Eur J Nucl Med Mol Imaging (2013) 40:133–140
DOI 10.1007/s00259-012-2247-0

REVIEW ARTICLE

Quantifying tumour heterogeneity in ^{18}F-FDG PET/CT imaging by texture analysis

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Received: 26 June 2012 / Accepted: 29 August 2012 / Published online: 13 October 2012

Abstract ^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is now routinely used in oncological imaging for diagnosis and staging and increasingly to determine early response to treatment, often employing semiquantitative measures of lesion activity such as the standardized uptake value (SUV). However, the ability to predict the behaviour of a tumour in terms of future therapy response or prognosis using SUVs from a baseline scan prior to treatment is limited. It is recognized that medical images contain more useful information than may be perceived with the naked eye, leading to the field of "radiomics" whereby additional features can be extracted by computational postprocessing techniques. In recent years, evidence has slowly accumulated showing that parameters obtained by texture analysis of radiological images, reflecting the underlying spatial variation and heterogeneity of voxel intensities within a tumour, may yield additional predictive and prognostic information. It is hoped that measurement of these textural features may allow better tissue characterization as well as better stratification of treatment in clinical trials, or individualization of future cancer treatment in the clinic, than is possible with current imaging biomarkers. In this review we focus on the literature describing the emerging methods of texture analysis in ^{18}FDG PET/CT, as well as other imaging modalities, and how the measurement of spatial variation of voxel grey-scale intensity within an image may provide additional predictive and prognostic information, and postulate the underlying biological mechanisms.

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Keywords ^{18}FDG PET/CT · Texture analysis · Radiomics · Heterogeneity

Introduction

Medical imaging is used routinely in oncology for diagnosis, staging and assessment of treatment response, but is less reliable for predicting response or for inferring prognosis before therapy has been instigated, such that the ability to stratify patients to different treatments or to personalize therapy remains largely limited to TNM staging information. Personalized medicine is a goal in modern cancer therapy that aims for optimal treatment for an individual patient that is dependent on tumour characteristics in that individual. The ability to predict the behaviour of a tumour to treatment before therapy has been instigated would be invaluable in enabling stratification in clinical trials or personalizing future cancer treatments in the clinic.

Whilst novel imaging sequences, contrast agents and tracers are being developed to explore new aspects of tumour biology, it is also recognized that standard medical images may contain more useful information than is being used in a routine clinical setting. The field of "radiomics", whereby additional features may be extracted from medical images, may not only allow more accurate measurement of treatment response but also non-invasive molecular and genetic profiling of tumours as a further step towards personalized medicine [1].

^{18}F-Fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) is already well established for staging certain cancers due to better sensitivity and specificity compared to anatomical imaging such as CT [2]. It also has the advantage of being able to measure therapy response relatively early in the course of treatment when anatomical changes have not occurred, such that serial

^{18}F-FDG PET/CT scans are being used successfully in a number of cancers to detect early treatment effect, in clinical routine and increasingly, in clinical trials [3, 4]. It is useful to have knowledge of the sensitivity of a tumour to a therapeutic regimen as early as possible as this will help tailor the treatment for individual patients, particularly if the patient is not responding to a drug. Nonresponding patients can have treatment intensified or can be switched to alternative therapies, increasing the probability of tumour control and avoiding toxicity from ineffective treatment.

As PET also lends itself to quantification, semiquantitative measurements of tracer uptake are frequently adopted in clinical trials and clinical routine, including standardized uptake values (SUVs; e.g. SUV_{mean}, SUV_{max}, SUV_{peak}) [5]. However, it is recognized that ^{18}F-FDG uptake may not always accurately reflect tumour response due to confounding factors such as early reduction in activity in the presence of viable tumour [6] or increases in uptake secondary to inflammatory processes following chemotherapy and radiotherapy [7, 8]. There is also variability in the reported accuracy of ^{18}F-FDG PET/CT in this context. For example, in non-small cell lung cancer (NSCLC), the ability of ^{18}F-FDG PET to predict histopathological response varies from 80 % to 97 % in terms of sensitivity and from 64 % to 100 % in terms of specificity [9].

There is only limited evidence that the level of uptake on pretreatment scans, as measured by various SUV parameters, may be predictive [10–14], but results sometimes conflict as to whether high or low SUVs are predictive depending on treatment modality, e.g. radiotherapy vs. chemotherapy in NSCLC [13, 14]. Also in NSCLC there are data that show that the baseline SUV prior to therapy may be prognostic, with low values being associated with longer survival, but the optimal cut-off SUV varies widely in the literature [9]. Baseline ^{18}F-FDG PET has also shown some predictive value in radioimmunotherapy in non-Hodgkin's lymphoma [15], high-grade gliomas [16], head and neck cancer [17, 18] and anal cancer [19], but not oesophageal carcinoma [20]. In this context, introducing predictive and prognostic parameters from baseline ^{18}F-FDG PET scans that perform better than SUV parameters would be invaluable and would open up the potential to stratify patients more appropriately for treatment.

