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SPECIAL SECTION: RADIOGENOMICS

A review of the principles of texture analysis and its role in imaging of genitourinary neoplasms

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Abstract

Advances in the management of genitourinary neoplasms have resulted in a trend towards providing patients with personalized care. Texture analysis of medical images, is one of the tools that is being explored to provide information such as detection and characterization of tumors, determining their aggressiveness including grade and metastatic potential and for prediction of survival rates and risk of recurrence. In this article we review the basic principles of texture analysis and then detail its current role in imaging of individual neoplasms of the genitourinary system.

Keywords Texture analysis · Genitourinary · Neoplasm · Cancer

Introduction

Burden of the disease and evolution of management

Genitourinary cancers typically refer to neoplasms of the kidneys, ureters, adrenal glands, urinary bladder, and urethra. In males, prostatic, testicular, and penile neoplasms are also included in this spectrum while neoplasms of the female reproductive system are usually separately categorized as gynecological cancers [1]. An estimated 326,670 new cases of genitourinary cancers are predicted for the year 2018 with a mortality of about 63,380. Among these, majority of deaths are predicted to be due to prostatic carcinoma in males and cancers of the kidney and renal pelvis in females [2]. Over the years there has been a significant reduction in mortality and morbidity associated with these neoplasms owing to advances in therapeutic strategies [3–6] and imaging techniques.

Radiogenomics, which has been defined as a science of identifying associations between imaging features and genomic characteristics of a disease [7], assumes great importance in this era of precision medicine [8]. There is an increasing interest in providing quantitative information along with subjective interpretation of radiologic images. Several of the newer techniques that provide quantitative data are modality specific. As examples, iodine quantification with dual energy computed tomography (CT) has been described as a tool in predicting outcomes in renal cell carcinoma (RCC) [9] and measurement of absolute diffusion coefficient (ADC) values on diffusion weighted (DWI) magnetic resonance imaging (MRI) as a means of determining the grade of prostate carcinoma [10]. Texture analysis, though, is one technique that evaluates images in

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general and therefore can be used as an add on tool to any imaging modality. Not surprisingly, medical imaging is only one of the many fields that this technique is used in. Texture analysis has been utilized in Radiology for many years with one of its early applications being classifying coal workers pneumoconiosis [11]. However, its use has seen a resurgence in recent times in this context of radiogenomics and precision medicine.

The purpose of this review is to briefly explain the principles of texture analysis, understand its applications in genitourinary imaging, and describe the current challenges and limitations that currently preclude its widespread utilization in clinical practice.

Principles of texture analysis

In a certain sense texture analysis has always been a part of radiology. The term heterogenous is often used to imply an aggressive nature of the lesion as opposed to the more homogenous, benign appearing ones. Being able to quantify this heterogeneity and help determine its association with pathological processes is essentially the goal of a texture analysis tool. Any image is ultimately defined by its pixels and a pixel simply is a gray scale unit within a defined range that represents a point in space. Just like the texture of a fabric is determined by the thickness and arrangement of its fibers the individual values of pixels and their interrelationships determine the texture of an image. Texture analysis extracts this information.

Textural information can serve two broad purposes:

1. Texture segmentation is a technique to divide the image into various segments that differ in their broad textural properties. This can help delineate anatomical structures or pathological lesions and is often a part of computer aided diagnosis. Examples include lung nodule and colonic polyp detection [12]. Some of the face detection softwares in our everyday social media platforms also use this technique.
2. Texture analysis seeks to provide more detailed information of the textural properties of the image, usually within a region of interest drawn by the observer. While several methods of texture analysis exist, the most commonly employed ones are based on statistical analysis of gray scale values of the pixels in the image. In this regard, it is useful to understand some of the basic principles of these statistical methods.

Brief technical considerations

Textures are defined by the inherent values or statistics of a pixel. The pixel can be evaluated in isolation (first order), in relation to its neighboring pixel (second order) or more complex relationships (higher orders).

First order statistics These methods take into consideration individual pixel intensity values and do not analyze the relationships between different pixels. This usually starts with a histogram that plots gray scale values of individual pixels against their number/percentage. A variety of information such as mean, standard deviation (SD), variation, and percentiles can be obtained from the graph obtained. Mean of positive pixels (MPP) is a self-explanatory term that refers to the mean of pixels with value > 0. In addition, features such as skew and kurtosis of the graph can also be evaluated. Skew is a measure of asymmetry of the distribution of variables about the mean. A positively skewed graph tapers (tail) to the right side and a negatively skewed graph tapers (tail) to the left side. Kurtosis is a measure of the sharpness of the peak of a distribution curve. Higher Kurtosis denotes a sharper peak and vice versa (Fig. 1).

