is increasing interest in extracting additional data from PET images, particularly novel features that describe the heterogeneity of voxel intensities, but a number of potential limitations need to be recognised and overcome. Nevertheless, some early data suggest that extraction of additional quantitative data may offer further predictive and prognostic information in individual patients.

keywords Radiomics · Tumour heterogeneity · Positron emission tomography

Introduction

The term "radiomics" describes the high-throughput extraction, analysis and interpretation of large amounts of features from medical images. It is assumed that medical images contain more information than can be appreciated by the human eye alone and that additional data extracted through automated or semi-automated analysis may complement the standard descriptive data or metrics available to the radiologist or nuclear medicine physician. There is an assumption that there is a relationship between the additional quantitative imaging parameters and the tumour molecular phenotype or genotype, which bioinformatic approaches may uncover [1–3]. Frequently the additional data is "free" in that its extraction only requires computational post-processing of data already acquired for clinical imaging protocols, without the need to resort to more complicated acquisition protocols or to subject the patient to additional examinations or visits.

The underlying hypothesis of radiomics is that this additional information from medical images can be used alone or in combination with other "omics" data (e.g. genomics, metabolomics, proteomics) to improve tumour phenotypic characterisation, treatment prediction or prognostication, to an extent that each patient's treatment may be individualised. For example, Segal et al. reported the extraction of 28 features from contrast-enhanced CT scans of hepatocellular carcinoma that can be used to reconstruct 78 % of the gene expression profiles associated with proliferation, hepatic synthetic function and prognosis [4].

The interest in radiomics has been heightened by the knowledge that there is intra- and inter-tumoural genetic heterogeneity both within and between patients and that the genetic profile may change over time, for example as a consequence of therapy [5, 6]. On a simpler level, it is recognised that malignant tumours show heterogeneity of molecular and cellular features, including cellular density and proliferation, necrosis, fibrosis, metabolism, hypoxia, angiogenesis and receptor expression, factors that have been independently associated with poor treatment response and more aggressive tumour behaviour. There is early evidence that some of these adverse biological

Color figures online at http://link.springer.com/article/10.1007/s40336-014-0064-0

G. J. R. Cook (✉) · M. Siddique · B. P. Taylor · C. Yip · S. Chicklore · V. Goh
Division of Imaging Sciences and Biomedical Engineering, Department of Cancer Imaging, Clinical PET Centre, St Thomas' Hospital, King's College London, London SE1 7EH, UK
e-mail: gary.cook@kcl.ac.uk

features may be reflected in medical images. For example, features extracted from CT scans of patients with non-small cell lung cancer (NSCLC) have been correlated with histological features of angiogenesis and hypoxia [7]. Also, it has been shown in a murine head and neck cancer model that the distribution of ^{18}F-fluoro-deoxyglucose (^{18}F-FDG) uptake on PET images is associated with underlying histological features of tumour cell density (areas containing more tumour cells were compared with areas showing more stromal tissue and necrosis) [8]. It is postulated that tumour phenotype (whole tumour or subsegments) could be characterised and associated with underlying regional genetic changes within or between tumours [6].

The major advantages of imaging in revealing underlying phenotypic and genetic information is that it allows a whole tumour, and any metastases, to be sampled non-invasively and repeatedly; in other words, it overcomes the invasiveness and sampling errors associated with the examination of biopsy material. Imaging therefore seems to be in a strong position as regards its potential use, in the future, to characterise tumours, select patients for optimum therapy and monitor genetic and biological changes that may subsequently inform the best management for an individual patient. PET on its own is unlikely to be able to meet all these requirements but with the increasing use of novel tracers exploring different aspects of tumour biology, in conjunction with the routine use of multimodality imaging including PET/CT, and more recently PET/MRI, it is likely to play a large part.

Radiomics and PET

The overall process of radiomics in PET is not significantly different from that of other imaging modalities. The image data have to be acquired and then reconstructed; this is followed by tumour segmentation and feature extraction and finally the application of informatics analyses and data mining, without necessarily having a priori hypotheses.

To some extent, we are already beginning to extract additional data from standard PET images to supplement routine clinical parameters such as the standardised uptake value (SUV). Indeed, there are many ways of measuring or applying corrections to SUVs, and there already exist published recommendations for standardisation for clinical trials and clinical practice [9–11]. Examples of the additional quantitative features now widely reported in the literature include the metabolically active tumour volume (MTV) and total lesion glycolysis (SUVmean × MTV). Both of these parameters have yielded better discriminatory, predictive or prognostic information than SUV alone [12–16] and a recommendation of the published PERCIST guidelines was that these parameters should be measured as secondary or exploratory endpoints in future trials to allow their subsequent evaluation in this role [10].

