Differentiating T1a-T1b from T2 in Gastric Cancer Lesions with Three Different Measurement Approaches Based on Contrast-enhanced T1W Imaging at 3.0 Tesla

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Abstract

Background

To explore the diagnostic value of three different measurement approaches in differentiating T1a-T1b from T2 gastric cancer (GC) lesions.

Methods

A total of 95 consecutive patients who performed preoperative MRI with T1a-T2 stage were retrospectively enrolled between January 2017 and November 2020. The parameters MRI T stage (subjective evaluation), thickness, maximum area and volume of the lesions were evaluated by two radiologists. Specific indices including AUC, optimal cutoff (if required), sensitivity, specificity, accuracy, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV) and negative predictive value (NPV) of MRI T stage, thickness, maximum area and volume for differentiating T1a-T1b from T2 staged lesions were calculated. The ROC curves were compared by the Delong test. Decision curve analysis (DCA) was used to evaluate the clinical benefit.

Results

The ROC curves for thickness (AUC = 0.926), maximum area (AUC = 0.902) and volume (AUC = 0.897) were all significantly better than those of the MRI T stage (AUC = 0.807) in differentiating T1a-T1b from T2 lesions, with *p* values of 0.004, 0.034 and 0.041, respectively. The values corresponding to the thickness (including AUC, sensitivity, specificity, accuracy, PPV, NPV, PLR and NLR) were all higher than those corresponding to the MRI T stage, maximum area and volume. The DCA curves indicated that the parameter thickness could provide the highest clinical benefit if the threshold probability was above 35%.

Conclusions

Thickness may provide an efficient approach to rapidly distinguish T1a-T1b from T2 staged GC lesions.

Background

Gastric cancer (GC) is the fifth most common cancer and has caused more than 780,000 deaths in 2018 worldwide (1). Early GC usually requires less intense treatment and exhibits better prognosis compared with advanced GCs. Patients with Tis and T1a stage lesions can receive minimal invasive treatment with endoscopic resection, whereas patients with T1b lesions can be treated by a direct surgery. In contrast to T1b lesions, patients presenting with T2 stage GC lesions prefer a perioperative chemotherapy to increase the probability for curative resection and to improve the survival rate according to the latest National Comprehensive Cancer Network (NCCN) Guidelines (2,3,4).

CT is the most conventional noninvasive preoperative assessment of GC, but it is reported that CT is not capable of measuring the depth of early GC or the rest normal tissue in deeper layer of gastric wall and most of the early GC were not able to detect due to its poor soft tissue resolution (5–7). However, magnetic resonance imaging (MRI) is a promising technique with high soft tissue resolution used in the evaluation of GC (8). Currently, no worldwide criteria have been defined with regard to T1 stage lesions (8–9). The majority of the previous studies described visible lesions that were enhanced in tissues that did not exceed the submucosal layer as T1 stage according to MRI (10–14). A limited number of studies described focal thickening of the inner layer of the gastric wall with slight enhancement as T1 stage tumors (15–16). The overall accuracy of diagnosing T1 stage by MRI ranged from 50 to 100% using a sample size of 1 to 12 (10–12, 14–17). These findings could be severely biased. Moreover, there was subjectivity in applying the aforementioned criteria and the observer agreement in evaluating the T1 and T2 stages with CE T1W imaging was moderate in some studies (13,16).

Other studies evaluated the diagnostic value of CT volumetry in T staging of GC tumors and demonstrated the ability of predicting the T1 stage, with a sample size of 19 and 13 patients, respectively and with an accuracy of 80.7% and 95% in differentiating T1 stage from other higher stages, respectively (18–19). Furthermore, the thickness of GC in untreated patients was relatively stable which is not affected by the degree of gastric filling (5). These results indicated high potential of this method for evaluating T staging in GC. To achieve optimal management for patient benefit, the accurate preoperative distinction of T1a-T1b from T2 stages is essential. To the best of our knowledge, the application of this diagnostic method has not been examined before, with the exception of the parameter tumor volume. Therefore, a precise and reproducible method of distinguishing T1 from T2 stage is vital.

The purpose of the present study was to investigate the diagnostic value of thickness in differentiating T1a-T1b from T2 GC lesions in CE MRI.

Methods

The present study was approved by our institutional review board and informed consent was waived for every patient.

