High resolution diffusion weighted imaging for neoadjuvant chemotherapy assessment of nasopharyngeal carcinoma

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Research article

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Abstract

Background

To evaluate the feasibility of high resolution diffusion weighted imaging (DWI) for the prediction about the response of neoadjuvant chemotherapy (NAC) in patients.

Methods

119 NPC patients who underwent magnetic resonance imaging (MRI) including readout-segmented diffusion weighted imaging (RESOLVE-DWI) before treatment enrolled in this study from September 2017 to December 2019, and all patients underwent follow-up MRI at 3 month after two cycles of NAC. Patients were classified into stable disease (SD), partial response (PR) or completed response (CR) based on Response Evaluation Criteria in Solid Tumors (RECIST). Apparent diffusion coefficient (ADC) values were measured from RESOLVE-DWI in the first MRI examination. The ADC values were compared between responders (CR and PR) and non-responders (SD) using Independent samples *t*-test, and the receiver operating characteristic curve (ROC) was calculated to assess the diagnostic efficacy.

Results

The ADC value of responders was significantly higher than that of non-responders ($719.73 \pm 100.44 \times 10^{-3}$ mm^2/s and $583.28 \pm 53.15 \times 10^{-3}$ mm^2/s, $p < 0.001$, respectively). The area under the curve (AUC) was 0.879 with a sensitivity at 82.8%, and specificity at 84.6%.

Conclusions

The ADC value obtained by RESOLVE-DWI, with a high diagnostic accuracy for NAC assessment, could be used as a pretreatment imaging biomarker to predict the early response to NAC in NPC patients.

Background

Nasopharyngeal carcinoma (NPC) is a common head and neck malignancy among Asians, especially in the southern provinces of China and Southeast Asia [1]. Neoadjuvant chemotherapy (NAC) followed by intensity modulated radiotherapy (IMRT) has gradually showed superiority in the treatment of patients with NPC[2–5], due to not only reduce the tumor size to optimize the IMRT plan[6] but also potentially protect the critical tissue and improve the quality of life of patients with NPC[7]. More importantly, the main reason of the failure to the treatment of NPC is distant metastasis[8] and the NAC could reduce the micro metastasis.

Magnetic resonance imaging (MRI) examination plays an important role in patients with NPC due to its excellent resolution [9], and diffusion-weighted imaging (DWI) has been widely applied to the NPC detection, staging, characterization, and treatment response prediction [10–13]. However, image quality of single-shot echo-planer imaging (SS-EPI) DWI is unsatisfactory due to the complex anatomic structure with a lot of cavity around the nasopharynx, which might cause motion and magnetic sensitive artifacts[14, 15], leading to geometric distortion, signal intensity dropouts[16, 17]. Based on segmenting k-space along the readout direction to shorten the echo spacing, the technique of readout-segmented echo-planar imaging diffusion weighted imaging (RESOLVE-DWI) exhibits reduced spatial distortion and improved image quality in the head and neck areas [16, 18]. The apparent diffusion coefficient (ADC) maps from RESOLVE-DWI have a higher signal-to-noise ratio and resolution compared with conventional DWI, thus potentially improving the diagnostic and reliability of ADC value [19]. Therefore, this study assessed the ADC value obtained by RESOLVE-DWI for NAC's response in patients with NPC and explored valuable imaging biomarker to predict the local outcome of primary tumor.

Methods

Study Population

The ethics committee of Sun Yat-sen University Cancer Center approved this prospective study and all patients signed written informed consent before the first treatment. We enrolled 122 newly diagnosed NPC patients with no prior treatment and referred to NAC from September 2017 to December 2019. However, we excluded three patients from the study for the following reasons: two patients were due to the small thickness, and one had inadequate image quality due to serious motion on MRI examination. Ultimately, the final study population consisted 119 patients. All enrolled patients were candidates to receive cisplatin-based NAC for 2 cycles every 21 days, and then underwent follow-up MRI. In each cycle, 100 patients received cisplatin (DDP, Qilu Pharmaceutical, Shandong, China) 100 mg/m^2 plus Taxol (PTX, Hainan Chuntch Pharmaceutical, Hainan, China) 135 mg/m^2 given on day 1. The other 19 patients received cisplatin 100 mg/m^2 given on days 1 plus Gemcitabine (GEM, Jiangsu Hansoh Pharmaceutical, Jiangsu, China) 1000 mg/m^2 given on days 1 and 8. All patients were hydrated one day before the application of Cisplatin and two days after the application of Cisplatin in order to protect the patients' renal function

