The clinical utility of prostate cancer heterogeneity using texture analysis of multi parametric prostate MRI.

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Abstract:

Purpose: To determine if multiparametric-MRI (mpMRI) derived filtration-histogram based texture analysis (TA) can differentiate between different Gleason scores (GS) and the D'Amico risk in prostate cancer.

Methods: We retrospectively studied patients whose pre-operative 1.5T mpMRI had shown a visible tumour and who subsequently underwent a radical prostatectomy (RP). Guided by tumour location from the histopathology report, we drew a region of interest (ROI) around the dominant visible lesion on a single axial slice on the T2, Apparent Diffusion Coefficient (ADC) map and early arterial phase post-contrast T1 image. We then performed TA with a filtration-histogram software (TexRAD - Feedback Medical Ltd, Cambridge, UK). We corelated GS and D'Amico risk with texture using the Spearman's rank correlation test.

Results: We had 26 RP patients with MR visible tumour. Mean of positive pixels (MPP) on ADC showed a significant negative correlation with GS at coarse texture scales. MPP showed a significant negative correlation with GS without filtration and with medium filtration. MRI contrast texture without filtration showed a significant, negative correlation with D'Amico score. MR T2 texture showed a significant, negative correlation with the D'Amico risk, particularly at textures without filtration, medium texture scales and coarse texture scales.

Conclusion: ADC map mpMRI TA correlated negatively with GS, and T2 and post-contrast images with the D'Amico risk score. These associations may allow for better assessment of disease prognosis and a non-invasive method of follow-up for patients on surveillance. Further, identifying clinically significant prostate cancer is important to reduce harm from over-diagnosis and over-treatment.

Keywords

Prostatic neoplasms; neoplasm grading; prostate-specific antigen; magnetic resonance imaging; image enhancement; texture analysis

Introduction

The histological Gleason score (GS) is an essential determinant for the management of prostate cancer. The D'Amico risk stratification score is another frequently used tool, which uses a combination of clinical and imaging data with histology to gauge the five-year risk of treatment failure [1]. Risk stratification in this way helps select patients suitable for active treatment and avoids over-treatment of clinically insignificant disease [2-4]. Current risk stratification is limited to clinical examination, serum prostate specific antigen, and transrectal prostate biopsy.

Multi-parametric MRI (mpMRI) has revolutionised the detection, staging, and management of early prostate cancer, and now plays a central role [5-8]. mpMRI provides anatomical as well as at least two functional sequences, and includes T1- and T2-weighted, dynamic contrast-enhanced, and diffusion weighting imaging [9]. This imaging modality provides a vast amount of data which may be exploited. In particular, there has been a surge of work regarding texture analysis in a variety of malignancies including prostate cancer [10-15].

Tumour heterogeneity is a key factor in predicting tumour malignant potential at a cellular level. Texture analysis (TA) provides a means to quantify signal heterogeneity in images through analysis of the regularity and coarseness of pixel value spatial distribution not visually perceptible by the human eye [16]. The filtration-histogram technique of TA is one of the methods commonly employed and

validated/qualified to derive quantitative textural features [17]. The revised Pi-RADS 2 guidelines now advocate the use of tumour signal homogeneity on mpMRI to grade disease [9]. In the patient subset where a tumour is not clearly visualised, the additional data provided by quantitative TA (QTA) may have utility in detecting clinically significant disease. Histogram analysis with/without an initial filtration step is a commonly employed technique in the field of TA [11-20].

The aim of this study was to evaluate the use of filtration-histogram TA derived from mpMRI to differentiate the Gleason score of prostatic tumour. A secondary outcome measure was the correlation between MR texture analysis and the D'Amico risk category as well as the total serum PSA.

Methods

According to the Health Research Authority, UK, recommendations [21], local institutional review board approval was not sought for this retrospective review of anonymised, routinely acquired patient clinical and imaging data.

Patients

The study population were men with prostate adenocarcinoma who underwent mpMRI followed by prostatectomy from June 2013 – September 2016. Men who did not have surgery or pre-operative MRI were excluded, as were men who did not have a visible tumour focus on imaging. In total, 26 men were included with mean age 64.7 ± 6.4 (48, 74) years, of which 13/26 = 50% had a Gleason score of 3+4 or less (ISUP grade group 1 and 2), and 13/26 = 50% had a Gleason's score of 4+3 or greater (ISUP grade group 3 or more), Table 1.

The D'Amico risk score was calculated from the biopsy GS, PSA value closest to the date of diagnosis and clinical stage. Details of the D'Amico risk classification is at Table 2 [1].

