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Investigating the WNT/TCF pathway and the value of DCE-MRI in predicting and evaluating the efficacy of neoadjuvant radiotherapy and chemotherapy for locally advanced rectal cancer

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ABSTRACT

The purpose of this research was to Detach the DCE-MRI value in predicting and evaluating the efficacy of neoadjuvant radiotherapy and chemotherapy in middle and low locally advanced rectal cancer (READ). For this purpose, 40 patients with READ were examined by DCE-MRI and DWI before CRT treatment and 4 weeks after CRT treatment, and examined by Avanto1.5T magnetic resonance imaging scanner. According to the comparison of the postoperative pathological T stage and pre-nCRT T stage, the patients with decreased stage were defined as the T-descending group, and those with unchanged or elevated staging were defined as the T-undescending group. The ROC curve was used to evaluate the value of ADC value and Ktrans value to predict the early curative effect of neoadjuvant radiation therapy and chemotherapy for READ. Results showed that The ADC values of the two groups after nCRT were higher than those before nCRT ($P<0.05$). Compared with the pre-nCRT T-decline group and T-non-decline group, the Ktrans value of the pre-T-decline group was higher than that of the T-non-decline group ($P<0.05$), and the Ktrans value of both groups after the nCRT was higher than that before nCRT ($P<0.05$). The difference and the rate of ADC in the T-depression group were higher than in the T-undescending group ($P<0.05$). Taking the change rate of the ADC value 0.17 as the optimal threshold, the sensitivity and specificity of predicting the T-descending stage of patients with READ after neoadjuvant radiotherapy and chemotherapy were 72.69% and 75.84%, respectively (95%CI:0.608-0.954); taking the pre-nCRTKtrans value 1.18/min as the optimal threshold, the sensitivity and specificity to predict the T-descending stage of READ patients after neoadjuvant radiation therapy and chemotherapy was 78.65% and 80.47%, respectively (95%CI:0.637-0.971). There was no significant difference between the change rate of ADC value and the Ktrans value before nCRT in predicting the early efficacy of neoadjuvant radiotherapy and chemotherapy for READ. In conclusion, ADC value and Ktrans value can reflect the tissue structure changes of READ after neoadjuvant chemotherapy. It can be seen that the change rate of ADC value and pre-nCRTKtrans value can predict the early efficacy of neoadjuvant radiotherapy and chemotherapy for READ. The results showed that Axin2 and β-catenin factors along with other factors such as APC and CKI proteins are effective at the molecular level along with other factors in the WNT/TCF signaling pathway. These agents start their activity in the cytoplasm and exert their final effect on the genes in the nucleus.

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Introduction

Rectal cancer has a high prevalence in the world. In the United States, up to 135,000 cases are diagnosed annually. Many cancers have different genetic and hereditary backgrounds, and understanding their cellular mechanisms and intermolecular behaviors provides a deeper understanding of the functioning of their regulatory systems. At the molecular level, different biological activities occur through different intracellular messenger pathways (1). Neoadjuvant radiotherapy and chemotherapy (nCRT) combined with standardized surgical techniques (total mesorectal resection) can improve the prognosis of patients with locally advanced rectal cancer (READ) (2-3). It has been found that neoadjuvant CRT therapy 6 to 8 weeks before operation can achieve the clinical descending stage of READ, and 15-27% of patients can even achieve pathological complete remission (pCR) (4), it is of positive significance to decreases the postoperative recurrence of READ and improves the success rate of sphincter preservation. However, for the patients who are not sensitive to CRT treatment, the best treatment time will be delayed because the operation is not carried out in time, which will increase the risk of cancer spread and metastasis and worsen the prognosis of the patients. Therefore, it is very important to predict and evaluate the neoadjuvant radiotherapy and chemotherapy efficacy for locally advanced READ. Unlike biopsies, MRI can be repeated many times. Traditional preoperative staging investigation and tissue biopsy cannot predict individual treatment response. Although MRIT2 weighted sequences can define staging and guide therapies (5), but it is not enough to

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predict and evaluate the clinical response of individuals to CRT. Diffusion-weighted imaging (DWI) and dynamic contrast-enhanced (DCE) MRI has advantages in predicting the efficacy, prognosis, and biological characteristics of CRT. (6-8). In this study, patients with middle and low locally advanced READ who received neoadjuvant radiotherapy and chemotherapy were selected as the subjects. MRI was examined and evaluated before and after neoadjuvant radiotherapy and chemotherapy, and the value of DWI and DCE-MRI in predicting and evaluating the efficacy of neoadjuvant radiotherapy and chemotherapy in middle and low local advanced READ was compared and analyzed, to provide perspective for follow-up clinical treatment evaluation.

