Histogram-based analysis of diffusion-weighted imaging for predicting aggressiveness in papillary thyroid carcinoma

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Research Article

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Abstract

Background: To assess whole-tumor histogram-based analysis of apparent diffusion coefficient (ADC) map for its potential in predicting aggressiveness in papillary thyroid carcinoma (PTC).

Methods: Totally 88 patients administered neck magnetic resonance imaging (MRI) with PTC confirmed by pathology were enrolled in the current retrospective study. Whole-lesion histogram features were extracted from ADC maps. The aggressive and non-aggressive groups were compared for histogram features by Mann-Whitney U test. Backward stepwise logistic regression analysis was carried out for identifying independent predictive factors. Receiver operating characteristic curve analysis was implemented to evaluate the performances of factors showing significance, and an optimal predictive model for PTC aggressiveness was developed.

Results: The aggressive and non-aggressive groups comprised 67 (44.03±13.99 years old) and 21 (43.86±12.16 years old) patients, respectively. Six histogram features were included into the final predictive model. ADC_firstorder_Maximum had the best performance (area under the curve [AUC]=0.83). The final combined model showed an optimal performance, with AUC and accuracy of 0.88 and 0.82, respectively.

Conclusions: Whole-lesion histogram analysis based on ADC maps could be utilized for evaluating aggressiveness in PTC, with satisfactory accuracy.

Background

Papillary thyroid carcinoma (PTC) represents the commonest pathological type of thyroid cancer, making up 65%-92.8% of all thyroid malignant tumors[1, 2]. PTC generally has a good prognosis [3], with 1–2% mortality and a survival rate for lowly aggressive PTC above 99%[4]. Aggressive PTC is different from non-aggressive counterpart in terms of clinical treatment strategy. The 2015 ATA guidelines[5, 6] recommend ipsilateral lobectomy in lieu of total thyroidectomy for low-risk PTC, while not supporting prophylactic central neck lymph node dissection, to avoid unnecessary complications. However, for aggressive PTC, total thyroidectomy and prophylactic central lymph node dissection are required, often with subsequent radioactive iodine-131 treatment. Currently, the aggressiveness characteristics of tumors may only be assessed by pathologically evaluating specimens obtained by thyroidectomy [7]. Therefore, preoperatively evaluating PTC aggressiveness is quite important, which determines the clinical treatment [6]. The determination of PTC invasiveness comprises several different aspects, including the presence of thyroid capsule invasion, regional lymph node and distant metastases, and a special pathological subtype.

Ultrasound, the first method of choice for the examination of thyroid lesion[8, 9], has certain limitations, including the difficult assessment of retrotracheal lymph nodes, a low specificity in the diagnosis of capsular invasion, especially minimal extrathyroidal extension (ETE) [10, 11], and a high dependence on the operator's skills [6]. Fine-needle aspiration (FNA) biopsy is an essential method to obtain pathological specimens before surgery, but with too little tissue obtained, limited data related to invasiveness are collected, and the method cannot be used as a diagnostic criterion for invasiveness[12].

MR DWI is a widely applied functional imaging method, which uses the diffusion of water molecules to quantitatively analyze lesions without the use of contrast agents[13]. ADC is a quantitative index of DWI, and histogram analysis of ADC values can reflect the overall molecular characteristics of the lesion objectively. It has been reported that ADC is of certain value in predicting the preoperative grade of tumors[13–15]. ADC is related to aggressiveness in PTC[16]. However, most previous studies were subjective and lacked repeatability because ADC was calculated by a manually selected single region of interest (ROI). In addition, PTC is heterogeneous, and ADC largely depends on the delineated ROI, with possible incomplete assessment. ADC histogram assessment represents a more objective approach for

examining ADC value distribution throughout the tumor, avoiding the subjectivity of ROI selection and ensuring the reproducibility of measurements. It was reported ADC histogram assessment could be used to evaluate invasiveness in prostate cancer[17], and to distinguish invasive meningiomas from non-invasive ones[18].

Therefore, the current study aimed to explore the predictive performance of histogram analysis of ADC maps in assessing PTC aggressiveness.

Methods

Patients

This retrospective study examined consecutive patients with thyroid nodules firstly diagnosed by US between January 2019 and March 2021. Based on the American College of Radiology Thyroid Imaging, Reporting, and Data System [19], tumor grades were TR3-TR5.