It is recognized that malignant tumours exhibit intratumoral biological heterogeneity associated with cellular and molecular characteristics such as cellular proliferation, necrosis, fibrosis, differences in blood flow and angiogenesis, cellular metabolism, hypoxia and expression of specific receptors, some of which may be evident on histological analysis. Similarly, heterogeneity of ^{18}F-FDG uptake within tumours has been attributed to a number of factors including cellularity, proliferation, angiogenesis, necrosis and hypoxia, factors that independently have been associated with more aggressive behaviour, poorer response to treatment and worse prognosis. However, there is currently little evidence to confirm what biological and molecular features underlie differences in tumour texture in ^{18}F-FDG PET images.

Texture analysis is emerging as a new tool for assessing intratumoral heterogeneity in medical imaging. Tumour heterogeneity in baseline ^{18}F-FDG PET imaging may allow better tissue characterization, image segmentation and improved prediction of therapy response and survival [21–28]. Whilst the data have been rapidly accumulating for contrast-enhanced CT and MRI in this field, the evidence for texture analysis in PET imaging is only just emerging, and the aim of our review is to collate the existing evidence supporting the role of texture analysis in ^{18}F-FDG PET tumour imaging and to explore the potential applications.

Texture analysis

Texture analysis refers to a variety of mathematical methods that may be applied to describe the relationships between the grey level intensity of pixels or voxels and their position within an image. An advantage of measuring textural parameters is that it is a postprocessing technique that can be applied to data acquired during standard clinical imaging protocols thereby maximizing the information that can be derived from standard clinical images.

A number of textural features can be derived that provide a measure of intralesional heterogeneity [26, 29]. Textural parameters can be derived from statistics-based [30, 31], model-based [32–35], or transform-based [36, 37] methods. Statistics-based techniques have been most commonly applied and are based on the spatial distribution of pixel or voxel values, calculating local features at each pixel in the image and deriving parameters from the distributions of the local features. The statistical methods are categorized into first-order (one pixel), second-order (two pixels) and higher-order (three or more pixels) statistics.

First-order parameters describe global textural features that relate to the grey level frequency distribution within the region of interest. They are based on histogram analysis and include mean, minimum and maximum intensity, standard deviation, skewness and kurtosis. Second-order features describe local texture features and are calculated using spatial grey level dependence (SGLDM) or co-occurrence matrices. These matrices determine how often a pixel of intensity *i* finds itself within a certain relationship to another pixel of intensity *j*. Second-order features based on a co-occurrence matrices include entropy, energy, contrast, homogeneity, dissimilarity and correlation. Higher-order parameters can be calculated using neighbourhood grey-tone (intensity) difference matrices (NGTDMs) to describe

local features [26, 38]. Local textural parameters derived from NGTDMs are based on differences between each voxel and the neighbouring voxels in adjacent image planes, and are thought to closely resemble the human experience of the image [38]. For example, coarseness, one of the local textural parameters, has been likened to granularity within an image and is the most fundamental property of texture. Contrast relates to the dynamic range of intensity levels in an image and the level of local intensity variation and busyness relates to the rate of intensity change within an image [24, 38]. Regional features can also be calculated from voxel alignment (e.g. run length and run-length variability) and grey level size-zone matrices that reflect regional intensity variations or the distribution of homogeneous regions (e.g. zone emphasis and size-zone variability) [26] (Table 1).

To illustrate the difference between different order statistics, Fig. 1 shows four simulated cases with different intensity patterns. All four cases will give the same features based on first-order statistics (e.g. histogram, mean, energy, entropy etc.), as properties are calculated using individual pixel values ignoring the spatial relationships between pixels. Second-order statistics based on a co-occurrence matrix will give different features between Fig. 1a and b as the properties of two pixel values occurring at specific locations relative to each other are estimated. However, features will be the same for cases Fig. 1b, c and d when the offset is one pixel in the *x*-direction. Higher order statistics, e.g. NGTDM, estimate properties based on more pixels occurring at specific locations relative to each other and will give different results for all the cases shown in Fig. 1.

Table 1 Textural features

Order of textural feature	Description		Examples
First	Grey level frequency distribution from histogram analysis	Global	Minimum, mean and maximum intensity
			Standard deviation
			Skewness
			Kurtosis
Second	From spatial grey level dependence matrices	Local	Entropy
			Energy
			Contrast
			Homogeneity
			Dissimilarity
			Uniformity
			Correlation
Higher	From neighbourhood grey-tone difference matrices	Local	Coarseness
			Contrast
			Busyness
			Complexity
	From voxel alignment matrices	Regional	Run-length and emphasis
			Run-length variability
	From grey level size zone matrices	Regional	Zone emphasis
			Size-zone variability

Texture analysis in ^{18}F-FDG PET

Whilst the high spatial resolution of CT and MRI with small pixel sizes allows texture analysis of relatively small tumours, the poorer spatial resolution of PET with pixel sizes of up to 5 mm, limits the size of small volume tumours that may be assessed, the requirement being for a reasonable number of adjacent pixels to be present to be able to measure some of the textural features. The accuracy and precision of texture analysis in clinical evaluation depends significantly on individual scanning protocols. Factors such as image acquisition, reconstruction and inherent image quality parameters such as noise, motion artefacts and slice thickness, may be important. It is to be expected that all texture analysis methods are influenced to some extent by these factors and the sensitivity of various texture features may be based on different image models.