Materials and Methods

Patient

40 patients with READ treated in our hospital from June 2020 to May 2022 were selected, aged 31 to 72 years old, with an average age of (52.68 ±13.75) years. All patients were examined by DCE-MRI and DWI before and 4 weeks after CRT treatment, and examined by Avanto1.5T magnetic resonance imaging scanner. According to the comparison between the postoperative pathological T stage and the pre-nCRT T stage, the patients with decreased stage were defined as the T-descending group, and those with unchanged or elevated staging were defined as T-undescending group. This study was approved by the hospital ethics committee.

Inclusion and exclusion criteria

Inclusion criteria: a. all patients were examined and admitted to the hospital for the first time; b. primary middle and low READ was diagnosed by colonoscopy histopathology; c. Magnetic resonance imaging stage was locally advanced READ (T3 or T4, any N stage); d. patients had not received any antitumour treatment in the past; e. patients and their families knew and signed the informed consent form.

Exclusion criteria: a. patients complicated with other malignant tumors; b. 2 patients with neurological and mental system diseases; c. patients with serious functional disorders of the heart, liver, lung, kidney, and other important organs; d. MRI examination contraindications; e. patients refused this experiment or terminated this trial for other reasons.

Instruments and equipment

Avanto1.5T magnetic resonance imaging scanner (Siemens, Germany) was used.

Inspection method

All patients were examined by DCE-MRI and DWI before CRT treatment and 4 weeks after CRT treatment, and examined by Avanto1.5T magnetic resonance imaging scanner.

(i) DWI examination, axial DWI scanning parameters: repetition time (TR) was 7900ms, echo time (TE) was 73ms, excitation times (NEX) was 4, visual field 42cm × 42cm, visual field (FOV) 380 × 380mm, layer number 20, layer spacing 1mm, slice thickness 5mm, set diffusion coefficient, b=1000s/mm^2, fit apparent diffusion coefficient (ADC) image, and measure ADC value of lesions through the region of interest.

(ii) DCE-MRI. The axial volume ultra-fast multi-phase dynamic enhanced scanning sequence was used. The contrast medium was meglumine gadolinium, injection dose 0.2mmol/kg, speed 3.0ml/s. 15 seconds after injection, the 3DFLASH sequence was scanned continuously again. Scanning parameters: TR 2.9ms, TE 1.2ms, resolution 448, flip 15 °, voxel 0.9mm × 0.8mm × 0.8mm, FOV 370 × 370mm, slice thickness 5mm. The number of layers was 72 and the time of a single scan was the 30s. The scanned image is automatically subtracted, and multiplane reconstruction and maximum density projection are implemented.

Observation and evaluation index

(i) DCE-MRI. The images were sent to the ADW4.2 workstation, and the interesting parts were selected layer by layer. After 3D fusion, the linear reference region model was used to calculate the blood perfusion parameters. Quantitative parameter of contrast medium perfusion for the whole tumor volume transport constant (K^{trans}).

(ii) DWI. Select the DWI image to transmit to the ADW4.2 processing studio, select the focus of interest for image post-processing, and get the ADC value. The average ADC value was calculated 3 times.

Statistical analyzes

The data are analyzed using the SPSS20.0 software package, the measurement data by the normal distribution are expressed by the mean ±standard deviation (x±s), and the comparison between groups is analyzed by the independent sample t-test; those that do not agree with normal distribution are tested by the rank sum test; the counting data are expressed as a percentage (%) and the comparison between groups is expressed by χ^2test. Pearson linear correlation was used to analyze the correlation of the changes in each factor.

Bioinformatics analysis

UCSC database was used for detailed analysis of molecular factors effective in the WNT/TCF signaling pathway. Cell comparisons were analyzed by Human Protein Atlas database OMIM, Gene Cards, and Genome Browser.