Multiparametric MRI was carried out in the totality of patients, with subsequent thyroid surgery (subtotal or total thyroidectomy) within 7 days post-MRI. Pathological confirmation of PTC utilized surgical specimens. Exclusion criteria were: (1) pathology not reflecting PTC; (2) tumor size below 5 mm; (3) completely different pathological data for tumor samples and MR imaging data; (4) poor MR image quality. Ultimately, 88 patients were enrolled in the current study. Figure 1 shows the study flowchart.

This trial had approval from the Institutional Review Board of Minhang Hospital, Fudan University, with no requirement for written informed consent because of the retrospective nature of the trial.

MRI acquisition

An EXCITE HD 1.5 T scanner (GE Healthcare, USA) with an 8-channel special neck surface coil was utilized to examine the patients as follows. (1) Axial T2-weighted (T2WI) fast recovery fast spin-echo with fat suppression: echo time (TE), 85 ms; repetition time (TR), 3000 ms; slice thickness, 4 mm; matrix, 320×224; spacing, 0.5 mm; field of view (FOV), 25 cm; number of excitations (NEX), 4. DWI with a single-shot echo planar imaging (EPI) sequence: minimal TE; TR, 6550 ms; slice thickness, 4 mm; matrix, 128×128; spacing, 0.5 mm; FOV, 25 cm; NEX, 6 (b value of 800 s/mm^2). Spatial saturation bands were utilized to remove signals from overlying fat and neighboring tissues.

Histopathologic analysis

Surgical tumor specimens were assessed by a pathologist with > 10 years of related experience). Paraffin-embedded specimens were sectioned and stained with hematoxylin and eosin (H&E). Then, the pathologist evaluated aggressiveness by histology based on set criteria. All individuals were then grouped into the aggressive and non-aggressive categories.

PTC aggressiveness was examined based on the American Thyroid Association (ATA) 2015 risk stratification system for differentiating thyroid carcinoma[6].

Image Processing and Analysis

Tumor segmentation ITK-SNAP (http://www.itk-snap.org) was utilized for thyroid tumor segmentation. Totally 88 regions of interest (ROIs) were manually delineated on ADC maps by two radiologists with 10 and 13 years of experience, respectively. Consensual discussion was performed in case of discrepancy. ROIs were drawn slice-by-slice to reflect the tumor's 3D volume. The largest tumors were assessed in various patients for reducing potential bias with many lesions in a given patient and improving the applicability of results.

For interobserver agreement assessment, 30 random cases were chosen to calculate intraclass correlation coefficients (ICCs) for select parameters. Reliability was characterized as follows: (1) ICC < 0.4, poor; (2) ICC from 0.41 to 0.60, medium; (3) ICC from 0.61 to 0.80, good; (4) ICC > 0.80, excellent[20].

Firstly, the Mann-Whitney U test was carried out for examining whether the features had a significant between-group difference. Next, univariable logistic regression analysis was performed to assess whether the parameters could distinguish the two groups. Multivariate logistic regression analysis was carried out to identify independent discriminative features and build the final model.

The model's performance in detecting aggressiveness in PTC was assessed by receiver operating characteristic (ROC) curve analysis, determining the area under the curve (AUC), sensitivity, specificity, accuracy, and negative and positive predictive values.

Results

Patient features

Totally 88 patients aged 43.99 ± 13.51 years (range, 13–71 years) were enrolled in the final analysis. According to pathologic results, 67 (44.03 ± 13.99 years old) and 21 (43.86 ± 12.16 years old) cases were in the aggressive and non-aggressive groups, respectively. The characteristics of the included PTC cases are summarized in Table 1.

PTC aggressiveness prediction

To predict aggressive and non-aggressive lesions, six histogram features were retained by the Mann-Whitney U test (Fig. 2). Figure 2 depicts the box-plots of select features in the two groups. The totality of 6 features were significantly different between the aggressive and non-aggressive PTC groups ($P < 0.05$). Then, optimal predictive features were selected by backward stepwise selection using the likelihood ratio test, and the final model was established. Table 2 shows the odds ratios of the six features. Figure 3 depicts ROC curves for the six significant features, respectively, as well as the final model, in differentiating aggressive and non-aggressive lesions. The predictive model had an AUC of 0.88 (95%CI 0.80–0.95). Table 3 shows the final model's diagnostic performance: sensitivity, specificity and accuracy were 0.833, 0.762 and 0.816 (95%CI 0.719–0.891), respectively, for positive and negative predictive values of 0.917 and 0.593, respectively.