A large number of alternative parameters that can be extracted from PET images have also been proposed; these describe the shape, size and texture or heterogeneity within a tumour (Table 1) [17–19]. In particular, there has been recent interest in measuring heterogeneity within medical images and, following work with morphological imaging such as CT and MRI [7, 20–22], there are now more and more reports showing that the measurement of texture or heterogeneity within PET images may give additional information on the tumour phenotype compared to simple SUV-based measurements alone [17, 23–29]. Heterogeneity measurements may be temporal, interrogating changes in signal over time, or spatial, where what is measured are the relationships between voxels in a static image. The measurement of spatial heterogeneity has received most interest.

The methods for measuring image spatial heterogeneity can be divided into global, regional or local parameters representing the relationships between voxel intensities. The most commonly used statistical methods include first-order (one voxel), second-order (two voxels) and high-order (three of more voxels) parameters, but other methods exist, such as model-based, e.g. fractal analysis, or transform-based ones [17–19]. First-order methods are the simplest, describing global measurements of a tumour or region of interest (ROI), e.g. mean, minimum, maximum, range, standard deviation, skewness (asymmetry of the histogram), kurtosis (flatness of the histogram), uniformity (regularity) and entropy (randomness) of voxel intensities, from intensity histograms. First-order parameters do not convey spatial information from within the tumour because the above properties are calculated using individual voxel values, ignoring the spatial relationships between voxels. By contrast, second- and high-order features describe properties of the intensities of two or more voxels occurring at separate locations relative to each other and therefore maintain spatial information.

Second-order parameters describe local textural features and can be calculated using spatial grey-level dependence or co-occurrence matrices (GLCM) [30]. The matrices determine the frequency with which a voxel of intensity *i* finds itself in a certain relationship to another voxel of intensity *j*. The most commonly used second-order parameters based on GLCMs include entropy (randomness of the matrix), uniformity (orderliness/homogeneity), contrast (local variation), homogeneity, dissimilarity (difference between elements in the matrix) and correlation (grey-level linear dependencies).

High-order parameters can be calculated using neighbourhood grey-tone difference matrices (NGTDMs) [31]. Local textural features calculated from NGTDMs relate to

Table 1 Common imaging heterogeneity parameters

Parameters	Order, (matrix), type	Description
Mean [19]	First order, global	Average of all pixel intensities
Median [19]	First order, global	Half of the voxels have value less than or equal to median
Skewness [19]	First order, global	Measure of asymmetry and deviation from a normal distribution. Skewness >0: right skewed, most values concentrated on the left of the mean. Skewness <0: left skewed, most values concentrated on the right of the mean. Skewness = 0: symmetrical distribution around the mean
Kurtosis [19]	First order, global	Describes "peakedness" of a distribution
		Kurtosis >3: sharper than a normal distribution, with values concentrated around the mean and thicker tails. This means high probability for extreme values
		Kurtosis <3: flatter than a normal distribution with a wider peak. The probability for extreme values is less than for a normal distribution, and the values are spread more widely around the mean
		Kurtosis = 3: normal distribution
Uniformity[a] [19]	First order, global	Sum of squared elements in the ROI
Entropy[a] [19]	First order, global	Measures texture randomness or irregularity
Homogeneity [30]	Second order, (GLCM), local	Measures the closeness of the distribution of elements in the matrix to the diagonal
Uniformity[a] [30]	Second order, (GLCM), local	Measures the sum of squared elements in the matrix. Uniformity = 1 for a constant image
Contrast[a] [30]	Second order, (GLCM), local	Measures contrast or local intensity variation and favours contributions away from the diagonal
Entropy[a] [30]	Second order, (GLCM), local	A measure of randomness. Inhomogeneous textures have low entropy, whilst homogeneous textures will have high entropy
Short zone emphasis [33]	High order, (GLSZM), regional	Measures the distribution of small zones. The value is large for fine textures
Intensity non-uniformity [33]	High order, (GLSZM), regional	Measures the similarity of grey level values throughout the image. It is small if the grey level values are alike throughout the image
Zone percentage [33]	High order, (GLSZM), regional	Measures the homogeneity and the distribution of zones of an image in a specific direction. It is largest when the size of the zones is 1 for all grey levels
Intensity variability [33]	High order, (GLSZM), regional	Measures the similarity of grey level values throughout the image. It is small if the grey level values are alike throughout the image
Size zone variability [33]	High order, (GLSZM), regional	Measures the similarity of the size of zones throughout the image. It small if the zone sizes are alike throughout the image
Short run emphasis [32]	High order, (GLRLM), regional	Measures the distribution of short runs. It depends on the occurrence of short runs. The value is expected to be large for fine textures
Grey-level non-uniformity [32]	High order, (GLRLM), regional	Measures the similarity of grey level values throughout the image. The value is small if the grey level values are similar in an image
Run percentage [32]	High order, (GLRLM), regional	Measures the homogeneity and the distribution of runs of an image in a specific direction. It is largest when the length of runs is 1 for all grey levels in a specific direction
Intensity variability [32]	High order, (GLRLM), regional	Measures the similarity of grey level values throughout the image. It is small if the grey level values are alike throughout the image
Run length variability [32]	High order, (GLRLM), regional	Measures the similarity of the size of zones throughout the image. It is small if the run lengths are alike throughout the image
Coarseness [31]	High order, (NGTDM), local	Based on differences between each voxel and the neighbouring voxels in adjacent image planes, it measures the granularity within an image. Described as the most fundamental property of texture
Complexity [31]	High order, (NGTDM), local	A texture has high complexity if the information content is high and there are many grey values present. Complexity is the sum of pairs of normalised differences between intensity values
Contrast[a] [31]	High order, (NGTDM), local	This value increases with the amount of local variation in intensity. An image is said to have a high level of contrast if areas of different intensity levels are clearly visible. Thus, a high contrast means that the intensity difference between neighbouring regions is large. This is usually the case when the dynamic range of the grey scale is large or when it is stretched