Veenland et al. [39] investigated the sensitivity of four different texture analysis methods for image noise and blur and found that the discriminative performance of all texture features was reduced by noise. The influence of noise on the discriminative performance was dependent on the image type used. The discrimination of more gradually different images, such as fractal images, is poor for relatively low noise levels but when the images are more different, only high noise levels decrease the discriminative performance. Galavis et al. [40] studied the variability of the textural features in PET images due to different acquisition modes and reconstruction parameters. Textural features such as entropy, energy, maximal correlation coefficient and low grey level run emphasis exhibited small variations due to differences on acquisition mode and reconstruction parameters. Features such as contrast-NGTD, coarseness, homogeneity, and busyness showed larger variations. These are obviously important potential limitations of texture analysis and these aspects would require further evaluation if texture analysis of PET images were to be used in multicentre studies, for example.

Further factors that will require careful assessment are the methods used for ROI definition on PET images and related intraobserver and interobserver variation. An initial study has shown that the reproducibility of a number of textural

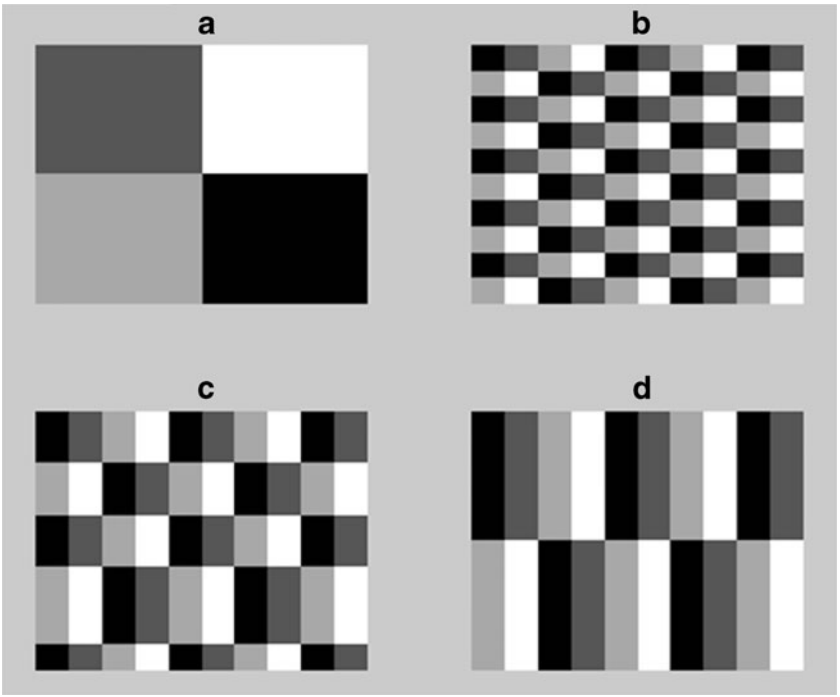

Fig. 1 Four simulations of different intensity variations. First-order parameters are the same for all four cases. Although the second-order features (derived from the grey level co-occurrence matrix with offset [1 0]) will be different for **a** compared to **b**, **c** and **d**, the latter three will be the same. Third-order features (derived from neighbourhood grey tone difference matrices or grey level size-zone matrices) will be different for all four cases

parameters is as good as or better than that for SUVs [41]. However, it will also need to be determined whether textural parameters vary with time after injection as do SUVs in ^{18}F-FDG PET imaging [42].

Following radiological reports of the use of textural features, there has been more recent interest in the use of texture analysis in ^{18}F-FDG PET imaging in oncology. The literature describing the use of ^{18}F-FDG PET in analysing tumour heterogeneity is summarized in Table 2. Types of cancer that have been investigated with texture analysis include head and neck cancer, cervical cancer, soft tissue sarcomas, oesophageal cancer and NSCLC [22–28].

Tissue characterization and segmentation

Textural analysis has been used for adaptive smoothing, segmentation and classification of medical images [43, 44]. Whilst we are not aware that this approach has yet been used in PET, there is the potential for improving the reproducibility of conventional parameters such as SUV.