MRI Acquisition

All of the examinations were performed using a 1.5 T MRI scanner (Aera, Siemens Healthcare, Germany) with a 20-channel head and neck combined coil. Routine clinical MRI examination contained RESOLVE-DWI sequence, and the parameters were as follows: field of view, 24 cm × 24 cm; section thickness, 5 mm; intersection gap, 1 mm; number of sections, 30; repetition time, 6100 milliseconds; echo time, 84 milliseconds; matrix, 208 × 208; number of readout segment, 5; fat suppression, fat sat. Strong; b value, 0 and 1000s/mm^2; acquisition time, 2 minutes 45 seconds. Every patient enrolled was done the MRI examinations above before the treatment and after two cycles of NAC.

Images Analysis

The T2-weighted and DWI images were evaluated independently by three radiologists with more than 10 years experiences, and any differences were resolved by consensus. The morphological regression of tumors was measured according to T2-weighted images from the both MRI examinations. Meanwhile, at the first MRI examination, three region of interests (ROIs) were drawn manually at the largest section of the tumor and its adjacent up/down sections on ADC maps referring to T2-weighted images, avoiding the hemorrhagic and necrotic region, and the ADC values obtained from the above three ROIs were averaged to obtained the final results (Fig. 1).

The patients were classified into responders and non-responders based on Response Evaluation Criteria in Solid Tumors (RECIST)[20]. Responders were defined as completed response (CR) and partially response (PR) patients, while non-responders were referred to as stable response (SD) or progressed on the follow-up MRI.

All patients' TNM stage were determined by radiologists with reference to the 8th edition of the International Union against Cancer/ American Joint Committee on Cancer (UICC/AJCC) manual.

Statistical Analysis

The consistency between observers was evaluated by intra-class correlation coefficient (ICC), and an ICC of 1.0 was considered to indicate perfect agreement; 0.81–0.99 indicated almost perfect agreement; 0.61–0.80, substantial agreement; 0.41–0.60, moderate agreement; 0.21–0.40, fair agreement; and ≤ 0.20, slight agreement[21]. The data of ADC values was assessed for normality with the Shapiro-Wilk test. The Independent sample *t*-test was used to compare the ADC values of responders and non-responders. Categorical or continuous variables (age, gender, T classification, N classification and clinical stage) were compared using the Chi-square test. Receiver operating characteristic (ROC) curves were plotted, and the area under the curve (AUC) and 95% confidence intervals (CI) were calculated to evaluate the diagnostic efficiency of the ADC values in distinguishing responders and non-responders. All of the analyses were performed using the SPSS 25.0 statistical software package (https://www.ibm.com/support/pages/node/589145), with a value of two-tailed $p < 0.05$ considered to be a significant difference.

Results

A total of 119 patients were enrolled in this study finally, including 87 (73.2%) males and 32 (26.8%) females with the median age 46 years (19–63 years). The primary tumor treatment responses were distributed as follows: responders, 93 (78.2%) patients; non-responders, 26 (21.8%) patients. Baseline characteristics of patients were shown in Table 1.