Table 1 continued

Parameters	Order, (matrix), type	Description
Busyness [31]	High order, (NGTDM), local	A busy texture is one in which there are rapid changes in intensity from one pixel to its neighbour; that is the spatial frequency of intensity changes is very high. A higher value of busyness would tend to emphasise the frequency of spatial changes in intensity values

GLCM grey level co-occurrence matrix, *GLSZM* grey level size-zone matrix, *GLRLM* grey level run length matrix, *NGTDM* neighbourhood grey tone difference matrix, *ROI* region of interest

[a] Some parameters carry the same name but belong to different orders and are calculated by different formulae

differences between each voxel and its neighbouring voxels in adjacent image planes, and are thought to closely resemble the human experience of the image. Examples include the parameters coarseness, contrast and busyness. Coarseness describes the granularity of an image and is considered one of the most fundamental texture properties. Contrast relates to the dynamic range of intensity levels in an image and the level of local intensity variation, while busyness relates to the rate of intensity change within an image [31]. Regional parameters describe run-lengths of consecutive voxels, or zones with similar intensities, such that short run-lengths with similar intensities give fine texture and long runs with differing intensities give coarse texture. Examples include short run (or small zone) emphasis, long run (or large zone) emphasis and run length (or size zone) variability [32, 33].

Technical factors

Textural features can vary depending on image acquisition and reconstruction parameters in PET. Indeed, different textural features have been found to show different variability when varying the acquisition method (2D vs. 3D), matrix size (128 × 128 vs. 256 × 256), reconstruction algorithm and post-reconstruction filter [34]. For example, features with <5 % variability included entropy and uniformity (first order), maximum correlation coefficient (second order) and low-grey level sum emphasis (high order), whereas the majority of calculated features (40 out of 50) were found to show >30 % variability; these included coarseness, contrast and busyness (high order). A similar study examined the effects on smoothing, ROI segmentation thresholds and bin widths on the precision of a number of first-, second- and high-order features [35]. It was concluded that changes in smoothing and ROI segmentation thresholds had relatively small effects and that GLCM and grey level run length (GLRL) methods were the most robust. By contrast, bin width had larger effects on precision and it was suggested that a normalisation process might reduce this effect.

Image noise can also adversely influence the discriminatory ability of textural analysis but this can depend on the type of image [36]. For gradually changing images, the discriminatory performance is poor for low noise levels whilst images with greater differences are more robust until higher levels of noise are present.

The majority of clinical studies that measure tumour heterogeneity with PET or other imaging modalities use operator-defined or threshold-defined ROIs for tumour segmentation. However, it has been argued that a fuzzy locally adaptive Bayesian segmentation approach more accurately defines the tumour volume, particularly for heterogeneous tumours, and could improve the prognostic evaluation [37–39].