Textural analysis based on first order statistics has its limitations. Different images with the same percentages of individual pixel values will have the same histogram appearance (Fig. 2).

Second order statistics These methods analyze the interrelationship or co-occurrence of pixel intensities. Several methods exist to analyze second order statistics, a few of which are summarized below [13–16]:

Gradient A gradient image plots the difference in gray scale values between adjacent pixels. A higher change in pixel intensity results in a higher gradient value at that point, and a lower change in a lower value. From this image, one can again estimate first order statistical information like mean, SD, etc.

Run-length matrix (RLM) This involves estimating how many times one can find groups of pixels that have the same gray scale value, in a specified direction, for a specified group size. For example, in Fig. 3, in the vertical direction, pixel value 1 has occurred thrice by itself and once in group sizes of two and three (Fig. 3).

Gray-level co-occurrence matrix (GLCM) This involves calculating how many times different pixel values occur next to each other in a specified direction. For example, in Fig. 4, in the vertical direction, pixel value of 1 is followed by 2 three times whereas pixel value 1 is followed by 3 two times (Fig. 4).

Note that both RLM and GLCM are direction specific and can be calculated in multiple directions. In general, GLCM based textural parameters are less affected by ROI size and acquisition parameters, including spatial resolution [17].

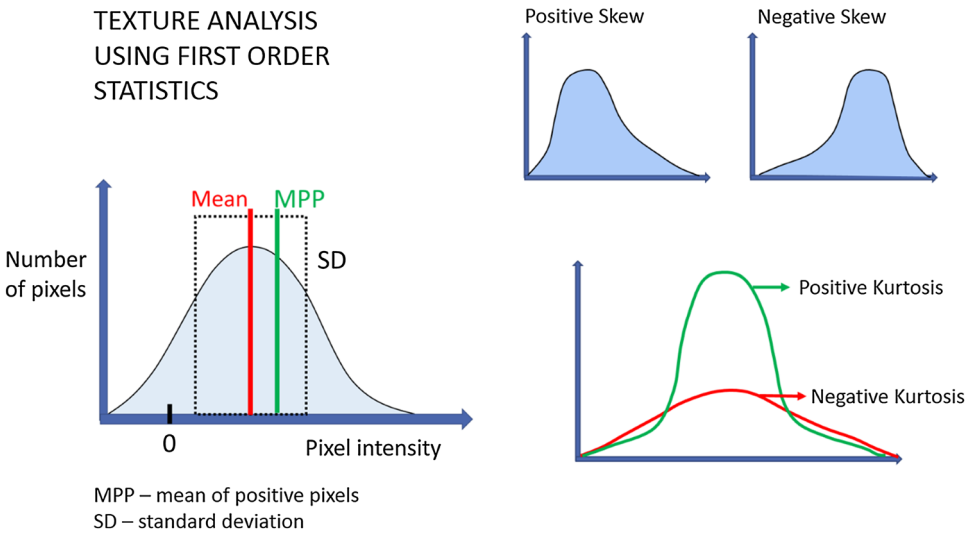

Fig. 1 First order statistical parameters. The graph plots the range of pixel intensities on the horizontal axis and number of pixels on the vertical axis. Parameters like mean, SD, MPP, skew, and kurtosis can be estimated from this graph