Results

Changes in the WNT signaling pathway have been commonly reported in rectal cancer. Among the critical activities of this path, we can mention the role in carcinogenesis, cell proliferation, cell migration, etc. β-catenin is a protein with multiple functions and works to modify the transcription of target genes of the WNT pathway (9). Axin2 acts as a negative regulator in the WNT/TCF signaling pathway and helps in the formation of the β-catenin

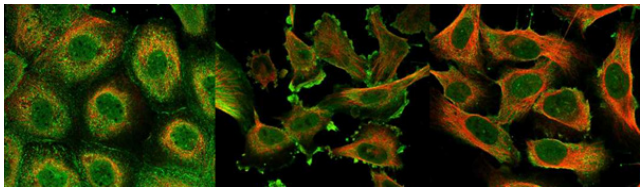

Figure 1. Immunofluorescence staining of human cell line A-431 showed Axin2 gene localization to the nucleoplasm, plasma membrane and cytosol.

degradation complex; Cell analysis of the Axin2 gene without nuclear labeling by antibodies that bind to target gene proteins showed that this gene is mostly present in the nucleoplasm, plasma membrane, and cytosol. Figure 1 (10-11). Research has shown that this protein is mutated in many cases of rectal cancer. Somatic mutations in the Axin2 gene affect the β-catenin-dependent WNT pathway and regulate cell differentiation during development and cell homeostasis (12). The signaling cascade begins when the WNT protein binds to the Frizzled receptor family, a distinct family of G protein-coupled receptors. This leads to an increase in β-catenin in the cell cytoplasm and eventual translocation to the nucleus, where it acts as a transcriptional activator of transcription factors belonging to the TCF/LEF family. APC proteins, Axin1 and Axin2, are involved in the assembly of a degradation complex that degrades β-catenin and provides negative feedback regulation. Figure 2 (13). Fluorescence in situ hybridization analysis shows that Axin2 loses its heterozygosis in breast cancers, neuroblastomas, and other tumors (14). Axin2 mutations are mainly in the form of premature shortening of the c-terminal domain of this protein. Although it seems that these mutations only affect one of the alleles of this gene. On the other hand, Axin2 mutation has been seen in germ cells of families with familial CRC (15).

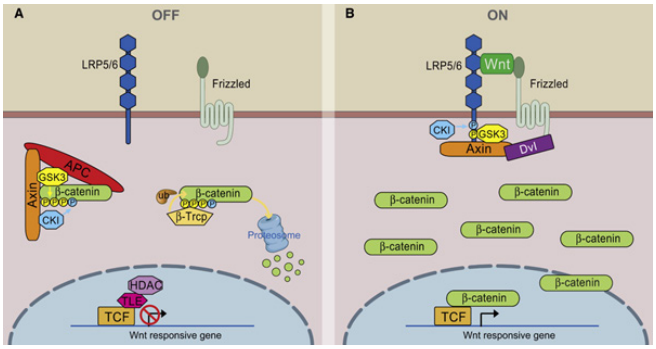

Figure 2. β-catenin-dependent WNT pathway A. Closing the WNT responsive gene pathway B. Opening of the WNT responsive gene pathway (16).

Comparison of ADC value and KT value before and after neoadjuvant radiotherapy and chemotherapy in the T-descending group and T-undescending group

There was no difference in the ADC value between the two groups before nCRT(P>0.05), the ADC values of the two groups after nCRTincreased more than those before nCRT(P<0.05). Compared with the pre-T-decline group and the T-non-decline group before nCRT, the K^{trans} value of the pre-T-decline group was higher than that of the T-non-decline group(P<0.05), the K^{trans} value of the two groups after the nCRT was higher than that before nCRT(P<0.05), but there K^{trans} value was no significant difference(P>0.05) (Table 1).

Comparison of the difference and change rate of ADC and Ktrans before and after neoadjuvant radiotherapy and chemotherapy between the T-descending group and the T-undescending group

The difference and change rate of ADC in the T-depression group were greater than those in the non-decline group (P<0.05) (Table 2).