Whilst it is attractive to hypothesise that image heterogeneity may reflect underlying tumour biology there is no evidence of a direct relationship between ^{18}F-FDG PET images and histological features in humans. Given the microscopic nature of tumour biology and the tumour microenvironment (e.g. angiogenesis, hypoxia, proliferation, necrosis etc.), the macroscopic scale of the PET image (e.g. 0.5 cm voxels) is unlikely to allow a direct reflection of the tumour biology although it has been hypothesised that ^{18}F-FDG heterogeneity in NSCLC may reflect the distribution of hypoxic cells associated with higher expression of glucose transporters [40]. Exploring heterogeneity within tumours also has the potential to reveal underlying aspects of tumour physiology and biology. For example, measurement of spatial heterogeneity of kinetic parameters of ^{18}F-FDG uptake within a number of tumours (predominantly NSCLC) segmented into quartiles showed variability across quartiles leading to the hypothesis that the tumour glucose phosphorylation rate is independent of ^{18}F-FDG delivery and transport [41].

Measurement of heterogeneity within images requires the inclusion of a reasonable number of voxels in a ROI, so as to be able to measure some of the textural features. It has been postulated that some heterogeneity parameters may be surrogates for size below a certain volume. Brooks and Grigsby, using probability theory, calculated that measurements from cervical tumour volumes of <45 cm^3 can be very sensitive to size, and may reflect size rather than

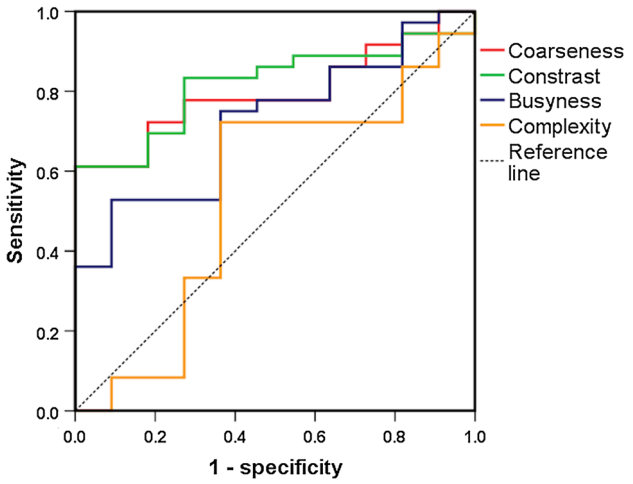

Fig. 1 ROC curves for baseline ^{18}F-FDG PET primary tumour coarseness, contrast, busyness, and complexity for identification of responders vs. non-responders by RECIST at 12 weeks in patients treated with chemoradiotherapy for NSCLC. [This research was originally published in JNM [28]. © by the Society of Nuclear Medicine and Molecular Imaging, Inc.] (color figure online)

underlying heterogeneity as measured by the parameter, local entropy [42]. The calculated minimum volume may vary with different tumour datasets, scanner resolution and voxel size and dynamic range of intensities in tumour voxels, but it is nevertheless recommended that this calculation be made so that tumours below a minimum volume may be excluded from analyses. This dependence on size also means that it may not be possible to perform analyses of heterogeneity within different parts of a tumour or small structures such as lymph nodes. For example, differences in entropy between the edge and core of lung cancers have been reported to show an inverse correlation with survival on CT scans [6], but this type of analysis may not be possible with lower-resolution PET data.

A detailed study of the robustness of a number of first-, second- and high-order features was carried out on ^{18}F-FDG PET images of three tumour types, namely NSCLC, metastatic colorectal cancer and breast cancer, and showed further potential limitations. A number of features were correlated with each other, with tumour volume or with standard indices such as SUV [43]. As expected, some textural features were more sensitive than SUVmax to segmentation methods, but less sensitive than SUVmean. It was concluded that none of the first-order features and only half of the other textural features were robust to the tumour segmentation method. It was also recommended that at least 32 grey levels should be used for resampling to avoid spurious correlations with SUV.