Table 1
Characteristics of patients in the aggressive and non-aggressive groups

	Aggressive group (n = 67)	Non-aggressive group (n = 21)	P value
Age(years)	44.03 ± 13.99	43.86 ± 12.16	0.96
Diameter(mm)	1.41 ± 0.71	0.93 ± 0.36	0.004
Sex			
Female	48	18	0.312
Male	19	3	
Location			
Right lobe	43	12	0.214
Isthmus of thyroid	4	0	
Left lobe	20	9	

Table 2
Features with significant potential in distinguishing aggressive and non-aggressive cases.

Variable	OddsRatio	Lower	Upper	P value
ADC_firstorder_90Percentile	2.523014273	1.294081	4.919012116	0.006592346
ADC_firstorder_Energy	3750.411856	2.397373	5867084.879	0.02831029
ADC_firstorder_Maximum	7.268379624	2.605385	20.27698461	0.000151067
ADC_firstorder_Range	2.966920146	1.47314	5.975407898	0.002331015
ADC_firstorder_TotalEnergy	180187.028	8.473629	3831577400	0.017299484
ADC_firstorder_Variance	2.265817839	1.015335	5.056391406	0.045811894

Table 3
Predictive performances of significant variables and the final model

Variable	Cutoff	AUC(95%CI)	Accuracy	Sensitivity	Specificity	PPV	NPV
ADC_firstorder_Maximum	-0.508568128	0.83(0.72–0.93)	0.85	0.86	0.81	0.93	0.65
ADC_firstorder_TotalEnergy	-0.291801478	0.78(0.67–0.89)	0.83	0.91	0.57	0.87	0.67
ADC_firstorder_Energy	-0.283609929	0.74(0.62–0.85)	0.70	0.71	0.67	0.87	0.42
ADC_firstorder_Range	-0.189251825	0.74(0.63–0.84)	0.67	0.62	0.81	0.91	0.40
ADC_firstorder_90Percentile	0.056415137	0.70(0.57–0.83)	0.63	0.58	0.81	0.90	0.38
ADC_firstorder_Variance	-0.507636863	0.66(0.53–0.79)	0.68	0.70	0.62	0.85	0.39
predictive model	0.882847792	0.88(0.80–0.95)	0.82	0.83	0.76	0.92	0.59

Discussion

Our study suggests that histogram assessment of the ADC map, a non-invasive tool, could predict aggressiveness in papillary thyroid carcinoma. A total of six features were selected for the final model. ADC_firstorder_Maximum was the most promising predictive parameter with an AUC of 0.83. The final model had a satisfactory potential in predicting PTC aggressiveness, with an accuracy of 0.82 and an AUC of 0.88.

Radiomics has been widely applied in predicting clinical prognosis, pathological grading and response to treatment recently since it enables the quantitative assessment of intratumor parameters, transforming them into high-throughput parameters, mostly comprising histogram and texture features[21, 22]. Histogram analysis through conversion of MRI-based parameters in primary tumors could successfully detect aggressiveness in multiple lesions[23, 24]. This study aimed to examine whole-lesion histogram analysis based on ADC maps for its ability to predict the aggressiveness of PTC. As a result, a predictive model was built, with an improved performance in predicting tumor aggressiveness (AUC of 0.88). The above finding indicates histogram analysis of ADC maps may provide more biological data and constitute a better surrogate imaging-derived tool for detecting PTC aggressiveness. Additionally, histogram assessment may better meet the clinical needs, for its easy implementation and data interpretation without requirement of sound mathematical knowledge.

Routine DWI is not reliable in providing good thyroid image quality because of susceptibility and motion artifacts, potentially rendering lesion determination difficult. Here, we utilized the reduced FOV diffusion strategy in lieu of routine DWI to image the thyroid, which is considered to provide high-resolution and high-quality DWI for small structures[25–27]. An 8-channel special neck surface coil was used to allow higher image quality while reducing susceptibility artifacts and distortions around the thyroid. In addition, ADC obtained according to manually selected ROIs is very subjective and variable. In this study, whole-lesion histogram assessment was utilized to examine the whole tumor, eliminating sample bias and enhancing the evaluation of intra-tumor heterogeneity[17, 28–30]. We found 6 ADC histogram parameters showed reduced values in aggressive PTC compared with non-aggressive cases, and ADC_firstorder_Maximum had the best discriminative performance. The discrepant ADC histogram features may reflect histopathological differences between aggressive and non-aggressive PTCs. For example, severer desmoplastic response and higher cell density in

aggressive PTCs reduce diffusion, lowering ADC, while follicle and extracellular fluid abundance as well as reduced cell density in non-aggressive cases yield higher ADC values. These findings indicate the greater the heterogeneity of tumor cellularity, the more aggressive the PTC, reflected by ETE, nodular metastasis and aggressive histopathology.