MRI

MpMRI of the prostate gland was performed with a 1.5T MRI scanner (Aera, Siemens Healthcare, Erlangen, Germany). The MRI protocol included axial small field-of-view T2 weighted, axial diffusion weighted imaging (DWI) and dynamic post-contrast sequences (DWI) following administration of 20mg of Hyoscine Butylbromide (Buscopan, Boehringer Ingelheim, Ingelheim, Germany). MpMRI acquisition parameters are outlined in Table 3.

Histopathology

Prostatectomy specimens were reviewed by a histopathologist specialising in prostate cancer. Gleason grade and ISUP grade groups were evaluated with patients scored as clinically significant (4+3 or greater) or clinically not significant (3+4 or less) [22].

Histology-MRI matching

Following identification of MRI visible tumour matched to the histopathology report, the tumour focus was contoured on the single axial image containing the largest visible tumor diameter to form a region of interest (ROI) on the T2, ADC and early post contrast sequences.

Texture analysis

MR texture analysis (MRTA) was performed on the ROIs using commercially available TA research software (TexRAD, Feedback Medical Ltd, Cambridge, UK -

www.fbkmed.com). MRTA comprised a filtration-histogram technique which has been completely described previously [17,19]. In brief filtration step extracted and enhanced features of different signal intensity and sizes corresponding to a spatial scale filter (SSF) which varied from 0 (without-filtration), 2mm (fine texture scale), 3-5mm (medium texture scale) and 6mm (coarse texture scale). An illustration of the image segmentation and texture feature extraction at different spatial frequencies is outlined in figure 1. Following the filtration step, quantification of texture using statistical and histogram characteristics comprised of mean intensity, standard deviation (SD), entropy, mean of positive pixels (MPP), skewness and kurtosis. Mean intensity describes the average intensity value of pixels in a defined region of interest. SD reflects variation/deviation of the pixel values about the mean. Entropy is a statistical parameter which measure irregularity, higher the value more irregular the texture is. In addition to the mean intensity, MPP measures the average intensity of the pixels with only positive values. Skewness reflect asymmetry in the histogram distribution about the mean. Kurtosis indicates how peaked/pointed the histogram is relative to a normal distribution. An illustration of the quantification process using histogram based statistical analysis is highlighted in figure 2**.** Miles et al [17] described in detail what does filtration-histogram based TA actually means and how does the above texture features reflects different components of heterogeneity (object size, number of objects, variation in intensity of the objects in relation to the background)

Unlike ADC, absolute T2 weighted and post-contrast weighted pixel values are not normalized. Consequently, texture features that are calculated from absolute T2 and post-contrast pixel values such as the mean, SD, MPP were excluded from the analysis of T2 and post contrast T1. Texture features that are calculated from the

shape of the T2 or post-contrast histogram (such as entropy, skewness, kurtosis) are not affected by the absolute pixel value and were included.

Statistical analysis

We used the non-parametric Spearman's rank correlation to assess the primary end point of the association between MRTA parameters and GS. Additionally, we assessed the correlation with the D'Amico score and PSA as secondary outcome measures. We used SPSS statistics for Windows (version 25; IBM, Armonk, NY, USA) for statistical analysis and p-value < 0.05 was considered as significant.

Results

Of the 26 men included, tumours were visible on ADC in 25, Contrast in 26 and T2 in 24 cases. Therefore, details of these 26 patients were used for the purpose of the study. The demographic details of these patients along with their GS, D'Amico risk and PSA are in Table 2.

MR ADC texture parameters showed a significant, negative correlation with Gleason score particularly at medium texture scale SSF = 5 (MPP: rs=-0.493, p=0.009, SD: rs=-0.382, p=0.049) and coarse texture scale SSF = 6 (MPP: rs=-0.490, p=0.009, SD: rs=-0.485, p=0.010). ADC mean demonstrated a negative correlation with Gleason score (rs=-0.402, p=0.038). MR Contrast texture without filtration showed a significant, negative correlation with D'Amico risk (skewness: rs=-0.492, p=0.006). MR T2 texture parameters showed a significant, negative correlation with D'Amico at texture without filtration (Skewness: rs=-0.455, p=0.019), medium texture scales (Skewness: rs=-0.399, p=0.043) and coarse texture scales (Skewness: rs=-0.400, p=0.043, Kurtosis: rs=-0.424, p=0.031). A summary of significant results is detailed in Table 4.

