REVIEW

Application and Progress of Texture Analysis in the Therapeutic Effect Prediction and Prognosis of Neoadjuvant Chemoradiotherapy for Colorectal Cancer

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Abstract Colorectal cancer is one of the most common malignant tumors, and the morbidity and mortality are increasing gradually over the last years in China. Neoadjuvant chemoradiotherapy (nCRT) is currently applied to the treatment of colorectal cancer patients, and it is helpful to improve the prognosis. The sensitivity of patients to nCRT is different due to individual differences. Predicting the therapeutic effect of nCRT is of great importance for the further treatment methods. Texture analysis, as an image post-processing technique, has been more and more utilized in the field of oncologic imaging. This article reviews the application and progress of texture analysis in the therapeutic effect prediction and prognosis of nCRT for colorectal cancer.

COLORECTAL cancer (CRC) is one of the most common malignant tumors. The morbidity and mortality rank the fourth and the second in the world, respectively. Similarly, they are increasing gradually over the last years in China.^[1] The radical resection is the primary treatment for CRC patients. However, about 25%-30% of them

are inoperable as they have been confirmed hepatic metastasis at the initial diagnosis.^[2] Neoadjuvant chemoradiotherapy (nCRT) refers to accept the local radiotherapy and systemic chemotherapy before the operation. It can down tumor staging, reduce the recurrence rate and distant metastasis rate of tumors, and help patients improve the prognosis.^[3] Currently, nCRT has been mostly applied in patients with CRC. The sensitivity to nCRT varies because of individual variations and tumor heterogeneity,^[4] so it is crucial to predict the therapeutic effect of nCRT for patients for choosing further treatment methods. The imaging examinations have become the vital means to evaluate and predict the therapeutic effect of CRC patients with the development of medical imaging technology. In recent years, the texture analysis technology has

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been applied frequently in oncological imaging. By analyzing the pixel distribution of the lesion displayed on the images, the internal information of the lesion could be quantified, and the heterogeneity and other histopathological characteristics could be reflected more accurately as well.^[5-6] This article reviews the application and progress of texture analysis in the therapeutic effect prediction and prognosis of nCRT for CRC patients.

NEOADJUVANT CHEMORADIOTHERAPY

Importance of neoadjuvant chemoradiotherapy

nCRT is one of the most significant methods for CRC treatment. Its advantages are mainly manifested as follow: (1) nCRT can shrink the volume of the primary or metastatic tumors, thus reducing staging of the tumors, and increasing resection rate of the lesions. (2) It has been confirmed that activity of tumor cells would decrease, necrosis and fibrosis of the lesions would appear, and intraoperative dissemination rate and recurrence rate would reduce further after nCRT.^[7-8] (3) Tumors would be more sensitive to radiation and relatively high concentration of chemotherapeutic drugs as blood supply and lymphatic vessels of the tumors are not destroyed before operation.^[8] (4) nCRT can inhibit or eliminate some potential micrometastases and reduce possibility of long-term metastasis of malignant tumors. (5) Compared with the patients receiving chemoradiotherapy after an operation, most of them are in better physical condition and have a higher tolerance to receive chemoradiotherapy before operation.^[8] (6) nCRT can also improve overall survival rate of patients.^[9-10]

Evaluation criteria for therapeutic effect of neoadjuvant chemoradiotherapy

Evaluating and predicting therapeutic effect of chemoradiotherapy can reduce overtreatment of patients who are insensitive to the response, avoid the related side effects, and help doctors make more individualized, rigorous, and reasonable treatment plans. Therefore, it is necessary to predict the therapeutic effect of chemoradiotherapy before treatment. Dworak *et al.*^[11] proposed using the tumor regression grading (TRG) to judge the therapeutic effect: 0, no regression; 1, mild regression (less than 25% of the tumor tissue with fibrosis); 2, moderate regression (26%-50% of the tumor tissue with fibrosis); 3, obvious regression (more than 50% of the tumor tissue with fibrosis); 4, com-

plete regression (the tumor tissue is not visible and only fibrous tissue is observed). Someone who has scored grade 4 means pathologic complete response (pCR) to the chemoradiotherapy, grade 2-3 means partial response (PR), and grade 0-1 means no response (NR).