Table 1
Baseline characteristics of 119 patients with NPC

	Responders	Non-responders	*p* value[a]
Total	93	26	
Age (years)			0.841
Median (range)	46 (19–62)	47 (27–63)	
Gender			0.001
Male	75 (63.0%)	12 (10.1%)	
Female	18 (15.1%)	14 (11.8%)	
T classification[b]			0.043
T1-2	13 (10.9%)	0	
T3-4	80 (67.2%)	26 (21.9%)	
N classification[b]			0.230
N0-1	37 (31.1%)	7 (5.9%)	
N2-3	56 (47.1%)	19 (15.9%)	
Overall stage[b]			0.122
I-II	8 (6.7%)	0	
III-IV	85 (71.4%)	26 (21.9%)	
[a]*p* values were calculated by Chi-square test			
[b]According to the 8th edition of UICC/AJCC staging system			

The ICC between the two measurements of ADC values were identified as excellent (ICC = 0.936; 95% CI: 0.899, 0.960). Accordingly, all of the analyses in the following section were based on the average ADC values of the three observers.

The mean ADC value of responders was significantly higher than that of non-responders ($720.05 \pm 102.38 \times 10^{-3}$ mm^2/s and $583.28 \pm 53.15 \times 10^{-3}$ mm^2/s, $p < 0.001$, respectively) (Table 2, Fig. 2). The primary tumor ADC for differentiating responders and non-responders using ROC curve analysis was 624.45×10^{-3} mm^2/s, and the AUC was 0.879 with a sensitivity of 82.8% and specificity of 84.6% (Fig. 3).

Table 2
Difference of ADC value between responders and non-responders

	Responders	Non-responders	*p* value
ADC ($\times 10^{-3}$ mm^2/s)	719.73 ± 100.44	583.28 ± 53.15	< 0.001

Discussion

Our study demonstrated that ADC values obtained from RESOVLE-DWI was able to predict tumor response to NAC treatment in patients with NPC, and there was a greater diagnostic accuracy to distinguish responders from non-responders after two NAC cycle treatments. The patients with higher pretreatment ADCs had a better response to NAC compared to those with lower pretreatment ADCs. This could promote the individualized treatment for patients with NPC and protect some patients from ineffective and unnecessary treatment toxicities.

As a useful MRI functional sequence, DWI provides functional and structural information on the microanatomy in tissues, which plays a significant role in routine MRI examination and serves as a good supplement to improve the accuracy of assessing the properties and biological behaviors of nasopharyngeal carcinoma. Meanwhile, ADC value derived from DWI has been shown to have potential as imaging bio-markers for predicting the histopathological grade and indicating the aggressiveness of nasopharyngeal carcinoma[12, 22]. In this study, the mean ADC value of responders was significantly higher than that of non-responders, which were consistent with those of previous research [23, 24]. However, Zhang et al[25] reported that the mean ADC value of responders was significantly lower than that of non-responders, the reason might be that the patients in their study were obtained three cycles NAC.

In addition, they used SS-EPI DWI sequence to obtain ADC values, which is challenging to perform ADC measurement in the head and neck due to susceptibility and motion artifacts. In the present study, the ADC values were obtained by RESOLVE-DWI. Based on a two-dimensional navigator reacquisition, “Readout Segmentation Of Long Variable Echo-trains” divides the k-space into multiple segments to shorten the echo spacing and accelerates the k-space traversal along the phase-encoding direction to diminish geometric distortion, signal dropout and image blurring [26–28]. RESOLVE technology can effectively reduce these artifacts and provide high resolution images,which can better display the tumor to delineate the target area, thus greatly improving the accuracy of ADC value. Zhao et al[29] reported that RESOLVE-DWI significantly improved the image quality for evaluations of Sino nasal lesions and offered more accurate ADC value than SS-EPI.

Based on ROC analysis, The ADC value had a better AUC and relatively high sensitivity of differentiation between responders and non-responders for NAC treatment of NPC, suggesting that ADC value obtained by RESOLVE-DWI may serve as a valuable imaging biomarker for NAC.

The present study has several limitations. First, a small sample size in this study, and most of the patients with patients responded to NAC, which could result in statistical bias. Second, this study is a single-center study, and the findings should be validated in other institutions with diverse population.

Conclusions

In conclusion, the ADC value obtained by RESOLVE-DWI could serve as a valuable imaging biomarker to predict the response to NAC, and the higher pretreatment ADCs tended to response better for NAC.