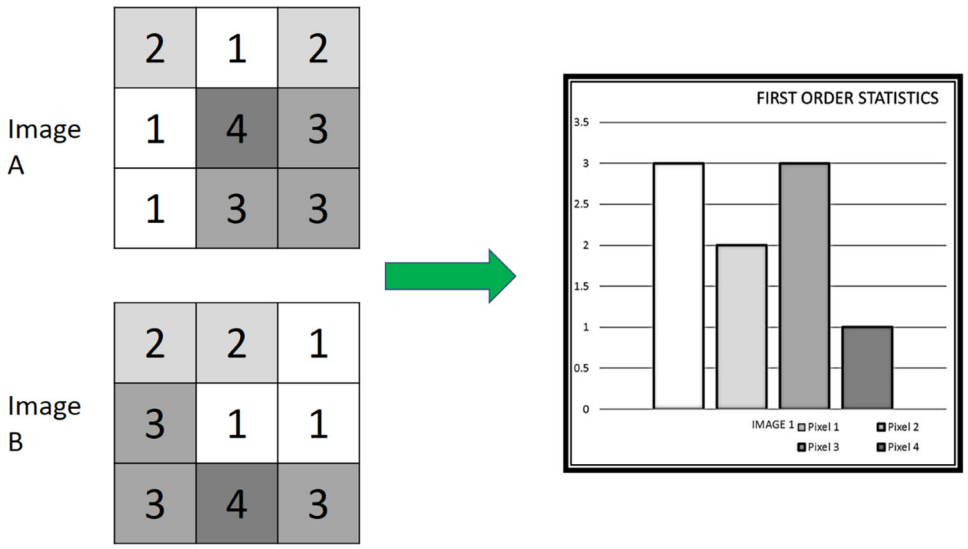

Fig. 2 Limitation of first order statistics. Image A and Image B have different distribution of pixel intensities. However, as the total number of each pixel intensity is the same, the histogram is identical

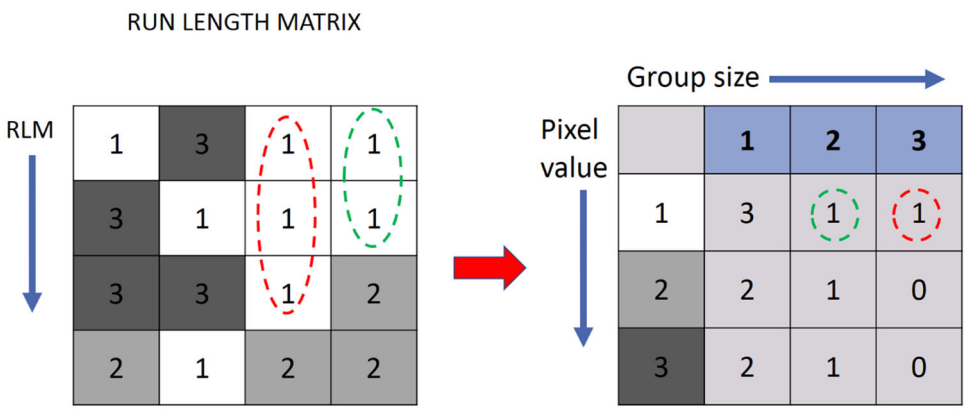

Fig. 3 Run-length matrix. From the image on the left, a RLM in the vertical direction is calculated and represented on the right. The group sizes are shown in the top row and the pixel values in the first column

Entropy Entropy is an often-used parameter in textural analysis. It is a measure of the randomness of distribution and higher entropy indicates more heterogenous image. With first order statistics Entropy is calculated using histogram counts and with second order statistics it can be calculated using RLM or GLCM counts. A converse of this is angular second moment (ASM) which is a higher in more homogenous images.

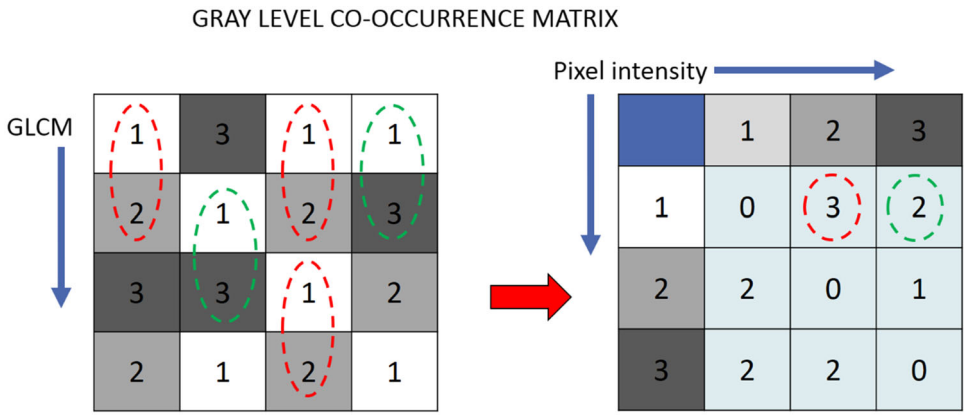

Fig. 4 Gray-level co-occurrence matrix. From the image on the left, a GLCM in the vertical direction is calculated and represented on the right. Pixel values are shown in the top row and first column

Others There are several other higher order methods of statistical analysis. Some of these analyze the relationship between adjacent voxels. Some of these methods use mathematical models to analyze an image (model based analysis) and some convert the spatial information in images into wavelets for textural analysis (wavelet based analysis) [15, 18, 19].