Another important factor when using any imaging parameters for response assessment is the reproducibility of the measurements. For first-order parameters, good test–retest reproducibility and reliability were found for area under the SUV volume histogram, although skewness and kurtosis were less robust [44]. In a study of ^{18}F-FDG PET scans in patients with oesophageal cancer repeated within 4 days, local heterogeneity parameters including entropy and homogeneity showed better reproducibility than did SUV measurements (2 vs. 5 %), and a number of regional heterogeneity features were found to be similar to SUVs [45]. The same group examined the robustness of textural features of ^{18}F-FDG PET in oesophageal cancer to the partial volume effect and segmentation method and the ability to predict treatment response. They found that local features (e.g. entropy, homogeneity, dissimilarity) and regional features (e.g. zone percentage) were robust and maintained differentiation power for response prediction [46]. A further study has also shown moderately good test–retest and inter-observer stability of features, including first-order, intensity-volume histogram, geometric and textural features in ^{18}F-FDG PET [47]. We do not know how sensitive textural feature analysis is to measurements from scans performed at different times post injection. The accuracy and precision of texture analysis may therefore depend on individual scan acquisition and image reconstruction protocols as well as image quality parameters such as noise, resolution and motion artefacts. The technical features that may affect texture analysis are obviously important considerations when designing studies, particularly multicentre studies in which the methodology has to be carefully evaluated and standardised.

Clinical applications

Characterisation and segmentation

High-order textural features including coarseness, contrast and busyness have been used to differentiate head and neck primary and nodal tumours from normal tissues [48] and in a subsequent study by the same group, ROIs were segmented using textural features, an approach that showed feasibility for improving accuracy of radiotherapy planning of head and neck tumours [49]. Model-based fractal methods have also been investigated as a means of characterising pulmonary nodules on ^{18}F-FDG PET images. A significant difference was found between benign and malignant nodules for fractal indices as well as SUVmax. However, SUVmax was significantly correlated with tumour size whereas fractal indices were not [27]. In some tumour types, such as peripheral nerve sheath tumours, it has proved possible to improve characterisation between benign and malignant lesions through qualitative scoring of ^{18}F-FDG heterogeneity [50].

Prediction and prognosis

A number of studies have demonstrated the predictive and prognostic ability of textural parameters derived from ^{18}F-FDG PET images and have shown these parameters to be superior to standard ones such as SUV. This applied to studies in sarcomas [23], head and neck cancer [24], oesophageal cancer [17, 51] and lung cancer [25–28], Fig. 1. Conversely, textural features were not able to predict nodal status or outcome in cervical cancers [52, 53]. Some initial work using ^{18}F-fluorothymidine PET in breast cancer has shown good test–retest repeatability in the evaluation of some features. In addition, tumours with fewer highly proliferating cells tended to respond less well to chemotherapy and a decrease in heterogeneity was found in the majority of responders at 1 week [54].

Radiogenomics and PET

Whereas there are increasing numbers of studies investigating radiogenomics with CT and MRI in oncology, there are relatively few investigating radiogenomics with PET. Nair et al. extracted 14 SUV-based uptake features from ^{18}F-FDG PET scans of patients with resected NSCLC and showed associations with distinct genes and gene signatures; they also showed a multivariate ^{18}F-FDG uptake feature to be prognostic [55]. These authors concluded that the prognostic models they evaluated could increase understanding of ^{18}F-FDG as a biomarker at the genomic level. A radiogenomics strategy has also been tested in patients with NSCLC linking gene expression and 180 image features from PET and CT images. A number of metagenes could be predicted from CT features, and CT features and PET SUV could be predicted using the metagenes [56].

Conclusion and future directions

Radiomics with medical imaging and PET are in an early phase of study and there are technical issues that still need to be further developed, evaluated and addressed. However, if these challenges for technical validation can be overcome, it is expected that radiomic data, alone or in combination with other-omic data, may lead to a personalised approach to cancer management in the future. With the growth of hybrid imaging such as SPECT/CT, PET/CT, and more recently PET/MRI, the volume of potentially useful image parameters and metrics available is likely to increase. With the wealth of additional information that is available but unused in medical images, a radiomics approach whereby additional data are extracted automatically and then subjected to bioinformatic analysis may be a way forward to achieve better tumour segmentation, definition, characterisation, prediction and prognostication. This approach, in combination with the use of molecular analysis of tumours that is now becoming routine in some cases for treatment stratification, may contribute to improvements in cancer care.

Acknowledgments The authors acknowledge support from the National Institute for Health Research Biomedical Research Centre of Guys and St Thomas' NHS Trust in partnership with Kings College London and also the King's College London and University College London Comprehensive Cancer Imaging Centre funded by Cancer Research UK and the Engineering and Physical Sciences Research Council in association with the Medical Research Council and Department of Health (England).

