Clinical Researches of Magnetic Resonance Diffusion Weighted Imaging in Radiotherapy of Nasopharyngeal Carcinoma

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Abstract: Intensity modulated radiation therapy (IMRT) is the standard treatment for nasopharyngeal carcinoma, and the accuracy of its target can improve the local control rate of tumor and improve the quality of life of patients. Almost all nasopharyngeal carcinomas undergo tumor retraction and weight changes to varying degrees during radiotherapy, especially concurrent chemoradiotherapy, which affects the drift of the anatomical position of the head and neck and affects the accuracy of the target area. Therefore, the rewildering plan in the process of radiotherapy and chemotherapy for nasopharyngeal carcinoma is extremely important, and when to change the wilderness and which part of the population needs to change the wilderness is the main research hotspot of this issue.
***Keywords*:** Nasopharyngeal carcinoma, IMRT, Radiotherapy

1. Preface

In the process of radiotherapy, there are many uncertain bias factors that affect the accuracy of treatment, including set-up error, systematic error of treatment equipment, movement of organs or targets during treatment, and fractional treatment interval due to tumor retreat, body shape changes, etc., a series of factors such as changes in the relative position between the target area and the surrounding normal tissues and organs. These uncertain biases can be overcome clinically by expanding the discharge boundary, but at the same time, it will cause excessive irradiation of too many normal tissues and organs around. The active approach is to monitor the changes in the position and shape of the patient's treatment site through imaging during treatment, and take corresponding measures to correct the dose deviation caused by the above changes and errors. Adaptive radiation therapy (ART) is one such aggressive approach to reducing bias.

2. IMRT adaptive radiotherapy for nasopharyngeal carcinoma

Radiotherapy is the preferred radical treatment for nasopharyngeal carcinoma, and conventional radiotherapy has been shown to achieve good local control rates in the past few decades, so it has become the standard treatment for nasopharyngeal carcinoma. However, long-term toxic side reactions caused by conventional treatment, including dry mouth, hearing loss, difficulty opening the mouth, neck mobility disorders, radiation brain necrosis, etc., seriously affect the quality of life of patients. In the past decade, IMRT has rapidly replaced conventional radiotherapy as the most important treatment for nasopharyngeal carcinoma due to its dosimetric advantages. IMRT can significantly improve the local control rate of tumors and the survival rate of patients in terms of therapeutic efficacy. Wolden et al. reported that IMRT treatment for nasopharyngeal carcinoma had a 3-year survival rate of 91% without local recurrence, a survival rate of 97% without regional lymph node recurrence, and a survival rate of 78% without distant metastasis. Lee et al. reported a 4-year overall survival rate of 97%, and the no local recurrence rate and distant survival rate were 98% and 66%, respectively. The phase III randomized controlled study of conventional radiotherapy and IMRT by Peng et al. showed that the 5-year local control rate and overall survival rate of IMRT were 90.5% and 79.6%, respectively, while conventional radiotherapy was only 84.7% and 67.1%. More importantly, IMRT can significantly reduce long-term toxic side effects and improve the quality of life of patients compared with conventional radiotherapy. Many researchers used EORTC QLQ-C30 and EORTC QLQ-H&N35 scales to evaluate the quality of life of nasopharyngeal carcinoma patients, and found that the quality of life symptoms associated with dry mouth can be significantly improved, especially within 1 year after treatment, IMRT has obvious advantages. There have also been studies showing no advantage in the control of dry mouth with 1MRT unless the average dose of control to the parotid gland is below 24-26Gy. Therefore, high-quality IMRT programs can absolutely improve the local control rate of the disease and improve the quality of life.

3. Research status of ART for nasopharyngeal carcinoma

In online ART, in order to simplify the process and save time, researchers have proposed many algorithms to achieve online adaptation in combination with clinical applications. Based on the image registration information of planned CT and daily CT, Court et al. proposed an algorithm to adjust the position of multi-leaf collimator (MLC) leaves, which can compensate for the displacement of the irradiation area and the deformation of the target area, and they found that this algorithm can improve the uniformity of the target dose of prostate and head and neck tumors. Mohan et al. obtained changes in the anatomical position and shape of the irradiation area based on the field direction (BEV) map information of planned CT and pretreatment CT, so as to re-optimize the dose intensity map and obtain a new subfield irradiation sequence. Feng et al. proposed the direct subfield deformation (DAD) algorithm to realize online adaptation, which adjusts the shape of the MLC subfield according to the deformation matrix of planned CT and pre-treatment CT deformation registration, which can achieve plan adjustment within minutes. Wang et al. conducted real-time online monitoring of cone-beam CT on 22 cases of nasopharyngeal carcinoma, and the results showed that online ART could correct the set-up error, reduce the expansion boundary from CTV to PTV from 5-6 mm to 3 mm, greatly reducing the irradiation range of normal tissues. However, the above method can achieve relatively rapid correction for the small change of target shape, which is obviously not accurate enough in nasopharyngeal carcinoma I MRT.