This study had three major limitations. First, the sample size was small (88 cases), which could result from selection bias due to exclusion criteria including small tumor size and poor image quality. Advances in MRI might help detect smaller PTC lesions and achieve high image quality. Secondly, another selection bias may exist because some PTC cases who underwent ultrasound examination without MR scanning were not enrolled in this study. Thirdly, for predicting PTC aggressiveness, ADC values were not compared to other imaging features, including diffusion kurtosis imaging (DKI), which have also been utilized to assess thyroid nodules and related histological features. Nevertheless, these results were encouraging, and whole-lesion histogram analysis deserves popularization and wide application because it is convenient to carry out as a non-invasive imaging marker for predicting aggressiveness and therapeutic outcome in PTC.

Conclusions

Overall, whole-lesion histogram analysis based on ADC maps, a non-invasive and quantitative tool, may help assess aggressiveness in PTC with satisfactory accuracy. Future larger-sample and independent multicenter studies are warranted to explore the potential clinical values of the histogram features detected in the current trial.

Abbreviations

ADC: Apparent diffusion coefficient; PTC: Papillary thyroid cancer; MRI: Magnetic resonance imaging; AUC: Area under the curve; ETE: Extrathyroidal extension; DWI: Diffusion weighted imaging; ROI: Regions of interest; T2WI: T2-weighted imaging; TE: Echo time; TR: Repetition time; FOV: Field of view; NEX: number of excitations; EPI: echo planar imaging; ICC: Intraclass correlation coefficient; CI: Confidence interval; ROC: Receiver operating characteristic; DKI: diffusion kurtosis imaging.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of Minhang Hospital approved this retrospective study and waived the requirement for written informed consent due to its retrospective nature. The study was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not Applicable.

Availability of data and materials

The datasets analyzed in this study are available from the corresponding author on request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

RW, YZ and BS conceived and designed this study. LW, XS, ZD and YG conducted the study and collected important background data. RW and HW drafted the manuscript. All authors read and approved the final manuscript.

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Figures

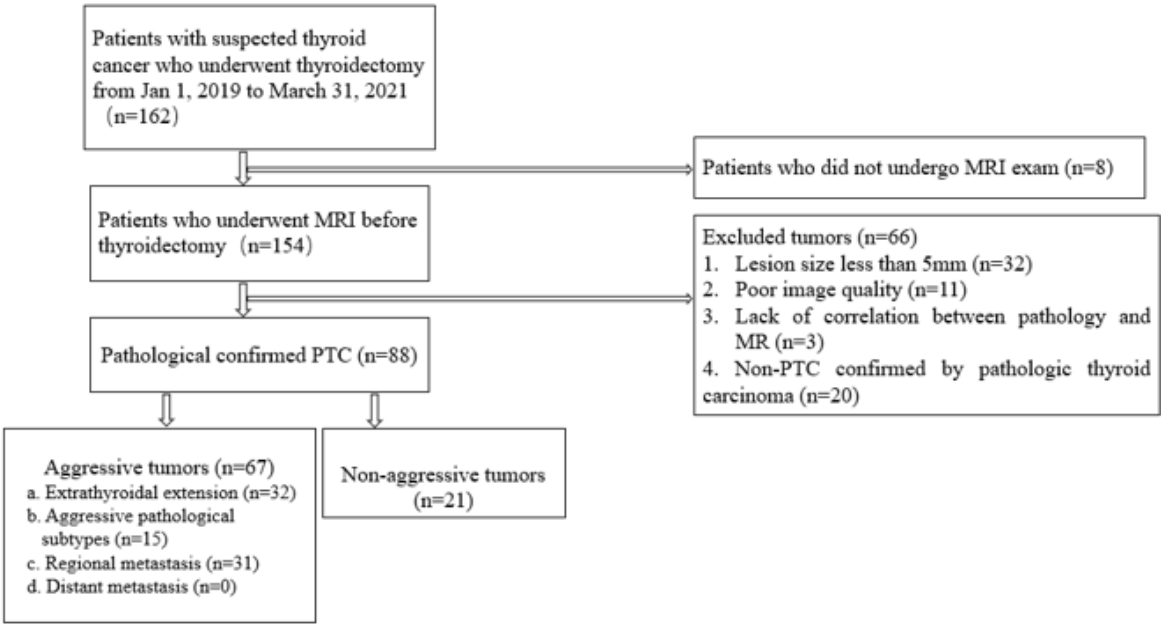

Figure 1

Study flowchart.