TEXTURE ANALYSIS TECHNOLOGY

Basic concepts of texture analysis

Texture analysis technology is an image post-processing technology, which generates a series of quantitative texture parameters based on the distribution of image pixels or voxels, invisible to the naked eye by using a special filtered algorithm.

Various methods are applied to obtain texture parameters, including the statistical-, transform- and model-based methods.^[12] Statistical-based technique has been most commonly applied and extracts specific parameter values by analyzing the distribution and relationships of gray-level values in the image with different methods, mainly including gray-level histogram analysis, gray-level co-occurrence matrix method (GLCM) and neighborhood gray difference matrix method.^[13] Gray-level histogram analysis describes the distribution and relationships of gray-level values in the image. It can generate the first-order statistics, such as Mean (mean intensity of a region), standard deviation (SD, variation from mean grey-level value), Skewness (asymmetry of the histogram), Kurtosis (flatness of the histogram), and Entropy (irregularity of gray-level distribution). The second-order texture features are based on GLCM, which describes the distribution relationship between adjacent pixels, and can generate Contrast (local variations and spread of matrix values), Uniformity (uniformity of gray-level distribution), local Entropy (randomness of matrix), and Homogeneity (uniformity of matrix). Higher-order texture features such as Coarseness (the edge density) are based on the neighborhood gray-tone-difference matrices, which mainly describe the spatial distribution among three or more pixels.^[13-14] Transform-based methods convert spatial information into Frequency (Fourier, Gabor) and/or Scale (wavelet) information, while model-based texture analysis uses sophisticated mathematical methods such as fractal analysis to represent the texture characteristics of images.^[15]

The basic operation flow of texture analysis

The following steps are needed to perform texture

analysis: (1) obtain the medical images based on the research purpose; (2) delineate the region of interest (ROI) on the selected image; (3) extract texture parameters generated from the texture analysis software from the ROI; (4) analyze data and conclude which texture parameter is significant statistically.

PREDICTION OF THERAPEUTIC EFFECT OF NEOADJUVANT CHEMORADIO THERAPY IN PATIENTS WITH COLORECTAL CANCER BY TEXTURE ANALYSIS

Prediction of therapeutic effect of primary lesions

Texture analysis can reflect the heterogeneity of tumor tissue,^[5-6] which is helpful to predict the therapeutic effect of nCRT. The magnetic resonance imaging (MRI) plays an important role in monitoring the therapeutic effect of nCRT in patients with CRC.^[16] Although MRI has the characteristics of multi-sequence imaging, most scholars at home and abroad predict the therapeutic effect of nCRT for CRC patients by analyzing the texture features of T2-weighted images (T2WI). De *et al.*^[17-18] found that the Kurtosis value of T2WI in the pCR group was lower than those in the PR group and the NR group of rectal cancer patients before nCRT. It suggested that the Kurtosis value of T2WI before treatment could be used as a predictor of the therapeutic effect of nCRT in rectal cancer patients and help physicians guide the follow-up clinical decision-making as well. Another study^[19] showed that the Contrast and Entropy of T2WI before treatment could also predict the therapeutic effect of nCRT for CRC. Liu *et al.*^[20] found that Energy-variance on pre-therapy apparent diffusion coefficient (ADC) mapping was significantly higher in non-responders than that in responders for patients with locally advanced rectal cancer. These studies all indicate that texture analysis based on MRI can be used to predict the effect of nCRT in CRC patients before treatment, and it is expected to be applied in clinical practice.