Offline ART refers to the measurement of positioning error or the adjustment of PTV spread distance by changing the ITV spacing based on the comparison of the initial positioning image and the current patient's anatomical image, or re-delineating the correction target and optimizing the dose distribution according to the change of the patient's anatomy, modifying the plan, and implementing follow-up treatment according to the modified treatment plan. However, due to the special anatomical position of nasopharyngeal carcinoma, the complexity and complexity of target and normal tissue delineation, and the strict requirements for treatment accuracy, each target delineation and re-planning optimization are very time-consuming and laborious, which is the main reason for the difficulty of AR7 implementation. In recent years, many studies have focused on solving this dilemma through automatic sketching software, and some studies have shown that automatic sketching software can save 30-60% of the delineation time and achieve similar accuracy. More studies have reported that compared with traditional manual sketching methods, it can save 87% of time. At present, ART has studied the use of automatic sketching to reduce manual workload.

4. Magnetic resonance apparent diffusion in nasopharyngeal carcinoma

Magnetic resonance plays an important role in the diagnosis, treatment, recurrence monitoring, and efficacy evaluation of nasopharyngeal carcinoma. In recent years, with the continuous progress of radiotherapy technology, especially with the development of radiotherapy technology from the era of two-dimensional radiotherapy to the era of three-dimensional conformal radiotherapy, especially the implementation of Intensity modulated radiation therapy (IMRT) technology, the accuracy of tumor localization and target area is getting higher and higher, making magnetic resonance play an increasingly important role in disease staging and target delineation in nasopharyngeal carcinoma. Diffusion-weighted magnetic resonance imaging (DWI) is a new magnetic resonance functional imaging technique whose signal attenuation parameter is called the Apparent Diffusion coefficient (ADC). Malignant tumors show high signal and low ADC value on DWI due to rapid growth, dense cells, and limited free diffusion movement of water molecules inside and outside the cell, which can be used to carry out early diagnosis, clinical staging and efficacy monitoring of tumor tissue. As a functional imaging method, DWI has the advantages of non-invasive and affordable compared with Positron Emission Tomography (PET CT). In recent years, DWI has been widely used in head and neck tumors, and can identify benign and malignant lymph nodes in the neck, identify lymphoma and metastatic lymph nodes, identify the activity of residual lymph nodes after radiotherapy and chemotherapy, and evaluate the efficacy after radiotherapy and chemotherapy.

Ichikawa Y et al. found that ADC values correlated with pathological types and could distinguish between cervical lymphoma and nasopharyngeal or oral cancer. In the study of Yan Danfang, the worse the degree of differentiation, the lower the ADC value, consistent with previous literature studies, Abdel Razek et al. have shown that in kidney cancer, the ADC value is significantly correlated with the degree of tumor differentiation, and the worse the differentiation, the lower the tumor ADC value. Pathological types of nasopharyngeal carcinoma include non-keratinizing (poorly differentiated and differentiated), keratinizing squamous cell carcinoma and basal cell type and other types, of which 75-99% of tumors are non-keratinizing tumors, which are characterized by dense plasma cell and lymphocyte infiltration, which is different from keratinizing squamous cell carcinoma. The results of this study showed that there was a significant difference between the ADC values of keratinizing squamous cell carcinoma and the lowest ADC values of undifferentiated tumors, and the ADC values of the other two types were between the two, but there was no significant difference.

In the study of 17 cases of head and neck squamous cell carcinoma, Driessen JP also found that the ADC values of tumors with different degrees of differentiation (high, medium, and low differentiation) were different, and the ADC values of poorly differentiated tumors were lower than those of the moderately differentiated type, but did not reach statistical significance. The study considered that the results may not be statistically significant due to insufficient sample size, but it can be suggested that ADC values partially reflect the degree of tumor differentiation, and in a similar study of 27 cases of breast cancer, positive reports were also reported with significant differences in ADC values between breast cancer tissue and normal breast tissue, and ADC values in invasive ductal carcinoma and non-invasive ductal breast cancer. According to the literature, undifferentiated carcinoma indicates a poor tumor prognosis.