Parameters derived from NGTDMs, describing features such as coarseness, contrast and busyness [38], have shown the ability to differentiate primary and nodal tumour from normal tissue in head and neck cancer [23]. It was shown that the primary tumour and metastatic nodes have lower coarseness and busyness but higher contrast than normal tissues. The same group studied 20 patients with head and neck cancers and 20 patients with NSCLC and manually segmented normal and abnormal tissues on ^{18}F-FDG PET images [24]. Textural features, including some derived from SGLDMs and NGTDMs, were selected for characterization of these segmented regions of interest. They concluded that NGTDM features, such as PET coarseness, PET contrast, and CT coarseness, extracted from the ^{18}F-FDG PET/CT images, provided good discrimination, and this may lead to improvement in the accuracy of radiation targeting of head and neck cancers. Another potential heterogeneity parameter using SUV–volume histograms in patients with NSCLC has been described but this has not been clinically tested [22].

Prediction and prognosis

Some studies have shown that textural parameters are better than SUV parameters in predicting response to therapy and survival in a number of cancers. Eary et al. retrospectively analysed 234 patients with sarcoma for tumour heterogeneity on baseline ^{18}F-FDG scans before either neoadjuvant chemotherapy or surgical resection [25]. The technique assessed a parameter derived from the variation from a three-dimensional ellipsoid model for homogeneous tissue. It was concluded that heterogeneity was a strong independent predictor of survival, and that SUV_{max} was somewhat less predictive of tumour survival. El Naqa et al. used first- and second-order textural features to predict outcome in head and neck cancers (9 patients) and cervix cancer (14 patients) [27]. It was concluded that textural

Table 2 Current literature describing texture analysis of ^{18}F-FDG PET

Cancer type	Study findings	Correlate	Reference
Head and neck squamous cell carcinoma (animal model)	Heterogeneity of FDG uptake within a tumour correlates with histopathological findings (p=0.028)	Histopathology	[21]
Sarcoma	Tumour spatial heterogeneity predicts patient outcome (p< 0.001)	SUV_{max}	[25]
Head and neck and cervix	Textural features explains tumour uptake and treatment resistance (cervical p=0.04; head and neck p=0.0012)	SUV_{max}	[27]
Head and neck	Neighbourhood grey-tone-difference matrix features such as PET coarseness, PET contrast, and CT coarseness provided good discrimination performance		[23, 24]
Oesophagus	Local (p< 0.0006) and regional (p=0.0002) textural features predict response to chemoradiotherapy	SUV_{max}, SUV_{peak} and SUV_{mean}	[26]
NSCLC	Potential use of heterogeneity parameter using SUV-volume histograms described		[22]
NSCLC	Multimodality image feature modelling is a predictor of locoregional recurrence after radiotherapy	SUV and Hounsfield unit	[28]

features could significantly aid in summarizing tumour uptake characteristics in its microenvironment and its relationship to treatment resistance in certain clinical scenarios.

Tixier et al. retrospectively studied response to chemoradiotherapy in 41 patients with oesophageal cancer [26]. CT RECIST criteria were used to categorize the patients as complete responders (CR), partial responders (PR) or nonresponders (NR). A Bayesian algorithm was used to automatically delineate tumour volume, and only primary tumours were considered. SUV parameters (max, peak and mean) and 38 textural parameters were extracted from the same tumour volumes. By receiver operating characteristic curve analysis it was found that texture analysis was able to differentiate CR, PR and NR with higher sensitivity than any SUV measurement, thus demonstrating that texture analysis of the intratumoral tracer heterogeneity on baseline ^{18}F-FDG PET scans can predict response to combined chemoradiation treatment in oesophageal cancer. Textural features derived from co-occurrence matrices strongly differentiated NRs from PRs, thus helping stratify patients appropriately. It was also suggested that regional and local characterization of ^{18}FDG PET tracer heterogeneity in tumours is more powerful than global measurements currently used in clinical practice.

Vaidya et al. analysed pretreatment ^{18}F-FDG PET/CT studies in 27 NSCLC patients for local and locoregional failures [28]. They extracted 32 tumour region features based on SUV or Hounsfield units, intensity–volume histogram and textural characteristics. Intensity–volume histogram variables showed the highest univariate association with locoregional recurrence and it was concluded that multimodality image feature modelling with ^{18}F-FDG PET and CT is a predictor of locoregional recurrence in NSCLC after radiotherapy.

Pathobiological basis of texture in ^{18}F-FDG PET imaging

Whilst a number of textural features in structural and functional imaging of cancer have been shown to differentiate tumour types and predict treatment response, and/or are associated with survival, it is largely unknown what the biological correlates of textural features are.

Henriksson et al. investigated the pattern of ^{18}F-FDG uptake in relation to the intratumoral histopathological appearance in nude mice with xenografted tumours originating from an established head and neck squamous cell carcinoma model [21]. Regions containing more than 50 % tumour cells showed significantly higher ^{18}F-FDG uptake than those with more stromal tissue and necrosis. It was concluded that heterogeneous ^{18}F-FDG uptake within a tumour is correlated with histopathological findings and that the variable appearance of tracer uptake on PET scan depends on the distribution of different tissue components in the tumour.