In addition to the wide applications in MRI, texture analysis technology has been likewise used in CT^[19, 21] and PET-CT^[22] images to predict the therapeutic effect of nCRT for CRC. Caruso *et al.*^[19] found that five texture parameters, including the Energy, Contrast and Correlation and so on, could be used as imaging markers to predict the sensitivity of nCRT in CRC patients. Chee *et al.*^[21] confirmed that for patients with locally advanced rectal cancer who responded well to nCRT

treatment, the lower the Entropy value was, the higher the uniformity of CT texture images was. When using PET-CT combined with texture parameters to study the effect of nCRT for locally advanced rectal cancer, researchers found that the higher the ratio of the preoperative standard deviation to the mean value was, the better the response to nCRT was.^[22]

Prediction of therapeutic effect of liver metastases

Liver metastases are one of the main causes of death in patients with CRC.^[23] Systemic chemotherapy can reduce liver metastases and prolong survival.^[24] Previous studies have suggested that size- or volume-based measurements are limited in evaluating response.^[25] Texture analysis technique can quantify the liver parenchyma so that provide more information about chemotherapy-induced changes.^[26]

In recent years, texture analysis has been confirmed to be helpful in predicting the response to chemotherapy for colorectal liver metastases. Rao *et al.*^[26] found relative differences after chemotherapy in Entropy and Uniformity (without filtration) in CT texture analysis may be better predictors of response to chemotherapy therapeutic effect in patients with colorectal liver metastases. Non-responders showed increased Entropy and decreased Uniformity compared to responders in pre-treatment portal venous phase CT examination. Ahn *et al.*^[27] found that the lower Skewness and SD on liver CT texture images indicated that liver metastases had a better response to chemotherapy. Another study^[28] demonstrated that the lower the Entropy value of liver metastasis on CT images was, the better response to chemotherapy was. The lower Skewness, SD, and Entropy indirectly reflect the homogeneity of texture features and also indicate that the lower heterogeneity of tumors is, the higher sensitivity to chemotherapy for candidates is.^[27] However, the application of MRI in predicting the chemotherapeutic response of colorectal cancer with liver metastasis is relatively rare. Liang *et al.*^[29] found that the value of Mean from the ADC maps of the responding group were significantly lower than that of the non-responding group in colorectal liver metastases. A latest study^[30] exhibited that the higher Entropy, Contrast and the lower Correlation were independently associated with a better chemotherapeutic response in colorectal liver metastases.

Prognosis analysis

Texture analysis is widely used to predict the survival

rates of CRC patients. Miles *et al.*^[31] evaluated whether hepatic CT texture and CT perfusion parameters could be related to the survival of patients with CRC. They found that Uniformity of liver texture on portal phase CT images was potentially a superior predictor of survival for patients with CRC than CT perfusion imaging. Ng *et al.*^[32] analyzed contrast-enhanced CT texture features of CRC lesions and found that Skewness and Kurtosis was associated with 5-year overall survival.

Different imaging techniques combined with texture analysis technology could also estimate the disease-free survival (DFS) of locally advanced rectal cancer. Chee *et al.*^[21] found that homogeneous texture features (higher Uniformity, lower Entropy and lower SD) were connected with higher DFS in patients with locally advanced rectal cancer. Jalil *et al.*^[33] used texture analysis based on MRI to find that Kurtosis was the independent factor to predict DFS for CRC patients. Lovinfosse *et al.*^[34] used ¹⁸F-FDG PET/CT combined with texture analysis to investigate the prognosis of rectal cancer patients. The results suggested that the Coarseness and Homogeneity were associated with DFS for locally advanced rectal cancer.

All of these studies indicate that it is feasible to assess the prognosis in CRC patients by utilizing texture analysis. We should choose the appropriate examination methods according to the requirements in the clinical work.

Limitations and challenges

The application of texture analysis technology is becoming more and more extensively, while it still faces challenges and controversies: first of all, most of the studies are retrospective study currently, and the selection bias exists in the enrollment and data acquisition. Second, there is no definite stipulation about optimizing a selection of texture parameters.^[35] At last, how to unify the settings and the scanning protocol of various equipment is a problem yet.^[36-38]

PROSPECT

In conclusion, texture analysis with its advantages of simplicity and easy operation offers help for predicting the therapeutic effect of nCRT and assessing prognosis for CRC. Given a large amount of data contained in the medical imaging,^[39] texture analysis should contribute to complementing and completing the method of extracting the texture features.^[40] It is

expected to quantify tumor heterogeneity more accurately^[41] and make a reasonable explanation of histopathological characteristics represented by different texture parameters under the strict guidance and multimodality imaging, which makes texture parameters as the new imaging biomarker to instruct the clinical diagnosis and treatment.

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