No significant correlation was obtained between MRTA parameters and serum PSA in our cohort.

In summary, ADC parameters negatively correlated with Gleason score, whereas T2 and post-contrast texture features negatively correlated with D'Amico score.

Discussion

We studied the ability of mpMRI derived TA to predict the Gleason Score, D'Amico risk and explored the association between texture analysis and total PSA in a cohort of prostate cancer patients who underwent prostatectomy. In most cases, we were able to exactly correlate the tumour focus from the histopathological specimen rather than inferring this from a representative biopsy.

We found that ADC texture parameters negatively correlated with GS, whereas T2 and post-contrast texture features negatively correlated with the D'Amico score. mpMRI has transformed oncological imaging and has been harnessed for tumour grading and detection, as well as for prognostication and monitor response to treatment. MRTA is emerging as a potential tool in prostate cancer imaging and may help to prevent over-treatment of clinically insignificant tumours. This is particularly an issue with anteriorly located tumours [24]. mpMRI has been shown to be able to differentiate central gland tumour from benign hyperplasia, a traditionally difficult area to evaluate on traditional MR imaging [25].

Our findings suggest that certain textural features aid classification of GS. We found that the mean, mean of positive pixels (MPP), and SD have a significant negative correlation with GS on ADC.

We chose to also include correlation with the D'Amico score as an outcome measure. This tool calculates the five-year risk of treatment failure based upon the serum PSA, Gleason grade and clinical stage, thus integrating clinical data with histology and radiology [1]. The score includes a GS of ≤6 as part of the low risk stratification criteria (*Table 1*). Our rationale was to attempt to address some of the limitations in defining 'clinically significant' disease based on the GS alone. The majority of prior work in the literature regarding texture analysis has focused only on the traditional GS in patient risk stratification [23, 26, 28].

We found that skewness showed a significant negative correlation with the D'Amico score on post-contrast MRTA without filtration. On T2-weighted sequences, skewness and kurtosis demonstrated a significant negative correlation with the D'Amico score at medium and coarse texture scales, particularly at texture without filtration. No significant correlation was found with GS alone for the aforementioned texture parameters on T2-weighted or contrast-enhanced sequences.

We could not demonstrate any correlation between texture parameters and the serum PSA alone in our cohort. This absence of correlation with the serum total PSA is not surprising, given the high level of false-positive results of this test when used alone [29].

Our findings suggest that high grade prostate malignancies, i.e. with adverse tumour biology, are more heterogenous than low grade, clinically insignificant tumours. Increased tumour heterogeneity has been previously linked to worse clinical prognosis in multiple tumour types, including oesophageal, colorectal, CNS, and non-small cell lung carcinoma. Furthermore, texture analysis can provide prognostic information from imaging, additional to that given by a radiologist, and be used as an

independent predictor of survival [19,30]. Texture analysis has also been harnessed in breast, rectal, renal cell and pancreatic cancer as an early indicator of treatment response [10-15,30].

Our study corroborates previous work by Dikaios et al. who used logistic regression models based upon quantitative mpMRI parameters, such as ADC, in 155 patients to differentiate between benign (GS 6 or less) and malignant lesions in the transition zone (TZ) [23]. This has also been demonstrated in a cohort of patients with peripheral zone tumours [24]. Wibmer et al. showed that peripheral zone tumours had significantly lower homogeneity on ADC maps and T2-weighted imaging compared to benign tissue in a cohort of 147 patients [26].

Regarding particular texture parameters, our results are supported by a previous study where there was reduced mean intensity, MPP and SD in TZ tumours [27]. In particular, these findings were present in TZ tumours with adverse biology as indicated by abnormal PSA expression on corresponding PET images. This indication of abnormal tumour biology by the mean, MPP and SD is likewise suggested by our findings of a negative correlation with a high GS or the D'Amico risk stratification. The lower mean and MPP post filtration of high-grade malignancy are in keeping with clinically significant tumours with high cellularity generally having low ADC values. This implies a translational benefit where these MRI parameters on texture analysis might better (than simply measuring the ADC mean which was less significant in our study) inform clinicians about the risks of high-grade disease through a non-invasive method.