It has also been postulated that increased image heterogeneity within tumours may be associated with differences in regional tumour cellularity, proliferation, hypoxia, angiogenesis and necrosis [26, 45], factors that independently have been associated with more aggressive behaviour, poorer response to treatment and worse prognosis. It is unlikely that structural and functional imaging textural features are associated with the same biological causes of spatial intensity variations within an image, although in

general, features that correspond to increased heterogeneity have been assumed to be related to a poorer prognosis and poor response to treatment. However, given the multitude of textural parameters that have been described, this is probably an oversimplification of the relationships between tumour biology and heterogeneity within an image. For example, CT features related to increased heterogeneity, including increased entropy or decreased uniformity, predict poor response and/or survival [46–48], whereas in ^{18}F-FDG PET imaging of oesophageal carcinoma, treatment responders showed greater local heterogeneity at baseline, but measures of regional tumour heterogeneity showed better response stratification [26]. In head and neck cancer, tumour and nodes have been reported as having lower coarseness and busyness but higher contrast than normal tissues [24]. The relationship between textural features and tissue characteristics is therefore complex and textural feature measurements can clearly not simply be regarded as lying on a spectrum between heterogeneity and homogeneity. There is therefore a need to carefully investigate textural features from different imaging modalities and using different PET tracers to correlate with histopathological features that may influence image texture including angiogenesis, hypoxia, proliferation etc., either in a preclinical model or in humans when tissue is available for complementary histological analysis.

Texture analysis in other imaging modalities

Texture analysis in other radiological imaging has been more extensively described than with PET. CT and MRI texture studies have shown improved tissue characterization, response prediction and prognostication, and studies are emerging in which the link between textural features and tumour biology has been analysed.

There is evidence that texture analysis may aid tissue characterization. Al-Kadi and Watson showed that CT features can be helpful in differentiating aggressive from non-aggressive NSCLC [30], while it has also been possible to show differences between histological subtypes using textural parameters on CT [49]. MRI studies have shown that textural features may differ between benign and malignant lesions. Co-occurrence matrix features of dynamic contrast-enhanced MRI images and signal enhancement ratio maps have been used in breast cancer to distinguish between benign and malignant lesions [50, 51], whilst Holli et al. have demonstrated that co-occurrence matrix features are significantly different between invasive lobular carcinoma and invasive ductal carcinoma [52]. Similarly, textural features have also been used in the brain, liver and prostate studies to distinguish between types of tumours and between benign and malignant disease [53–55].

There is also evidence that tumour heterogeneity on contrast-enhanced CT imaging is an independent predictor of response to therapy and survival. Goh et al. studied patients with renal carcinoma treated with tyrosine kinase inhibitors and found that changes in textural features related to heterogeneity of CT images are independent predictors of time to progression [46]. Ganeshan et al. analysed textural features in unenhanced CT scans of oesophageal carcinoma and concluded that these features are related to SUV parameters in corresponding ^{18}F-FDG PET scans and to tumour stage and survival [47].

MRI textural features have also been shown to predict response to treatment. Textural features change during treatment in non-Hodgkin's lymphoma [56], coherence and fractal dimension predict response in limb sarcomas [57], and low fractal dimension is associated with better response in colorectal cancer [58]. Recently studies have correlated textural parameters on CT with survival in NSCLC [48], glucose metabolism [59] and histological correlations, including angiogenic and hypoxia markers [45]. Segal et al. showed that with a number of image characteristics in hepatocellular carcinoma, including a texture heterogeneity score and estimated percentage of necrosis on contrast-enhanced CT images, it is possible to reconstruct the majority of the gene expression profiles, revealing cell proliferation, liver synthetic function and patient prognosis [60].

Conclusions

Clinical images contain more information than is routinely used. Additional information can easily be extracted to describe and quantify the spatial distribution of voxel intensities (textural features) from conventional radiological images and also from PET images obtained using ^{18}F-FDG and other tracers. Textural features of CT and MRI have shown the ability to characterize tissues as well as predict treatment response and survival in some tumour types. Recent interest in texture analysis of functional imaging, including ^{18}F-FDG PET, has shown similar properties, although the biological mechanisms are unproven. Further work is required to understand the biological basis of image texture in ^{18}F-FDG PET and to further validate the methodology in different cancers. It remains to be seen whether texture analysis of other metabolic tracers, e.g. ^{11}C- or ^{18}F-choline, or tracers reflecting other aspects of tumour biology such as proliferation with ^{18}F-FLT, angiogenesis/integrin expression with labelled R-G-D compounds or hypoxia-selective agents, may produce similar results.

Seeking more powerful imaging biomarkers through texture analysis is of high relevance to modern cancer treatment where the aim is to personalize treatment through non-invasive molecular and genomic profiling of tumours.