In the study of Chen C et al., 5-year overall survival for nasopharyngeal carcinoma large masses (>50ml) was significantly reduced, and the results were similar to T4. Large masses generally imply a higher risk of metastasis and are therefore a poor prognostic factor. There are also studies showing a positive correlation between tumor volume and TNM stage. Some studies have suggested that tumor volume be used as the basis for TNM staging of nasopharyngeal carcinoma. Although tumor volume was not found to be an independent prognostic factor in multivariate regression in our study, tumors with volume greater than the median (> 85 m1) had poor OS and DMFS in univariate stratified studies, but did not achieve statistical significance, with F values of 0.11 and 0.10, respectively. This may be due to the limited sample size of this study, so multivariate regression did not achieve statistically positive results.

Zhang et al. showed that high ADC values have good local control and disease-free survival in nasopharyngeal carcinoma, and they divided ADC values into high and low groups with a threshold of 0.747 X 10-3 mm2/s. In addition, some studies believe that the initial ADC value before treatment has no predictive effect on prognosis, but the difference between the ADC value and the pre-treatment value during treatment can predict the local control of tumors. Han et al. studied 305 patients with nasopharyngeal carcinoma treated with IMRT, and T stage was not a prognostic factor among the independent prognostic factors of LC and OS. In the study of Bilgin et al., it was also found that T stage and N stage were not independent prognostic factors for LC and RC, but N stage was an independent prognostic factor for OS.

Yan Danfang, a scholar, studied 20 patients with pathologically diagnosed nasopharyngeal carcinoma, all of whom received head and neck IMRT and single-agent platinum-based concurrent chemotherapy. Magnetic resonance imaging (MRI) enhancement and diffusion-weighted examination were performed before treatment, and non-contrast MRI scanning and diffusion examination were performed weekly during treatment, and the apparent diffusion coefficient (ADC) value of tumor was measured before and during treatment. Before treatment and weekly review of localization computed tomography (CT), after the fusion of the positioning CT image and the initial CT image, copy the target area (GTV, CTV and parotid tissue structure) before treatment to the localization CT reviewed weekly, modify and delineate the GTV, CTV and parotid tissue structure, measure the volume, and observe the changes of weekly GTV, CTV and parotid gland volume. The relationship between GTV volume change and initial tumor ADC value and initial mass size was observed. At the same time, the weekly weight change of patients was monitored before and during treatment, and the body mass index (BMI) of each patient before treatment was calculated to observe the relationship between CTV change and weight change, BMI and initial mass size. The relationship between the volume change of parotid gland structure and BMI and mass size was observed. The results showed that the BMI and tumor ADC values of patients before treatment had the value of predicting the re-field re-planning in IMRT of nasopharyngeal carcinoma, BMI The larger the increase, the significant change in CTV and parotid volume retraction during treatment; The smaller the ADC value of the tumor before treatment, the more GTV will shrink significantly during treatment, so patients with high BMI value and low ADC value need to change the field and plan again during treatment. At the same time, the results showed that the most obvious time for the volume change of GTV, CTV and parotid gland occurred in the third and fourth weeks, and it is recommended that the best time for re-planning is four weeks after radiotherapy.

5. Summary

In summary, radiotherapy has entered the era of precision medicine, and the accuracy of targets and plans will be increasingly required in the future. In patients with nasopharyngeal carcinoma IMR7, the anatomical contour changes occur during the process, and the lymph nodes of the primary lesion and/or neck metastasis will gradually shrink, resulting in different degrees of changes in the radiation target area, the irradiation volume of the risk organ and the irradiation dose, which all affect the accuracy of IMRT. ART can increase the dose and volume of radiotherapy in the target area of nasopharyngeal carcinoma to a certain extent, reduce the dose and volume of radiation to risk organs and normal tissues such as brainstem, spinal cord, and lunar gland, and provide better individualized and precise radiotherapy scheme. However, the appropriate timing of ART still needs to be confirmed by further studies, and most researchers believe that IMRT radiotherapy 15-25 times or radiotherapy dose accumulated to 30-50 Gy may be the appropriate time for ART for nasopharyngeal carcinoma;

The jury is out on which populations are more likely to need replanning, and ART may benefit more in patients with large nasopharyngeal or cervical lymph node lesions, more significant weight loss, and neck diameter reduction. In short, ART is the goal of personalized precision radiotherapy for nasopharyngeal carcinoma in the future, and convenient, fast and accurate ART technology will be the development direction of precision radiotherapy for nasopharyngeal carcinoma.

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