The value of ADC value and KT value in predicting the early efficacy of neoadjuvant radiotherapy and chemotherapy for READ

The ROC curve was used to analyze the value of ADC value and K^{trans} value in predicting the early evaluation of neoadjuvant radiotherapy and chemotherapy for READ. With the change rate of the ADC value 0.17 as the best threshold, the sensitivity, and specificity of predicting the T descending stage of READ patients after neoadjuvant radiotherapy and chemotherapy were 72.69% and 75.84%, respectively. The area under the 95% CI: 0.608 curve was 0.78 (95% CI: 0. 608-0.954). Taking the pre-nCRTK^{trans}

Table 1. Comparison of ADC value and K^{trans} value before and after neoadjuvant radiotherapy and chemotherapy in the T-descending group and T-undescending group.

group	n	ADC($\times10^{-3}mm^2/s$)	K^{trans}(/min)
T-descending	24		
Before nCRT		0.99±0.05	1.27±0.13$^{\#}$
after nCRT		1.18±0.08*	1.42±0.21*
T-undescending	16		
Bffore nCRT		1.01±0.05	1.07±0.26
After nCRT		1.12±0.04*	1.25±0.18*

Note: compared with pre-nCRT in the same group,$^{*}P$<0.05; compared with T-undescended group at the same time point,$^{\#}P$<0.05.

Table 2. Comparison of difference and change rate of ADC and K^{trans} before and after neoadjuvant radiotherapy and chemotherapy between the T-descending group and T-undescending group.

project	group	n	ADC	K^{trans}
difference value	T-descending	21	0.19±0.04*	0.15±0.11
	T-undescending	13	0.10±0.03	0.16±0.09
change rate	T-descending	21	0.19±0.05*	0.12±0.06
	T-undescending	13	0.10±0.04	0.15±0.08

Note: compared with T-undescended group,$^{*}P$<0.05.

Table 3. The role of ADC value and KT value in the early evaluation of neoadjuvant radiotherapy and chemotherapy for READ.

group	Optimal threshold	sensitivity (%)	specificity (%)	AUC(95%CI)
ADCchange rate	0.17	72.69	75.84	0.78(0.608-0.954)
$K^{trans}$of before nCRT	1.18(/min)	78.65	80.47	0.81(0.637-0.971)

value 1.18/min as the best threshold, the sensitivity and specificity of predicting the T-descending phase of READ patients after neoadjuvant radiotherapy and chemotherapy were 78.65% and 80.47%, respectively (95%CI:0.637-0.971). There were no significant differences between the rate of ADC value and the K^{trans} value before nCRTto predict the early efficacy of neoadjuvant radiation therapy and chemotherapy for READ (Table 3).

Discussion

ADC is a quantitative parameter used to evaluate the diffusion of water through tissues, which is inversely proportional to the structure of tissues and cells (17). Living tumour cells limit the mobility of water, while necrotic tumour cells increase the spread of water molecules. Increasing the distortion between the structure of tumor cells and the outer space of tumor cells will lead to a decrease in ADC value. Studies have shown that ADC value is related to tumor cell structure and grade (18). ADC has been proven to be able to distinguish persistent tumor from inflammation and necrosis after treatment, it is a powerful tool for monitoring the effect of radiotherapy. Radiation-related cell injury can occur within a few days after starting treatment. DWI can be used to predict early chemotherapy due to its value in detecting tumor microstructure (19).

Lower pretreatment ADC is valuable in predicting patient continued acquisition of PCR, Lambrecht et al. (20) DWI tests were performed at multiple time points to evaluate PCR in a prospective study involving 20 patients. The study found that pre-CRTADC had 100% sensitivity and 86% specificity in predicting PCR. Intven et al. (21) and Genovesi et al. (22) indicated that changes in ADC after CRT can identify PCR with 98% and 91% diagnostic accuracy. In addition, Lambrecht et al.found that ADC rate of change after CRT can also be used to detect PCR. However, some studies have also found that DWI cannot determine PCR (23). A retrospective multicenter study found that the qualitative index of DWI is beneficial to the judgment of pCR after CRT. However, the DWI analysis in the study is qualitative, and the ADC value is not used. Using T2-weighted MRI sequences alone, the sensitivity for identifying PCR is poor, while adding DWI increases the sensitivity to 52-65% with a specificity of 89-98% (24).