Thus, one could perform several such measurements of increasing complexity, limited only by the computational ability of the system at hand. These parameters can then be used to identify areas with similar or dissimilar textural features as in texture segmentation. Alternatively, one can attempt to identify associations between these textural features and pathology, treatment response, or any other relevant entity, as in texture analysis.

How it is done

One of the inherent advantages of texture analysis is the ability to apply it retrospectively to any image. Both commercially available software and ones that are developed within the institution are used. There is no need to modify the imaging protocols or techniques. A filter may be applied to the image with lower filter settings corresponding to fine textural features and higher filter setting corresponding to medium or coarse textural features [15]. Usually the software allows the user to select the filter settings or may provide textural features at every filter setting. A region of interest is manually drawn over the pathology and the software computes and displays the results. These results are then associated with multiple parameters.

Applications in genitourinary oncology

For genitourinary malignancies, texture analysis is finding applications such as detection and characterization of tumors, to determine their aggressiveness including grade and metastatic potential, and for prediction of treatment response.

Renal neoplasms

It is often challenging to differentiate fat poor angiomyolipomas (fpAML) from renal cell carcinomas (RCC), a decision of critical importance as the former is a benign entity while the latter often needs surgical excision. While the minimal fat within a fat poor angiomyolipoma may not be visible, it is often sufficient to cause a difference in the attenuation histograms of these two neoplasms in a study by Kim et al. Presence of at least 6% of pixels below − 10 Hounsfield unit (HU) was noted to be 100% specific for angiomyolipomas but was only 20% sensitive [20]. The authors describe that the differentiating capability of texture analysis was inferior to that seen with MRI by Kim et al. [21]. However, they argue that these lesions are often first detected on CT and texture analysis may obviate the need for MRI in certain cases. Higher entropy, RLM non uniformity and GLCM non uniformity were noticed in RCC compared to angiomyolipomas and the combination of these features was noted to be superior to subjective assessment of heterogeneity in a study by Hodgdon et al. [22]. The area under the curve (AUC) was higher than the study by Kim et al. which used attenuation histograms [20], and was comparable to the study by Kim et al. which used chemical shift MRI [21]. A study by Lee et al. extracted 64 quantitative features from contrast enhanced CT scan images and subsequently identified maximum intensity, percentage of pixels above 210 and percentage of pixels above 230, and gray-level co-occurrence matrix sum entropy, as being most consistent in differentiating fpAML from clear cell (CC) RCC [23]. However, the sample size of this study was small for the number of features extracted.

Texture analysis has been evaluated as a tool in predicting pathologic subtypes and oncologic outcomes in RCC. Entropy, mean of positive pixels and the SD of the

pixel distribution histogram on portal venous phase CT images have been shown to be positively associated with CC histology and negatively associated with non-CC subtype (Fig. 5). In a study by Lubner et al., these three features were also noted to be negatively associated with nuclear grade [24]. In addition, on unenhanced CT, mean of positive pixels was negatively associated with time to disease recurrence and death due to disease [24]. However, this study only selected large renal masses (> 7 cm). Further validation on small and intermediate sized RCC is necessary as noted by the authors. Haider et al. assessed the ability of CT textural parameters to predict survival in patients with metastatic RCC on Sunitinib. Notably, they used a parameter of 'size normalized SD' of the pixel intensities, as SD can be affected by the number of pixels in the ROI. Higher size normalized SD on both pre-treatment and post-treatment CT predicted for increased progression free survival and overall survival. Higher entropy after treatment and higher entropy change after treatment were associated with decreased overall survival [25].

Patients with sarcomatoid RCC have a worse prognosis. Tumors with such differentiation have been shown to demonstrate greater run-length nonuniformity and greater gray-level nonuniformity compared to CC-RCC [26]. This study compared textural features on unenhanced CT images and showed it to be superior to subjective assessment on contrast enhanced images.

Low stage CC-RCC can be managed with nephron sparing surgery and even among stage III and IV tumors, there are studies looking at the role of neoadjuvant chemotherapy. Therefore, ability to preoperatively stage these tumors can be helpful. A retrospective study comparing qualitative assessment of stage with textural features using histopathology as the gold standard, found higher skewness and higher co-occurrence matrix correlation on ADC maps to be associated with high stage CC-RCC compared to low stage ones while there was no significant difference in ADC values. These parameters were also superior to qualitative staging [27].