Abbreviations

DWI: diffusion weighted imaging; NAC:neoadjuvant chemotherapy; NPC:nasopharyngeal carcinoma; MRI:magnetic resonance imaging; RESOLVE-DWI:readout-segmented diffusion weighted imaging; SD:stable disease, PR:partial response; CR:completed response; RECIST:Response Evaluation Criteria in Solid Tumors; ADC:apparent diffusion coefficient; ROC:receiver operating characteristic curve; AUC:the area under the curve; IMRT:intensity modulated radiotherapy; SS-EPI:single-shot echo-planer imaging; ROI:region of interests; UIVV/AJCC:the International Union against Cancer/ American Joint Committee on Cancer; CI:confidence intervals.

Declarations

Ethics approval and consent to participate

The ethics committee of Sun Yat-sen University Cancer Center approved this prospective study and all patients signed written informed consent before the first treatment.

Consent for publication

Not applicable.

Availability of data and materials

The data are not available for public access because of patient privacy concerns but are available from the corresponding author on reasonable request approved by the institutional review boards of Sun Yat-sen University Cancer Center.

Competing interests

The authors have no conflict of interest.

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Author's contributions

MTB, KLR and XCM contributed to study design. MTB, LJ, WFX, DW, ZLL, MXG, HW and LH collected the study data. MTB, LJ and WFX contributed to data analysis. MTB, LJ and WFX contributed to manuscript writing. MTB, KLR and XCM contributed to quality control. All authors reviewed the manuscript and approved the final version.

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Figures

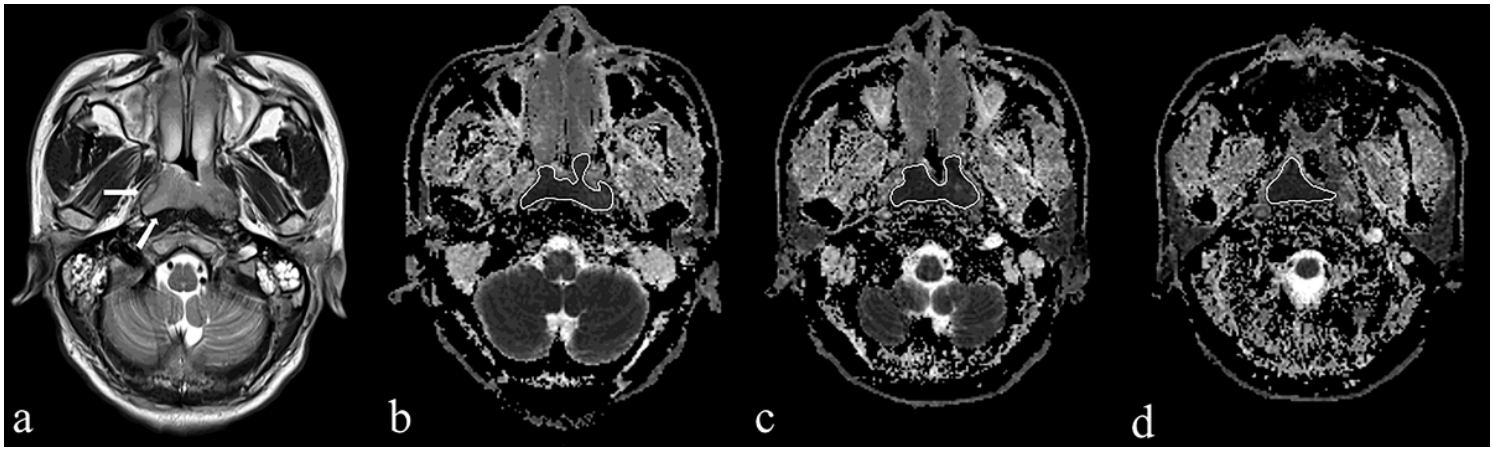

Figure 1

A 48 years old male patient with nasopharyngeal carcinoma who responded to neoadjuvant chemotherapy. (a) Pretreatment T2 weighted image showing nasopharyngeal lesion (white arrows); (b-d) ADC maps showing the largest section of the tumor and its adjacent up/down sections.