Acknowledgments The authors acknowledge support from the NIHR Biomedical Research Centre of Guys & St Thomas' NHS Trust in partnership and Kings College London and King's College London and UCL Comprehensive Cancer Imaging Centre funded by the CRUK and EPSRC in association with the MRC and DoH (England).

Conflicts of interest None.

References

1. Lambin P, Rios-Velazquez E, Leijenaar R, Carvalho S, van Stiphout RG, Granton P, et al. Radiomics: extracting more information from medical images using advanced feature analysis. Eur J Cancer. 2012;48:441–6.
2. Hillner BE, Siegel BA, Liu D, Shields AF, Gareen IF, Hanna L, et al. Impact of positron emission tomography/computed tomography and positron emission tomography (PET) alone on expected management of patients with cancer: initial results from the National Oncologic PET Registry. J Clin Oncol. 2007;26:2155–61.
3. Juweid ME, Cheson BD. Positron emission tomography and assessment of cancer therapy. N Engl J Med. 2006;354:496–507.
4. Ben-Haim S, Ell P. 18F-FDG PET and PET/CT in the evaluation of cancer treatment response. J Nucl Med. 2009;50:88–99.
5. Wahl RL, Jacene H, Kasamon Y, Lodge MA. From RECIST to PERCIST: evolving considerations for PET response criteria in solid tumors. J Nucl Med. 2009;50:122S–50.
6. Cremerius U, Effert PJ, Adam G, Sabri O, Zimmy M, Wagenknecht G, et al. FDG PET for detection and therapy control of metastatic germ cell tumor. J Nucl Med. 1998;39:815–22.
7. Dehdashti F, Mortimer JE, Trinkaus K, Naughton MJ, Ellis M, Katzenellenbogen JA, et al. PET-based estradiol challenge as a predictive biomarker of response to endocrine therapy in women with estrogen-receptor-positive breast cancer. Breast Cancer Res Treat. 2009;113:509–17.
8. Mac Manus MP, Ding Z, Hogg A, Herschtal A, Binns D, Ball DL, et al. Association between pulmonary uptake of fluorodeoxyglucose detected by positron emission tomography scanning after radiation therapy for non-small-cell lung cancer and radiation pneumonitis. Int J Radiat Oncol Biol Phys. 2011;80:1365–71.
9. de Geus-Oei LF, van der Heijden HF, Visser EP, Hermsen R, van Hoorn BA, Timmer-Bonte JN, et al. Chemotherapy response evaluation with 18F-FDG PET in patients with non-small cell lung cancer. J Nucl Med. 2007;48:1592–8.
10. Rizk NP, Tang L, Adusumilli PS, Bains MS, Akhurst TJ, Ilson D, et al. Predictive value of initial PET SUVmax in patients with locally advanced esophageal and gastroesophageal junction adenocarcinoma. J Thorac Oncol. 2009;4:875–9.
11. Ohno Y, Koyama H, Yoshikawa T, Matsumoto K, Aoyama N, Onishi Y, et al. Diffusion-weighted MRI versus 18F-FDG PET/CT: performance as predictors of tumor treatment response and patient survival in patients with non-small cell lung cancer receiving chemoradiotherapy. AJR Am J Roentgenol. 2012;198:75–82.
12. Zhang HQ, Yu JM, Meng X, Yue JB, Feng R, Ma L. Prognostic value of serial [18F]fluorodeoxyglucose PET-CT uptake in stage III patients with non-small cell lung cancer treated by concurrent chemoradiotherapy. Eur J Radiol. 2011;77:92–6.
13. 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.
14. 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;12:4232–6.
15. Cazaentre T, Morschhauser F, Vermandel M, Betrouni N, Prangère T, Steinling M, et al. Pre-therapy 18F-FDG PET quantitative parameters help in predicting the response to radioimmunotherapy in non-Hodgkin lymphoma. Eur J Nucl Med Mol Imaging. 2010;37:494–504.