Papillary (P) RCC have been sub-typed into type 1 and type 2 with the latter having been shown to have a poorer prognosis [28]. Entropy on HASTE and contrast enhanced nephrographic MRI was noted to be higher in type 2 P-RCC than type 1 P-RCC. However, in this study, subjective features of heterogenous enhancement and indistinct margin were better than quantitative imaging in identifying type 2 over type 1 P-RCC. Combined quantitative and qualitative assessment gave the highest differentiation [29].

Antunes et al. evaluated several textural features on Fluorothymidine (FLT) PET-MRI to assess treatment response in patients with metastatic RCC on sunitinib therapy. The standardized uptake value on FLT-PET and textural parameters on ADC maps demonstrated a

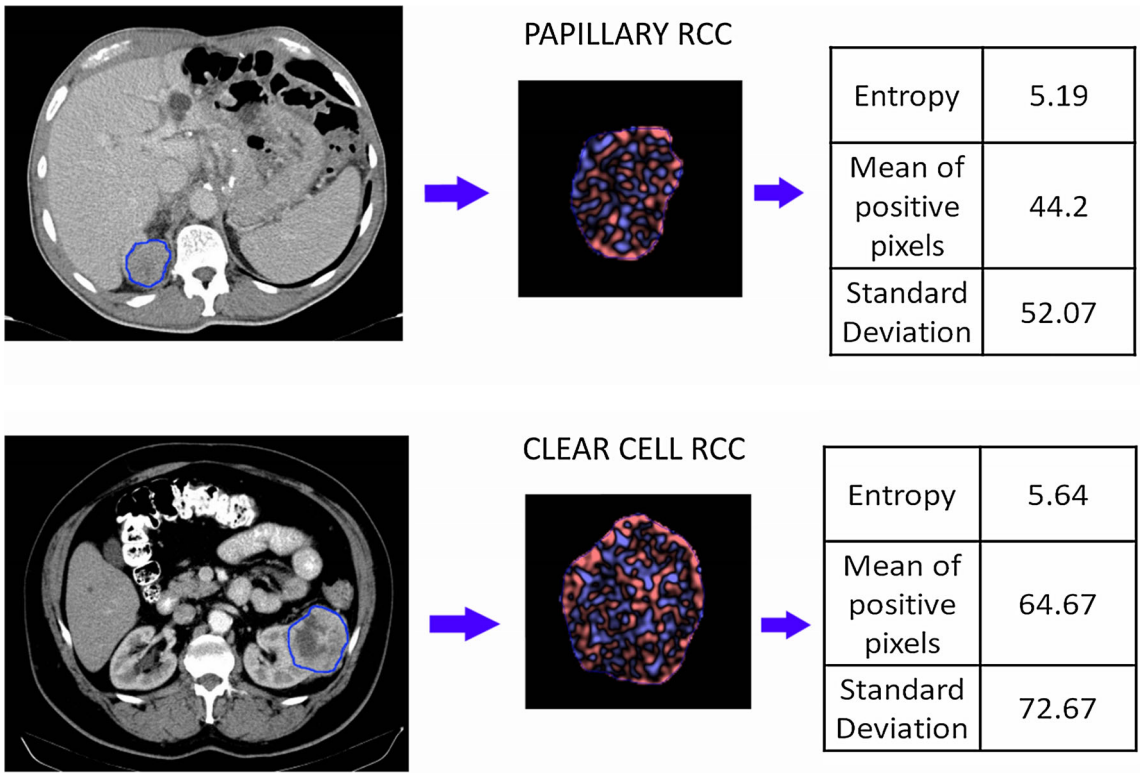

Fig. 5 Texture analysis shows lower entropy, MPP and SD in papillary RCC (top) compared to clear cell RCC (bottom)

significant change on the post-treatment images and therefore can potentially be used to monitor treatment response [30].

In patients with metastatic RCC treated with Tyrosine Kinase inhibitors, lower baseline entropy and higher entropy correlated with time to progression. In addition, higher change in uniformity after two cycles of treatment correlated with time to progression. Thus, texture analysis was useful both to predict and monitor treatment response [31].