A less peaked distribution (ie more plateaued distribution may reflect lower tissue contrast ie more cellularity) or lower kurtosis and lower/negative skewness (ie

preponderance of darker features ie more cellularity) of pixel signal intensity on T2-weighted sequences, predicted high grade tumours in our study. Sidhu at al. used a cohort of 26 patients to demonstrate that MRTA of TZ tumours can discriminate significant prostate cancer, as deemed by template-mapping biopsy and GS [28]. Reduced ADC kurtosis reflecting less peaked histogram distribution of pixel values, was found to be the best textural parameter for classifying significant TZ tumours. Furthermore, in a cohort of 180 endometrial cancer patients, kurtosis on contrast-enhanced images negatively predicted recurrence and progression-free survival [19].

Other groups have noted the significance of skewness in determining high grade cancer [20]. It has been proposed that histograms are less skewed in malignant tumours with high cellularity due to the densely packed cells [18].

An important distinct feature of our study is the use of whole gland prostatectomy specimens for histology. We had access to histopathology data which enabled a precise pathological correlate to mpMRI imaging features, rather than inferring this from a representative biopsy. Furthermore, to our knowledge, this is the only study to use variables other than GS alone to determine ‘clinically significant’ tumours as we additionally used the D’Amico score and serum PSA.

There are a few limitations to our study. Firstly, the sample size was small, as we only included patients who had MRI visible tumours. Secondly, 1.5T scanners were exclusively used in our cohort. Applicability of our findings to a higher Tesla scanner has not been formally assessed, although guidance from a European Consensus meeting advocate a 1.5 T mpMRI protocol [31]. The use of endorectal coils was not deemed necessary by this group, and accordingly, we did not use such coils. Studies have found equivocal performance of mpMRI at 1.5T using endorectal coils,

compared to imaging without endorectal coils [31-33]. A potential source of error may have been introduced during manual contouring of region of interests. We envisage that future use of machine learning with automated segmentation would negate this issue. There is much variability in prostate tumour cellularity which is not factored into the current Gleason grading system [34]. Hence, there are limitations of the Gleason score to determine significant high grade tumours. Indeed, sparse prostate tumours can have equivalent ADC and T2 pixel values to normal prostatic tissue. We have partially addressed this issue by including correlation with the D'Amico classification system. Our study population only includes patients who underwent prostatectomy and so there may have been a selection bias towards more aggressive tumours potentially missing lower grade cancers that may ultimately benefit from non-invasive assessment. As the purpose of our study was to examine for the applicability of MR texture analysis technology to assess if filtration-histogram analysis helps in defining clinically significant cancer, we did not study if the tumours arose from the peripheral zone or transition zone.

Our study has some strengths as well. Our study has only included patients with available radical prostatectomy specimens. This offsets a possible weak co-relationship that may exist between tumour focus and random prostate biopsy specimens. For the same reason, we have only selected patients with visible tumour focus, enabling an accurate co-relation with the tumour. The D'Amico classification is a clinical score that uses the whole gland and not just the ROI and, hence, may not be expected to correlate with TA. Therefore, our observations linking TA with a well validated prognostic scale such as the D'Amico adds strength to the value of our study.

In summary, MRTA may be used as a non-invasive imaging biomarker to guide risk stratification, prognosis, treatment, and follow up. Thus, MRTA can guide personalised decision making, including prevention of over-diagnosis and over-treatment of clinically insignificant disease. One potential future application of the work is in the group of patients with occult tumours which are not visible with conventional MRI yet malignancy is indicated on histology. Another potential application is for non-invasive follow up of less aggressive tumours or those on active surveillance, perhaps avoiding sequential biopsies. Currently there are only a small number of clinical studies on MRTA and its correlation to clinically relevant prognostic markers. Our findings would need validation in further studies.

When used as a multi-parametric computer aided detection (CAD) model, an objective textural assessment could improve prostate cancer classification, especially in cases where radiologists are uncertain. Furthermore, in the United Kingdom, the use of mpMRI in prostate cancer patients with a negative non-targeted TRUS biopsy has already been advocated by NICE guidelines [4]. The application of MR texture analysis to this cohort will lead to more appropriate selection of patients to individual treatment pathways.

Compliance with Ethical Standards

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Conflict of interest BG is a Director of Feedback Medical Ltd (www.fbkmed.com) and Shareholder of Feedback Plc, Cambridge, (which wholly owns Feedback Medical Ltd.), , a UK based medical imaging software company and manufacturer of TexRAD texture analysis research software used in this study.

Ethical approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

This article does not contain any studies with animals performed by any of the authors

Author contributions

AA: study conceptualisation.

BG: MR image analysis (guidance), statistics and inputs to manuscript

DB: Study conceptualisation, clinical data collection, manuscript revisions

JS: MR image analysis and manuscript revisions

MH: Initial draft, bibliography and manuscript revisions.