16. Colavolpe C, Metellus P, Mancini J, Barrie M, Béquet-Boucard C, Figarella-Branger D, et al. Independent prognostic value of pre-treatment 18-FDG-PET in high-grade gliomas. J Neurooncol. 2012;107:527–35.
17. Xie P, Li M, Zhao H, Sun X, Fu Z, Yu J. 18F-FDG PET or PET-CT to evaluate prognosis for head and neck cancer: a meta-analysis. J Cancer Res Clin Oncol. 2011;137:1085–93.
18. Kitagawa Y, Sano K, Nishizawa S, Nakamura M, Ogasawara T, Sadato N, et al. FDG-PET for prediction of tumour aggressiveness and response to intra-arterial chemotherapy and radiotherapy in head and neck cancer. Eur J Nucl Med Mol Imaging. 2003;30:63–71.
19. Kidd EA, Dehdashti F, Siegel BA, Grigsby PW. Anal cancer maximum F-18 fluorodeoxyglucose uptake on positron emission tomography is correlated with prognosis. Radiother Oncol. 2010;95:288–91.
20. Zhu W, Xing L, Yue J, Sun X, Sun X, Zhao H, et al. Prognostic significance of SUV on PET/CT in patients with localised oesophagogastric junction cancer receiving neoadjuvant chemotherapy/chemoradiation: a systematic review and meta-analysis. Br J Radiol. 2012;85:e694–701.
21. Henriksson E, Kjellen E, Wahlberg P, Ohlsson T, Wennerberg J, Brun E. 2-Deoxy-2-[18F]fluoro-D-glucose uptake and correlation to intratumoral heterogeneity. Anticancer Res. 2007;27:2155–9.
22. van Velden FH, Cheebsumon P, Yaqub M, Smit EF, Hoekstra OS, Lammertsma AA, et al. Evaluation of a cumulative SUV-volume histogram method for parameterizing heterogeneous intratumoural FDG uptake in non-small cell lung cancer PET studies. Eur J Nucl Med Mol Imaging. 2011;38:1636–47.
23. Yu H, Caldwell C, Mah K, Poon I, Balogh J, MacKenzie R, et al. Automated radiation targeting in head-and-neck cancer using region-based texture analysis of PET and CT images. Int J Radiat Oncol Biol Phys. 2009;75:618–25.
24. 2Yu H, Caldwell C, Mah K, Mozeg D. Coregistered FDG PET/CT-based textural characterization of head and neck cancer for radiation treatment planning. IEEE Trans Med Imaging. 2009;28:374–83.
25. Eary JF, O'Sullivan F, O'Sullivan J, Conrad EU. Spatial heterogeneity in sarcoma 18F-FDG uptake as a predictor of patient outcome. J Nucl Med. 2008;49:1973–9.
26. Tixier F, Cheze Le Rest C, Hatt M, Albarghach N, Pradier O, Metges JP, et al. Intratumor heterogeneity characterized by textural features on baseline 18F-FDG PET images predicts response to concomitant radiochemotherapy in esophageal cancer. J Nucl Med. 2011;52:369–78.
27. El Naqa I, Grigsby P, Apte A, Kidd E, Donnelly E, Khullar D, et al. Exploring feature-based approaches in PET images for predicting cancer treatment outcomes. Pattern Recognit. 2009;42:1162–71.
28. Vaidya M, Creach KM, Frye J, Dehdashti F, Bradley JD, El Naqa I. Combined PET/CT image characteristics for radiotherapy tumor response in lung cancer. Radiother Oncol. 2012;102:239–45.
29. Castellano G, Bonilha L, Li LM, Cendes F. Texture analysis of medical images. Clin Radiol. 2004;59:1061–9.
30. Al-Kadi OS, Watson D. Texture analysis of aggressive and non-aggressive lung tumor CE CT images. IEEE Trans Biomed Eng. 2008;55:1822–30.
31. Ganeshan B, Miles KA, Young RC, Chatwin CR. Hepatic entropy and uniformity: additional parameters that can potentially increase the effectiveness of contrast enhancement during abdominal CT. Clin Radiol. 2007;62:761–8.
32. Brown RA, Frayne R. A comparison of texture quantification techniques based on the Fourier and S transforms. Med Phys. 2008;35:4998–5008.