MRI, magnetic resonance imaging; PTC, papillary thyroid carcinoma

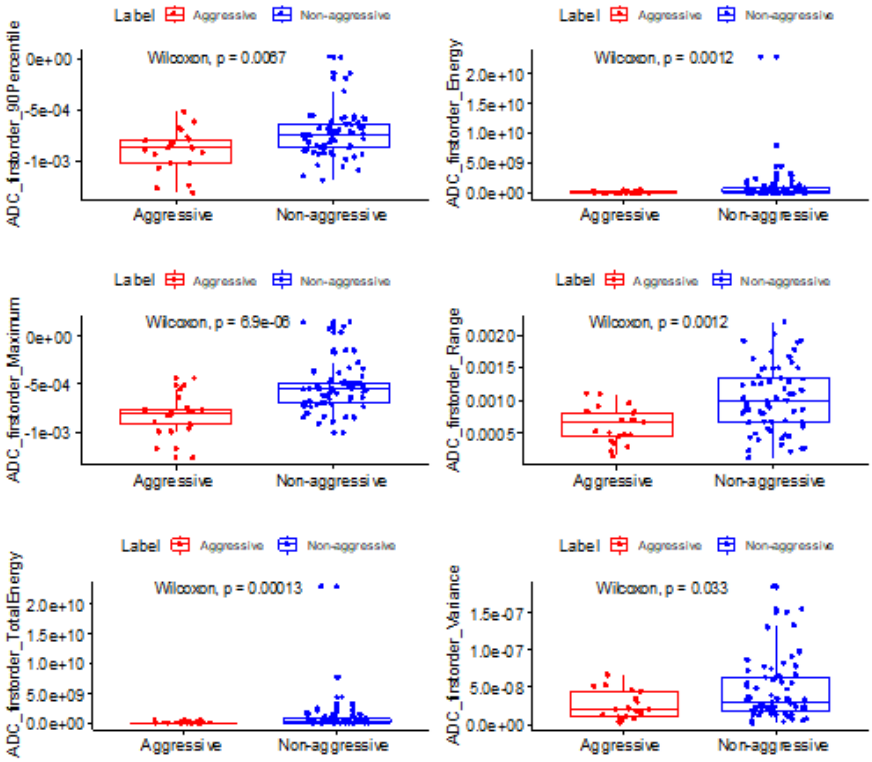

Figure 2

Scatterplots of ADC-derived histogram

Red points represent aggressive PTCs, and blue points are non-aggressive PTCs. Dotted lines show the best cutoffs of various histogram parameters for distinguishing aggressive and non-aggressive cases.

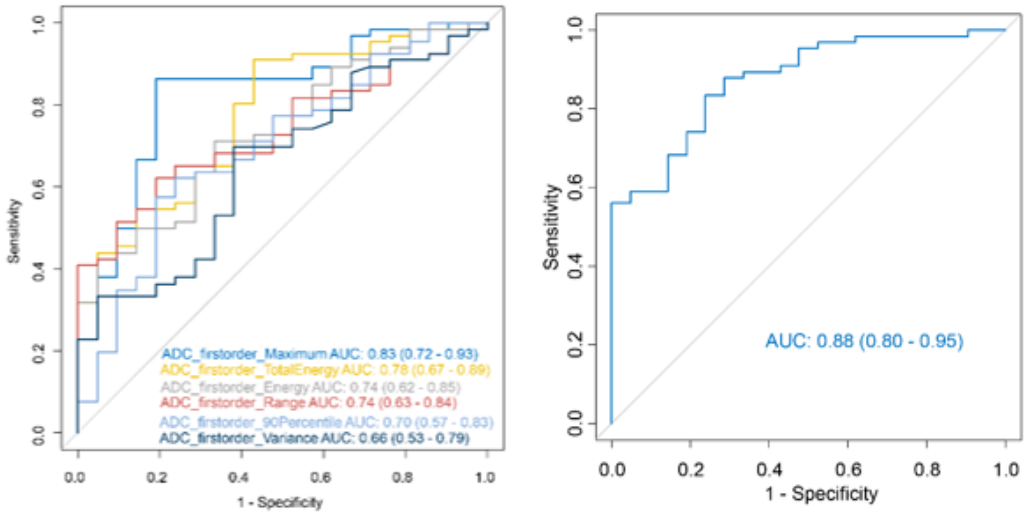

Figure 3

Predictive performances of significant histogram features and the final model.