This study found that the ADC values were significantly increased compared with those before nCRT($P<0.05$), and the difference and change rate of ADC in the T-downstaging group were higher than those in the T-undownstaging group ($P<0.05$), Using ROC curve to analyze the value of ADC value in predicting the early evaluation of the curative effect of neoadjuvant chemoradiotherapy for READ. Taking the change rate of the ADC value of 0.17 as the optimal threshold, the sensitivity to predict T downstaging after neoadjuvant chemoradiotherapy in patients with READ was 72.69 %, the specificity was 75.84%, and the ROC curve area was 0.78 (95%CI: 0.608-0.954); the change rate of the ADC value has the value of predicting the early efficacy of neoadjuvant radiation therapy and chemotherapy for READ.

Jang et al.indicated that 42% of patients with pCR still had diffusion restriction. In patients who achieved pCR after CRT, histopathologically confirmed that radiation proctitis and fibrosis were independent predictors of restricted diffusional motion. This study demonstrates that even in the absence of residual tumor, restriction of diffusional motion due to radiation-induced fibrosis can still occur (25). A study of 50 patients by Maas et al. found that qualitative T2-weighted imaging and DWI had a 35% sensitivity and a94%specificity for predicting pCR after CRT. However, the combination of MRI with clinical evaluation such as colonoscopy improved pCR prediction, and the precision of predicting pCR was 98% (26).

DCE-MRI provides much information about tumor microvascular perfusion, and extracellular-extracellular space composition by evaluating the change of signal intensity. ROI can produce enhancement time curves fortumoursdue to their microvascular abnormalities, indicating that rapid flushing and flushing of contrast agents and signal intensity are greater than those of normal tissues (27). DCE-MRI can evaluate the characteristics of tumor vascular microenvironment that affect the response to radiotherapy and radiotherapy caused vascular changes. It can evaluate the potential descending stage of the tumor to distinguish between patients with good or poor prognosis after treatment. Quantitative analysis involves modeling the pharmacokinetics of intravenous contrast media, and it is necessary to correct and pre-compare T1. Because there are few studies on DCE-MRI, the best evaluation techniques have not been determined.

Higher pretreatment K_{21} was positively related to good treatment response. In multivariate analysis, the higher K_{21} value was related to a better tumor response rate, while the amplitude and peak time of the quantitative parameters were not related to tumour response. In addition, the morphology of the mucinous tumors was linked to poor treatment response (28). Other studies have shown that high-level pre-CRT K^{trans} can predict tumor response. Among them, pre-CRT K^{trans} was increased in good treatment response patients (29).

In this study, compared to the pre-nCRT T-decline group, the K^{trans} value of the pre-T-decline group was higher ($P<0.05$), and the K^{trans} value of the two groups after nCRTalso was significantly higher ($P<0.05$). Taking the pre-nCRTK^{trans} value 1.18/min as the best threshold, the sensitivity and specificity of predicting the T-descending phase of READ patients after neoadjuvant radiotherapy and chemotherapy were 78.65% and 80.47%, respectively (95%CI:0.637-0.971). It can be seen that the pre-nCRTK^{trans} value has the value of predicting the early efficacy of neoadjuvant radiotherapy and chemotherapy for READ.

In summary, the ADC value and theK^{trans} value can reflect the changes in the tissue structure of READ after neoadjuvant chemotherapy, which shows that the change rate of the ADC value and pre-nCRTK^{trans} value has the value of predicting the early efficacy of neoadjuvant radio-

therapy and chemotherapy for READ.

Considering that many cancers have different genetic and hereditary backgrounds, understanding their cellular mechanisms and intermolecular behaviors provides a deeper understanding of the functioning of their regulatory systems. The results showed that Axin2 and β-catenin factors along with other factors such as APC and CKI proteins are effective at the molecular level along with other factors in the WNT/TCF signaling pathway. These agents start their activity in the cytoplasm and exert their final effect on the genes in the nucleus. Other roles of these molecular factors, especially Axin2 and β-catenin, are regulation of GTPase activity, regulation of cell death, cell proliferation, positive regulation of protein phosphorylation, and positive regulation of epithelial to mesenchymal transition.

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