Prostate carcinomas

One key role of imaging in prostatic carcinoma is to be able to identify the tumor focus and help guide biopsy. Several studies have demonstrated the ability of texture segmentation, using multiple parameters, to identify cancerous tissue from healthy tissue on both ultrasonography [32, 33] and MRI [34–36]. However, these studies had their limitations. For example Han et al. [32] noted high false positive level when using textural parameters alone and these had to be combined with location and shape/margin to be able to improve accuracy. The study by Mohammed et al. [33] applied two different segmentation methods to identify textural differences in regions that had already been segmented as cancerous and normal areas by a radiologist. No histopathological confirmation was done. Sidhu et al. identified lower kurtosis on ADC and lower entropy on post contrast T1 weighted images to be the best predictors for identifying the presence of tumor, when applied to the entire peripheral zone. The authors believe that textural parameters may be helpful to alert the radiologist to the presence of a tumor [37].

Gleason score (GS) remains the standard prognostic predictor in prostate carcinoma [38]. ADC maps have been shown to be useful in differentiating prostate carcinomas into low, intermediate and high grades. However, within intermediate grade carcinomas, differentiating GS 4 + 3 from GS 3 + 4 is of importance and yet remains challenging. In this regard, lower ASM and higher entropy on T2 weighted imaging (T2WI) texture analysis is associated with GS 4 + 3 compared to GS 3 + 4 carcinomas [39]. Likewise contrast and homogeneity calculated from GLCM, were noted to be positively and negatively associated with GS respectively [40]. In both these studies, these features outperformed traditional ADC parameters. Rozenberg et al. showed that a combination of kurtosis, heterogeneity, entropy, and skewness was superior to conventional ADC measurements in predicting pathologic upgrading of 3 + 4 prostatic carcinomas to 4 + 3. Mean ADC of the entire lesion, ADC ratio and ADC histogram analysis were not predictive of upgradation [41].

Management of recurrent prostatic carcinoma remains challenging and thus a tool that helps predict recurrence would be of great prognostic value. Gnep et al. analyzed several second order GLCM based textural features on T2WI and found them to be strongly associated with risk of biochemical recurrence following radiotherapy. To a lesser extent first order statistics based, gradient based and geometric parameters were also associated with recurrence [42]. The authors did not include transitional zone tumors in this study.

Reischauer et al. extracted multiple textural features from ADC maps of bone metastases in patients with prostate cancer. These showed a strong correlation with treatment response and serum prostate specific antigen levels. However, their added benefit compared to monitoring response based on changes in ADC values alone was not determined [43].

Urinary bladder carcinoma

Presence of muscle invasion and presence of metastases are the most important deterministic factors for management of urinary bladder carcinoma. MRI is an excellent modality for differentiating superficial tumors from muscle invasive tumors and organ-confined tumors from non-organ-confined tumors [44]. However, histopathological examination of cystoscopy and transurethral biopsy specimens remains the standard method for determining muscle invasiveness of bladder carcinoma. Thus, there is yet room for a reliable non-invasive method to stage T1 and T2 bladder carcinomas. Xu et al. applied GLCM and histogram based features to T2WI in patients with bladder carcinoma and could differentiate superficial tumors from muscle invasive ones. In addition, their results noted 3D textural analysis methods to be superior to 2D analysis methods [45]. However, the study does not compare the performance of texture analysis with qualitative analysis of MR images and a study comparing these two modalities would better evaluate the role of texture analysis. Garapati et al. applied texture features in a computer aided system and could separate bladder cancers into those less than stage T2 and those at or above stage T2 on CT images [46].

Being able to grade urinary bladder carcinoma on imaging is helpful as high grade T1 lesions may require repeat transurethral resection [47]. Higher contrast, variance and skewness and lower homogeneity and kurtosis has been noted in high grade carcinomas compared to low grade ones (Fig. 6). Zhang et al. identified 4 histogram and 18 GLCM based textural features on diffusion weighted imaging (DWI) and ADC maps on MRI, that can help differentiate high grade from low grade bladder cancers [48]. On CT imaging, Zhang et al. could demonstrate that low grade cancers had significantly lower mean gray-level