Conflict of interest Gary Cook, Musib Siddque, Benjamin Taylor, Connie Yip, Sugama Chicklore and Vicky Goh do not have any conflict of interest.

Compliance with ethics guidelines This article does not contain any studies, other than references, with human or animal subjects performed by any of the authors.

References

1. Rutman AM, Kuo MD (2009) Radiogenomics: creating a link between molecular diagnostics and diagnostic imaging. Eur J Radiol 70:232–241
2. Lambin P, Rios-Velazquez E, Leijenaar R et al (2012) Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer 48:441–446
3. Asselin MC, O'Connor JP, Boellaard R, Thacker NA, Jackson A (2012) Quantifying heterogeneity in human tumours using MRI and PET. Eur J Cancer 48:447–455
4. Segal E, Sirlin CB, Ooi C et al (2007) Decoding global gene expression programs in liver cancer by noninvasive imaging. Nat Biotechnol 25:675–680
5. Burrell RA, McGranahan N, Bartek J, Swanton C (2013) The causes and consequences of genetic heterogeneity in cancer evolution. Nature 501:338–345
6. Gatenby RA, Grove O, Gillies RJ (2013) Quantitative imaging in cancer evolution and ecology. Radiology 269:8–15
7. Ganeshan B, Goh V, Mandeville HC, Ng QS, Hoskin PJ, Miles KA (2013) Non-small cell lung cancer: histopathologic correlates for texture parameters at CT. Radiology 266:326–336
8. Henriksson E, Kjellen E, Wahlberg P, Ohlsson T, Wennerberg J, Brun E (2007) 2-Deoxy-2-[^{18}F]fluoro-D-glucose uptake and correlation to intratumoral heterogeneity. Anticancer Res 27:2155–2159
9. Young H, Baum R, Cremerius U, Herholz K, Hoekstra O, Lammertsma AA, Pruim J, Price P (1999) Measurement of clinical and subclinical tumour response using [^{18}F]-fluorodeoxyglucose and positron emission tomography: review and 1999 EORTC recommendations. EORTC PET Study Group. Eur J Cancer 35:1773–1782
10. Wahl RL, Jacene H, Kasamon Y, Lodge MA (2009) From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med 50:122S–150S
11. Boellaard R, O'Doherty MJ, Weber WA et al (2010) FDG PET and PET/CT: EANM procedure guidelines for tumour PET imaging: version 1.0. Eur J Nucl Med Mol Imaging 37:181–200