33. Goh V, Sanghera B, Wellsted DM, Sundin J, Halligan S. Assessment of the spatial pattern of colorectal tumour perfusion estimated at perfusion CT using two-dimensional fractal analysis. Eur Radiol. 2009;19:1358–65.
34. Sanghera B, Banerjee D, Khan A, Simcock I, Stirling JJ, Glynne Jones R, et al. Reproducibility of 2D and 3D fractal analysis techniques for the assessment of spatial heterogeneity of regional blood flow in rectal cancer. Radiology. 2012;263:865–73.
35. Craciunescu OI, Das SK, Clegg ST. Dynamic contrast-enhanced MRI and fractal characteristics of percolation clusters in two-dimensional tumor blood perfusion. J Biomech Eng. 1999;121:480–6.
36. Dettori L, Semler L. A comparison of wavelet, ridgelet, and curvelet-based texture classification algorithms in computed tomography. Comput Biol Med. 2007;37:486–98.
37. Al-Kadi OS. Assessment of texture measures susceptibility to noise in conventional and contrast enhanced computed tomography lung tumour images. Comput Med Imaging Graph. 2010;34:494–503.
38. Amadasun M, King R. Textural features corresponding to textural properties. IEEE Trans Syst Man Cybern. 1989;19:1264–74.
39. Veenland JF, Grashuis JL, Gelsema ES. Texture analysis in radiographs: the influence of modulation transfer function and noise on the discriminative ability of texture features. Med Phys. 1998;25:922–36.
40. Galavis PE, Hollensen C, Jallow N, Paliwal B, Jeraj R. Variability of textural features in FDG PET images due to different acquisition modes and reconstruction parameters. Acta Oncol. 2010;49:1012–6.
41. Tixier F, Hatt M, Le Rest CC, Le Pogam A, Corcos L, Visvikis D. Reproducibility of tumor uptake heterogeneity characterization through textural feature analysis in 18F-FDG PET. J Nucl Med. 2012;53:693–700.
42. Lodge MA, Lucas JD, Marsden PK, Cronin BF, O'Doherty MJ, Smith MA. A PET study of 18FDG uptake in soft tissue masses. Eur J Nucl Med. 1999;26:22–30.
43. Wang Z, Gierriero A, Sario M. Comparison of several approaches for segmentation of texture images. Patt Recog Lett. 1996;17:509–21.
44. Sharma N, Ray AK, Sharma S, Shukla KK, Pradhan S, Aggarwal LMJ. Segmentation and classification of medical images using texture-primitive features: application of BAM-type artificial neural network. Med Phys. 2008;33:119–26.
45. Ganeshan B, Goh V, Mandeville H, Ng QS, Hoskin P, Miles KA. CT of non-small cell lung cancer: Histopathological correlates for texture parameters. Radiology. 2012 (in press).
46. Goh V, Ganeshan B, Nathan P, Juttla JK, Vinayan A, Miles KA. Assessment of response to tyrosine kinase inhibitors in metastatic renal cell cancer: CT texture as a predictive biomarker. Radiology. 2011;26:165–71.
47. Ganeshan B, Skogen K, Pressney I, Coutroubis D, Miles K. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: preliminary evidence of an association with tumour metabolism, stage, and survival. Clin Radiol. 2012;67:157–64.
48. Ganeshan B, Panayiotou E, Burnand K, Dizdarevic S, Miles K. Tumour heterogeneity in non-small cell lung carcinoma assessed by CT texture analysis: a potential marker of survival. Eur Radiol. 2012;22:796–802.
49. Kido S, Kuriyama K, Higashiyama M, Kasugai T, Kuroda C. Fractal analysis of internal and peripheral textures of small peripheral bronchogenic carcinomas in thin-section computed tomography: comparison of bronchioloalveolar cell carcinomas with non bronchioloalveolar cell carcinomas. J Comput Assist Tomogr. 2003;27:56–61.
50. Chen W, Giger ML, Li H, Bick U, Newstead GM. Volumetric texture analysis of breast lesions on contrast-enhanced magnetic resonance image. Magn Reson Med. 2007;58:562–71.
51. Woods BJ, Clymer BD, Kurc T, Heverhagen JT, Stevens R, Orsdemir A, et al. Malignant-lesion segmentation using 4D co-occurrence texture analysis applied to dynamic contrast-enhanced magnetic resonance breast image data. J Magn Reson Imaging. 2007;25:495–501.
52. Holli K, Lääperi AL, Harrison L, Luukkaala T, Toivonen T, Ryymin P, et al. Characterization of breast cancer types by texture analysis of magnetic resonance images. Acad Radiol. 2010;17:135–41.
53. Eliat PA, Olivié D, Saïkali S, Carsin B, Saint-Jalmes H, de Certaines JD. Can dynamic contrast-enhanced magnetic resonance imaging combined with texture analysis differentiate malignant glioneuronal tumors from other glioblastoma? Neurol Res Int. 2012;2012:1951–76.
54. Mayerhoefer ME, Schima W, Trattnig S, Pinker K, Berger-Kulemann V, Ba-Ssalamah A. Texture-based classification of focal liver lesions on MRI at 3.0 Tesla: a feasibility study in cysts and hemangiomas. J Magn Reson Imaging. 2010;32:352–9.
55. Lopes R, Ayache A, Makni N, Puech P, Villers A, Mordon S, et al. Prostate cancer characterization on MR images using fractal features. Med Phys. 2011;38:83–95.
56. Harrison LC, Luukkaala T, Pertovaara H, Saarinen TO, Heinonen TT, Jarvenpaa R, et al. Non-Hodgkin lymphoma response evaluation with MRI texture classification. J Exp Clin Cancer Res. 2009;28:87.
57. Alic L, van Vliet M, van Dijke CF, Eggermont AM, Veenland JF, Niessen WJ. Heterogeneity in DCE-MRI parametric maps: a biomarker for treatment response? Phys Med Biol. 2011;56:1601–16.
58. O'Connor JP, Rose CJ, Jackson A, Watson Y, Cheung S, Maders F, et al. DCE-MRI biomarkers of tumour heterogeneity predict CRC liver metastasis shrinkage following bevacizumab and FOLFOX-6. Br J Cancer. 2011;105:139–45.
59. 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.
60. Segal E, Sirlin CB, Ooi C, Adler AS, Gollub J, Chen X, et al. Decoding global gene expression programs in liver cancer by noninvasive imaging. Nat Biotechnol. 2007;25:675–80.