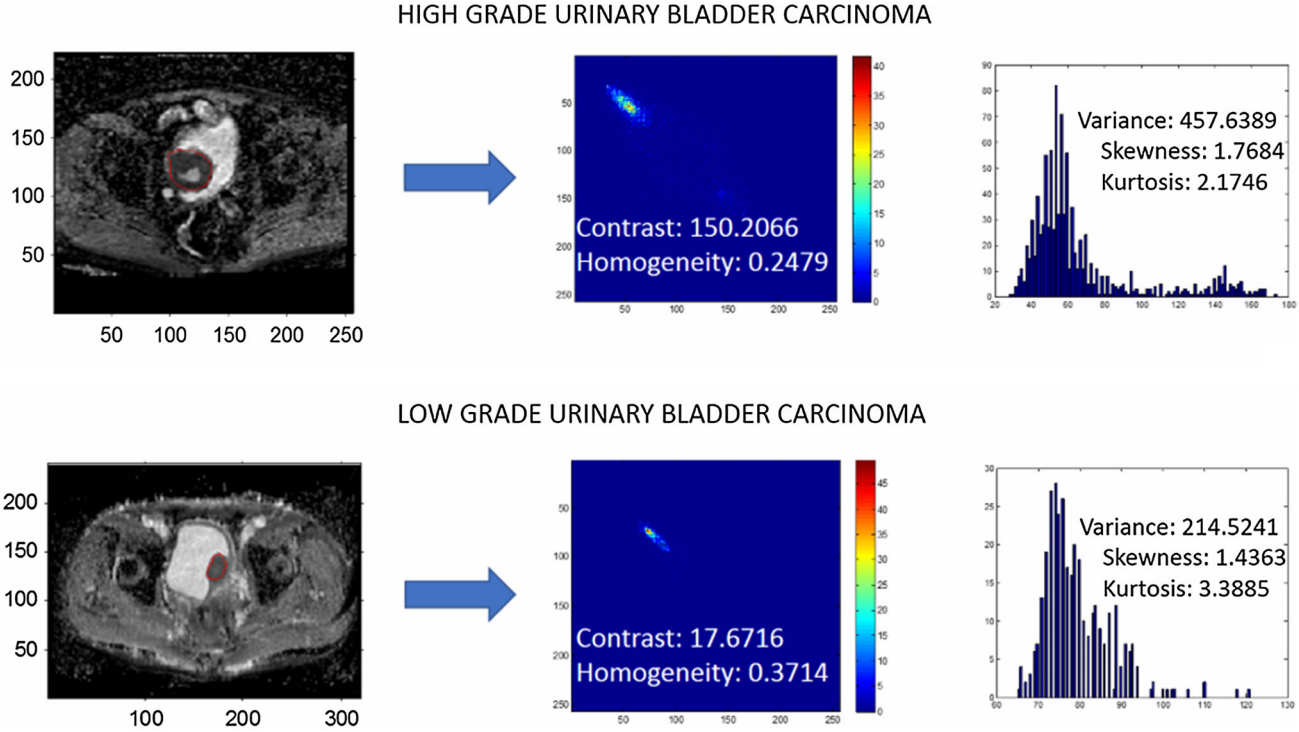

Fig. 6 Texture analysis shows lower homogeneity and kurtosis and higher contrast, variance and skew in high grade urinary bladder carcinoma (top) compared to a low grade one (bottom)

signal intensity, MPP and entropy on unenhanced and enhanced images while lower SD was noted on enhanced images [49]. Both these studies were retrospective in nature. Future prospective validation on larger samples may be helpful.

Shi et al. identified 33 different textural features on T2WI that differed between the affected and unaffected segments of bladder wall in patients with bladder carcinoma. They further compared uninvolved bladder wall of these patients to that of healthy volunteers and found that 7 of these 33 features differed in patients with early stage bladder carcinoma and 15 of these differed in patients with advanced stage bladder carcinoma [50]. Thus, they could demonstrate that bladder carcinoma induces textural changes even in normal appearing segments of the urinary bladder wall, more in patients with higher grade carcinoma.

In addition to determining the grade and stage of bladder cancers, texture analysis has been used in predicting presence of lymph nodal metastases. Wu et al. extracted 50 histogram features and 100 GLCM based features on a training set of 80 patients and then validated them on 38 patients to be able to predict presence of lymph nodal metastases in bladder carcinomas [51]. A radiomics nomogram based on the selected textural features combined with CT size criteria of > 8 mm and > 10 mm in short axis for pelvic and abdominal lymph nodes respectively, had a higher predictive value than either of them used alone. Thus, texture analysis could be demonstrated to only have an adjunct value to CT size criteria.

In a study by Cha et al., multiple radiomics features including gray-level histogram and RLM based features were demonstrated to be useful in determining the response of bladder carcinomas to systemic chemotherapy [52].