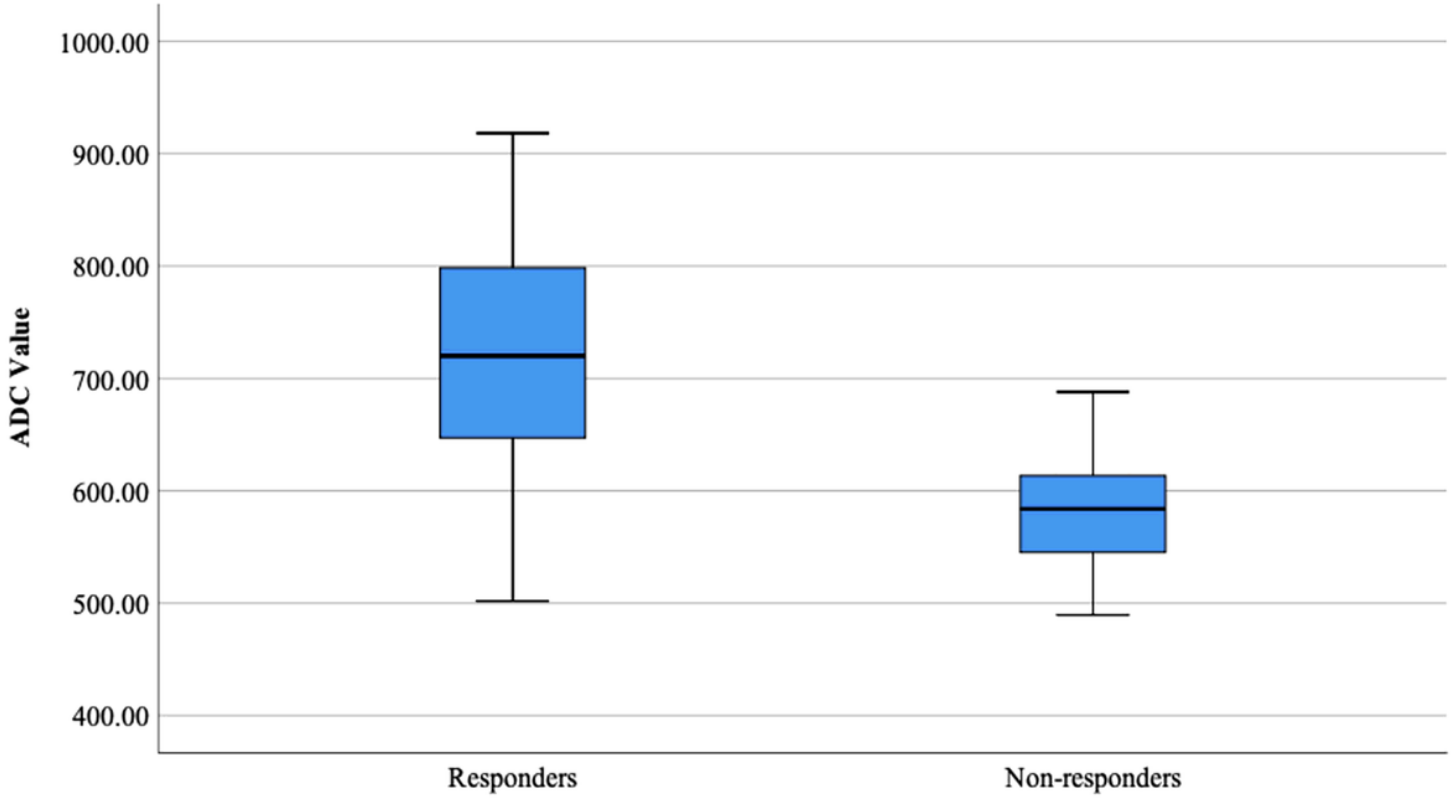

Figure 2

Box plot of ADC value for responders and non-responders. Abbreviation: ADC, apparent diffusion coefficient.