SM: Clinical data collection and validation

Control of data and final manuscript approval were undertaken by the first and last authors (Study-guarantors)

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Tables

	Mean ± (SD) (Range), Median
Age	64.7 ± 6.4 (48, 74), 66
PSA (ng/ml)	8.7 ± 5.2 (1.6, 23), 7.9
Prostate volume (cc)	37 ± 13.3 (15, 70), 34.5
PSA density (ng/ml/cc)	0.3 ± 0.2 (0.05, 0.79), 0.2
Tumour volume (ml)	2.6 ± 2.3 (0.99, 11), 1.98
Path Stage	**n (%)**
T2a	2 (7.7)
T2b	1 (3.8)
T2c	9 (34.6)
T3a	7 (26.9)
T3b	6 (23.1)
T3c	0
T4	1 (3.8)
Gleason	**n (%)**
3+3	1 (3.8)
3+4	12 (46.2)
4+3	9 (34.6)
4+4	0
4+5	3 (11.5)
5+4	1 (3.8)
D'Amico	**n (%)**
Intermediate	13 (50)
High	13 (50)

Table 1. Demographic data of study population. Prostate Specific Antigen (PSA)

Low risk	GS ≤ 6 and PSA ≤10ng/ml and Clinical Stage T1c or T2
Intermediate risk	GS =7 or PSA>10 and ≤20 ng/ml or Clinical stage T2b
High risk	GS ≥ 8 or PSA ≥20 ng/ml or Clinical stage T2c 0r T3

Table 2: D'Amico risk classification. GS= highest biopsy Gleason score, PSA=prostate specific antigen.

Sequence	TR (ms)	TE (ms)	NA	BR	ST (mm)	PAT	Fat suppression	Receiver Bandwidth (Hz/pixel)
T2 Blade	5500	100	1	320	3	2	None	382
DWI b0, 500, 1000, 1400	6800	99	5	160	3.5	2	SPAIR	1250
T1 3D VIBE axial dynamic	6.91	1.71	1	256	3	2	SPAIR	300

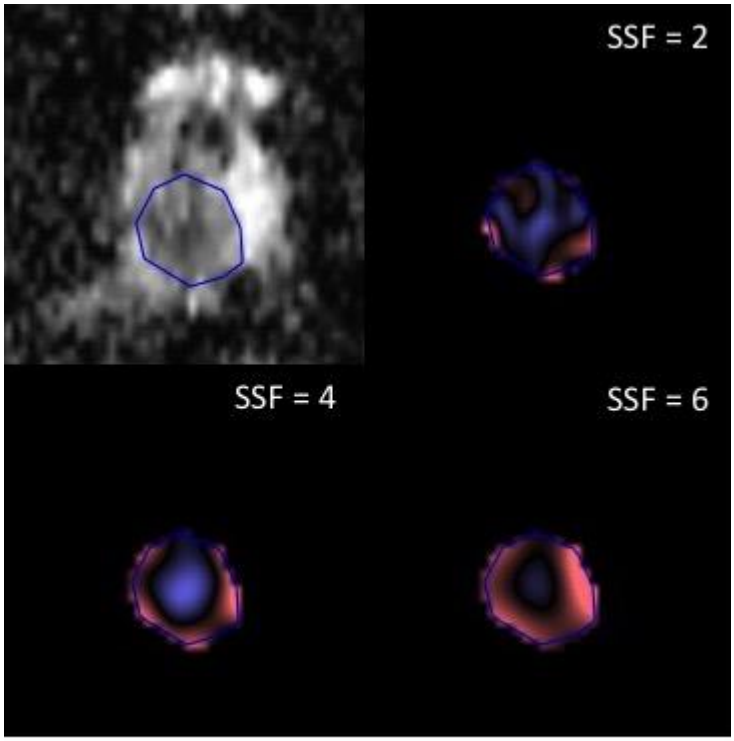
Table 3. MRI Acquisition parameters. TR: repetition time, TE: echo time, NA: number of averages, BR: base resolution, ST: slice thickness, PAT: parallel acquisition

technique, SPAIR: Spectral Attenuated Inversion Recovery, VIBE: Volumetric Interpolated Breath-hold Examination.