Adrenal neoplasms

Adrenal incidentalomas pose a diagnostic challenge when they do not have typical imaging characteristics of either a benign mass, such as an adenoma, or a malignant mass, such as carcinoma or metastasis. About 50% of adrenal masses in patients with known malignancy are likely to be metastasis [53]. A combination of higher signal intensity on T2WI and higher entropy on texture analysis was noted to help differentiate CC- RCC adrenal metastases when compared to adrenal adenomas [54]. However, the sample size of 10 CC-RCC in this study was small.

While FDG-PET is often useful in differentiating benign from malignant adrenal neoplasms, there can be several causes of false negative and false positive findings [55]. A combination of higher SUV max (with cut-off at 6.8), higher entropy and lower homogeneity on textural analysis has been shown to differentiate malignant from benign adrenal neoplasms [56]. Notably the study only included adrenal tumors with a metabolic tumor volume

of > 10.0 cc^3 and had a low sample size of 13 benign and 22 malignant lesions.

Limitations of texture analysis

Texture analysis, like the field of radiogenomics in general, must deal with a problem of plenty. The numerous and varied parameters that can be assessed, combined with the small sample size in several of these studies, makes analysis both challenging and difficult to interpret. For the same reasons, these studies are prone to type I errors. Type I error is to falsely imply an association that does not exist. Chalkidou et el applied a statistical analysis method to fifteen studies that reported an association between patient outcomes and texture features on PET and CT, and identified probability of type I error to be as high as 76% [57]. Several studies attempt to overcome this limitation by employing machine learning algorithms to identify features with highest discriminative capability, which are then revalidated on the sample.

There are also several factors unrelated to the lesion being analyzed that can independently affect the results of texture analysis. For example, radiomic features have been shown to differ among images generated across different scanners [58]. Even when analyzing images generated from a single scanner, parameters such as slice thickness or reconstruction filters can affect these parameters [59]. Voxel size and gray levels [60], radiation dose, and the type of image reconstruction method used (filtered back projection or iterative reconstruction) can also affect quantitative image features including texture [61]. A study by Brynolfsson et al. [62] found that noise, resolution, choice of quantization method and the number of gray levels in the quantized images had a significant influence on most texture features. Radiologists must routinely deal with artifacts due to patient motion and due to scatter radiation. These issues can also affect textural features [63].

As a tool, texture analysis is widely available, with several vendors providing diverse types and versions of the software. Many of these are developed within the institutions conducting the studies. However, no software is as of yet approved for clinical use [64]. The variability of the results across different software is yet to be determined. There is no standardization in the features analyzed across different studies with groups employing different textural parameters to make the same association. This limits comparison of the results across different studies. Together, these factors limit generalization of the abundant research data to the larger population.

Future directions

Although several studies describe the role of texture analysis in medical imaging, they must be demonstrated on larger samples and validated externally, before translating into everyday clinical practice. Currently texture analysis requires dedicated personnel to work on a separate workstation and segment relevant parts of images. Not only does this require extra human effort, but one may have to deal with variabilities introduced by human errors or subjective interpretations. With further advancements in technology, we can look forward to a time when textural analysis is seamlessly integrated into existing radiology viewing stations and results can be obtained at the click of a button. Advances in texture segmentation may vastly enhance the potential of computer aided detection. This would not only be of aid in clinical care but automated segmentation and texture analysis will also enable generation of large databases that can be used in research. Greater collaboration between different institutions to bring uniformity to the methods and analyses can hasten the clinical application of texture analysis.

An increasingly exciting aspect of medical imaging is artificial intelligence. This has been varyingly described both as a threat to the field of radiology and as a valuable tool for radiologists. Nevertheless computer aided detection and machine learning are here to stay and are likely to play an important role in imaging in the years to come [65–67]. Texture analysis is one of the many tools used by the deep learning processes of artificial intelligence [68] and in a matter of time it may be incorporated into clinical care, along with other quantitative imaging methods.

Conclusion

The discipline of radiology continues to evolve, paralleling advances in technology and clinical medicine. In the field of genitourinary oncology, texture analysis has been shown to aid in the detection of neoplasms, in the characterization of their pathological subtypes and grades, in predicting survival rates and in estimating risk of recurrence. Texture analysis is one essential tool that we must arm ourselves with as we endeavor to detect the unseen and continue to serve as the eye of medicine.

Compliance with ethical standards

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Ethical approval This article does not contain any studies with human participants oranimals performed by any of the authors.

Informed consent There was no need for informed consent as this is a review article.

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