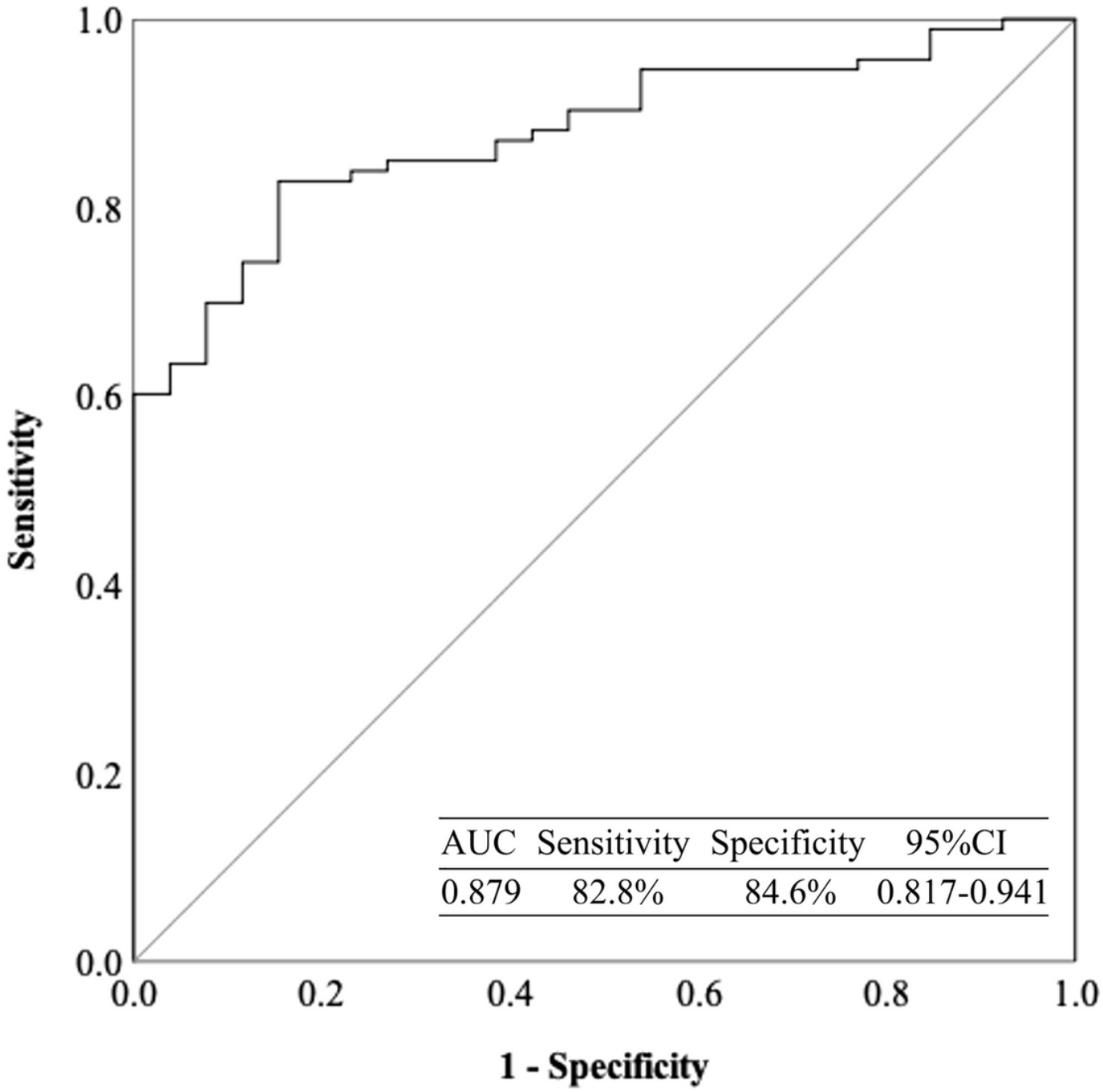

Figure 3

The diagnostic accuracy of ADC value in predicting the induction chemotherapy response of nasopharyngeal carcinoma. Abbreviation: AUC, the area under the curve; CI, confidence intervals.