12. Ryu IS, Kim JS, Roh JL, Cho KJ, Choi SH, Nam SY, Kim SY (2014) Prognostic significance of preoperative metabolic tumour volume and total lesion glycolysis measured by (^{18})F-FDG PET/CT in squamous cell carcinoma of the oral cavity. Eur J Nucl Med Mol Imaging 41:452–461
13. Klabatsa A, Chicklore S, Barrington SF, Goh V, Lang-Lazdunski L, Cook GJ (2014) The association of ^{18}F-FDG PET/CT parameters with survival in malignant pleural mesothelioma. Eur J Nucl Med Mol Imaging 41:276–282
14. Hyun SH, Ahn HK, Kim H, Ahn MJ, Park K, Ahn YC, Kim J, Shim YM, Choi JY (2014) Volume-based assessment by (^{18})F-FDG PET/CT predicts survival in patients with stage III non-small-cell lung cancer. Eur J Nucl Med Mol Imaging 41:50–58
15. Choi ES, Ha SG, Kim HS, Ha JH, Paeng JC, Han I (2013) Total lesion glycolysis by ^{18}F-FDG PET/CT is a reliable predictor of prognosis in soft-tissue sarcoma. Eur J Nucl Med Mol Imaging 40:1836–1842
16. Maffione AM, Ferretti A, Grassetto G et al (2013) Fifteen different ^{18}F-FDG PET/CT qualitative and quantitative parameters investigated as pathological response predictors of locally advanced rectal cancer treated by neoadjuvant chemoradiation therapy. Eur J Nucl Med Mol Imaging 40:853–864
17. Tixier F, Cheze Le Rest C, Hatt M et al (2011) Intratumor heterogeneity characterized by textural features on baseline ^{18}F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer. J Nucl Med 52:369–378
18. Chicklore S, Goh V, Siddique M, Roy A, Marsden PK, Cook GJ (2013) Quantifying tumour heterogeneity in ^{18}F-FDG PET/CT imaging by texture analysis. Eur J Nucl Med Mol Imaging 40:133–140
19. Davnall F, Yip CS, Ljungqvist G, Selmi M, Ng F, Sanghera B, Ganeshan B, Miles KA, Cook GJ, Goh V (2012) Assessment of tumor heterogeneity: an emerging imaging tool for clinical practice? Insights Imaging 3:573–589
20. Yip C, Landau D, Kozarski R, Ganeshan B, Thomas R, Michaelidou A, Goh V (2014) Primary esophageal cancer: heterogeneity as potential prognostic biomarker in patients treated with definitive chemotherapy and radiation therapy. Radiology 270:141–148
21. Ng F, Ganeshan B, Kozarski R, Miles KA, Goh V (2013) Assessment of primary colorectal cancer heterogeneity by using whole-tumor texture analysis: contrast-enhanced CT texture as a biomarker of 5-year survival. Radiology 266:177–184
22. Goh V, Ganeshan B, Nathan P, Juttla JK, Vinayan A, Miles KA (2011) Assessment of response to tyrosine kinase inhibitors in metastatic renal cell cancer: CT texture as a predictive biomarker. Radiology 261:165–171
23. O'Sullivan F, Roy S, Eary J (2003) A statistical measure of tissue heterogeneity with application to 3D PET sarcoma data. Biostatistics 4:433–448
24. O'Sullivan F, Roy S, O'Sullivan J, Vernon C, Eary J (2005) Incorporation of tumor shape into an assessment of spatial heterogeneity for human sarcomas imaged with FDG-PET. Biostatistics 6:293–301
25. Eary JF, O'Sullivan F, O'Sullivan J, Conrad EU (2008) Spatial heterogeneity in sarcoma ^{18}F-FDG uptake as a predictor of patient outcome. J Nucl Med 49:1973–1979
26. El Naqa I, Grigsby P, Apte A, Kidd E, Donnelly E, Khullar D et al (2009) Exploring feature-based approaches in PET images for predicting cancer treatment outcomes. Pattern Recognit 42:1162–1171
27. Vaidya M, Creach KM, Frye J, Dehdashti F, Bradley JD, El Naqa I (2012) Combined PET/CT image characteristics for radiotherapy tumor response in lung cancer. Radiother Oncol 102:239–245
28. Cook GJ, Yip C, Siddique M, Goh V, Chicklore S, Roy A, Marsden P, Ahmad S, Landau D (2013) 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 54:19–26
29. Miwa K, Inubushi M, Wagatsuma K et al (2014) FDG uptake heterogeneity evaluated by fractal analysis improves the differential diagnosis of pulmonary nodules. Eur J Radiol 83:715–719
30. Haralick RM, Shanmugam K, Dinstein I (1973) Textural features for image classification. IEEE Trans Syst Man Cybern 3:610–621
31. Amadasun M, King R (1989) Textural features corresponding to textural properties. IEEE Trans Syst Man Cybern 19:1264–1274
32. Galloway MM (1975) Texture analysis using gray level run lengths. Comput Graph Image Process 4:172–179
33. Thibault G, Angulo J, Meyer F (2014) Advanced statistical matrices for texture characterization: application to cell classification. IEEE Trans Biomed Eng 61:630–637
34. Galavis PE, Hollensen C, Jallow N, Paliwal B, Jeraj R (2010) Variability of textural features in FDG PET images due to different acquisition modes and reconstruction parameters. Acta Oncol 49:1012–1016
35. Doumou G, Siddique M, Tsoumpas C, Goh V, Cook G (2013) Exploring the precision of textural features in ^{18}F-FDG-PET scans of oesophageal cancer. Eur J Nucl Med Mol Imaging 40:S89–S567
36. Veenland JF, Grashuis JL, Gelsema ES (1998) Texture analysis in radiographs: the influence of modulation transfer function and noise on the discriminative ability of texture features. Med Phys 25:922–936
37. Hatt M, Cheze le Rest C, Turzo A, Roux C, Visvikis D (2009) A fuzzy locally adaptive Bayesian segmentation approach for volume determination in PET. IEEE Trans Med Imaging 28:881–893
38. Hatt M, Visvikis D, Albarghach NM, Tixier F, Pradier O, Cheze-le Rest C (2011) Prognostic value of ^{18}F-FDG PET image-based parameters in oesophageal cancer and impact of tumour delineation methodology. Eur J Nucl Med Mol Imaging 38:1191–1202
39. Hatt M, Cheze-le Rest C, van Baardwijk A, Lambin P, Pradier O, Visvikis D (2011) Impact of tumor size and tracer uptake heterogeneity in (^{18})F-FDG PET and CT non-small cell lung cancer tumor delineation. J Nucl Med 52:1690–1697
40. van Baardwijk A, Bosmans G, van Suylen RJ et al (2008) Correlation of intra-tumour heterogeneity on ^{18}F-FDG PET with pathologic features in non-small cell lung cancer: a feasibility study. Radiother Oncol 87:55–58
41. Vriens D, Disselhorst JA, Oyen WJ, de Geus-Oei LF, Visser EP (2012) Quantitative assessment of heterogeneity in tumor metabolism using FDG-PET. Int J Radiat Oncol Biol Phys 82:e725–e731
42. Brooks FJ, Grigsby PW (2014) The effect of small tumor volumes on studies of intratumoral heterogeneity of tracer uptake. J Nucl Med 55:37–42
43. Orlhac F, Soussan M, Maisonobe JA, Garcia CA, Vanderlinden B, Buvat I (2014) Tumor texture analysis in ^{18}F-FDG PET: relationships between texture parameters, histogram indices, standardized uptake values, metabolic volumes, and total lesion glycolysis. J Nucl Med 55:414–422
44. van Velden FH, Nissen IA, Jongsma F et al (2014) Test–retest variability of various quantitative measures to characterize tracer uptake and/or tracer uptake heterogeneity in metastasized liver for patients with colorectal carcinoma. Mol Imaging Biol 16:13–18
45. Tixier F, Hatt M, Le Rest CC, Le Pogam A, Corcos L, Visvikis D (2012) Reproducibility of tumor uptake heterogeneity characterization through textural feature analysis in ^{18}F-FDG PET. J Nucl Med 53:693–700
46. Hatt M, Tixier F, Cheze Le Rest C, Pradier O, Visvikis D (2013) Robustness of intratumour ^{18}F-FDG PET uptake heterogeneity