Sequence	Statistical test	Filter	Outcome	Feature	Correlation (rs)	P-value
ADC	Spearman	0	Gleason	mean	-0.402	0.038
ADC	Spearman	4	Gleason	mean	-0.404	0.037
ADC	Spearman	5	Gleason	mpp	-0.493	0.009
ADC	Spearman	5	Gleason	sd	-0.382	0.049
ADC	Spearman	6	Gleason	mpp	-0.49	0.009
ADC	Spearman	6	Gleason	sd	-0.485	0.01
ADC	KW	6	Gleason	Skewness		0.028
Contrast	Spearman	0	D'Amico	Skewness	-0.492	0.006
Contrast	KW	0	D'Amico	Skewness		0.029
T2	Spearman	0	D'Amico	Skewness	-0.455	0.019
T2	Spearman	5	D'Amico	Skewness	-0.399	0.043
T2	Spearman	6	D'Amico	Skewness	-0.400	0.043
T2	Spearman	6	D'Amico	Kurtosis	-0.424	0.031

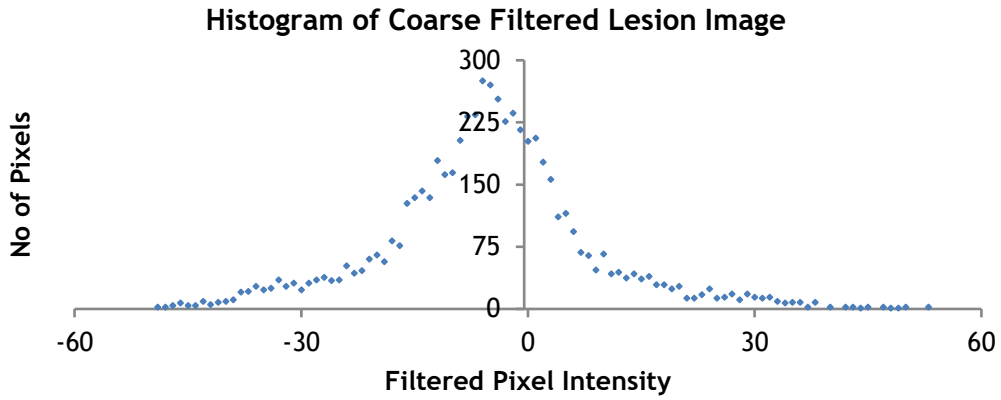
Table 4: Results summary of statistically significant correlations between ADC, contrast enhancement and T2 texture analysis with both Gleason grade and D'Amico score, SD: Standard Deviation, MPP: Mean of Positive Pixels.

Figures



Segmented ADC map high grade Gleason 4+5 MR visible tumor focus with fine (SSF = 2), medium (SSF = 4) and coarse (SSF = 6) spatial features extracted prior to texture analysis.

Figure 1. Segmented ADC map of high grade Gleason 4+5 MR visible tumor focus with fine (SSF =2), medium (SSF=4) and coarse (SSF=6) spatial features extracted prior to texture analysis.



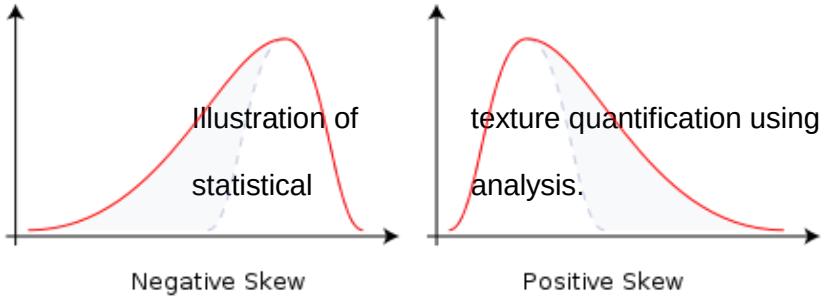
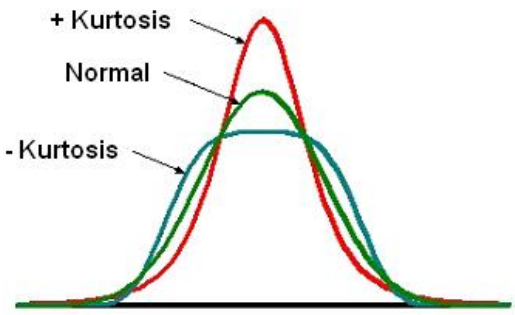


Figure 2. Illustration of texture quantification using histogram based statistical analysis.



- Mean: The average value of the pixels within the region of interest
- Standard deviation – A measure of how much variation or "dispersion" exists from the average
- Skewness – *symmetry of the distribution may reflect structures (bright or dark objects)*
- Kurtosis – *pointiness of the distribution may reflect increased contrast*