quantification for therapy response prediction in oesophageal carcinoma. Eur J Nucl Med Mol Imaging 40:1662–1671
47. Leijenaar RT, Carvalho S, Velazquez ER et al (2013) Stability of FDG-PET radiomics features: an integrated analysis of test–retest and inter-observer variability. Acta Oncol 52:1391–1397
48. Yu H, Caldwell C, Mah K et al (2009) Automated radiation targeting in head-and-neck cancer using region-based texture analysis of PET and CT images. Int J Radiat Oncol Biol Phys 75:618–625
49. Yu H, Caldwell C, Mah K, Mozeg D (2009) Coregistered FDG PET/CT based textural characterization of head and neck cancer for radiation treatment planning. IEEE Trans Med Imaging 28:374–383
50. Salamon J, Derlin T, Bannas P et al (2013) Evaluation of intra-tumoural heterogeneity on ^{18}F-FDG PET/CT for characterization of peripheral nerve sheath tumours in neurofibromatosis type 1. Eur J Nucl Med Mol Imaging 40:685–692
51. Tan S, Kligerman S, Chen W et al (2013) Spatial-temporal [^{18}F]FDG-PET features for predicting pathologic response of esophageal cancer to neoadjuvant chemoradiation therapy. Int J Radiat Oncol Biol Phys 85:1375–1382
52. Brooks FJ, Grigsby PW (2011) Current measures of metabolic heterogeneity within cervical cancer do not predict disease outcome. Radiat Oncol 6:69
53. Brooks FJ, Grigsby PW (2013) FDG uptake heterogeneity in FIGO IIb cervical carcinoma does not predict pelvic lymph node involvement. Radiat Oncol 8:294
54. Willaime JM, Turkheimer FE, Kenny LM, Aboagye EO (2013) Quantification of intra-tumour cell proliferation heterogeneity using imaging descriptors of ^{18}F-fluorothymidine-positron emission tomography. Phys Med Biol 58:187–203
55. Nair VS, Gevaert O, Davidzon G et al (2012) Prognostic PET ^{18}F-FDG uptake imaging features are associated with major oncogenomic alterations in patients with resected non-small cell lung cancer. Cancer Res 72:3725–3734
56. Gevaert O, Xu J, Hoang CD et al (2012) Non-small cell lung cancer: identifying prognostic imaging biomarkers by leveraging public gene expression microarray data—methods and preliminary results. Radiology 264:387–396