Patients

We retrospectively reviewed the PACS of 661 consecutive patients with GC who underwent preoperative stomach MRI from January 2017 to November 2020. The present study included patients with pathologically confirmed primary GC who underwent surgery within 1 week following MRI examination and received pathological diagnosis in the end. Patients were excluded if the pathological T stages were T3, T4a or T4b and in case of preoperative therapy, such as chemotherapy, radiotherapy and endoscopic resection. Patients were excluded if they exhibited poor image quality resulting in poor visualization of lesions and in case of lesions that were undetectable in CE MRI. Two radiologists (Y.Y. and T.W. with both 10 years of experience in abdominal radiology, respectively) determined the detection efficacy in

consensus, according to the criterion of a definite visualization of the GC lesion. Sex, age, CEA level, CA199 level, CA724 level, BMI index of all included patients were recorded.

MRI acquisition

Each patient was fasted for at least 5 h and warm water (500 ml) was administered to dilate the stomach before the MRI examination. No drugs were injected to inhibit gastrointestinal peristalsis. All MRI examinations were performed on one scanner (3.0 T MAGNETOM Skyra, Siemens Healthcare, Germany). 18-channel phased-array body and integrated spine coils were applied to obtain the MRI signal. The sequences were uniformed as a settled image set as follows: axial T2W imaging, three dimensional T1W volume interpolated body examination (3D T1W VIBE) and three phases of contrast-enhanced (CE) T1W imaging (arterial, venous and delayed phases). The parameters for T2W imaging were as follows: TR, 4560 ms; TE, 79 ms; FOV, 380*380 mm^2; matrix, 320*320; flip angle 140°; slice thickness, 6 mm; gap, 1.2 mm; fat saturation, yes; acquisition time 3–4 min. The following parameters were used for CE T1W imaging: TR, 3.46 ms; TE, 1.32 ms; FOV, 308*380 mm^2; matrix, 195*320; flip angle 12° ; slice thickness, 3 mm; gap, 0 mm; fat saturation, yes; acquisition time, 14 s. The CE T1W images were obtained at 30, 60, 90 s following contrast injection, which consisted of 0.2 ml/kilogram body weight Gd-DTPA (Beilu, Beijing, China) delivered using an automatic power injector (Medrad Spectris Solaris EP MR Injector System, PA, USA) at 2 ml/s followed by a 20 ml saline flush at the same rate.

Image analysis

All images were transferred to GE PACS RA1000 for further analysis. Two abdominal radiologists (Y.Y. and T.W. with both 10 years of experience in abdominal radiology, respectively) who were aware of the existence but not aware of any other clinical information of all GC lesions were selected for independent evaluation of the location (three categories of fundus, body and antrum) and the MRI T stage (subjective evaluation of $\leq$ T1 or $\geq$ T2 with combination of T2W and CE T1W imaging). The researchers reached a consensus when encountered inconsistent diagnosis. The MRI T stage was determined according to the AJCC 8th edition GC staging. The MRI T stage criteria were as follows: enhanced tissues not exceeding the submucosal layer were termed T1a-T1b stage, whereas enhanced tissues exceeding the submucosal layer were termed T2 stage (10,20).

The parameters thickness, maximum area and volume were evaluated based on CE- T1W imaging (venous phase). The parameters thickness and drawing regions of interest (ROIs) were measured for all the lesions and were moved to the center of the screen and zoomed in two times in order to achieve more precise measurements by two radiologists. Thickness was measured at the thickest part of the maximum area which presented as abnormal high signal intensity perpendicular to the gastric wall direction (Fig. 1b). The regions of interest (ROIs) were drawn along the edge of the lesion according to abnormal signal intensity compared with the adjacent normal gastric wall on each slice within one week. The volume was estimated by the following formula: volume = sum of area of ROIs × slice thickness (57). The maximum area was selected from the ROIs (Fig. 1c). The average value of thickness, maximum area and volume was provided from two radiologists for final analysis.

Pathological evaluation

All specimens were pathologically confirmed as GC. The location and T stage were assessed. The T stage was determined according to the American Joint Committee on Cancer (AJCC, 8th edition). The tumor invasion of the lamina propria or muscularis mucosae was considered T1a, whereas the tumor invasion of the submucosa was considered T1b and the tumor invasion of the muscularis propria was condisered T2 (20). T1a and T1b were grouped together, whereas T2 was an independent group.

Statistical analysis

The Kolmogorov-Smirnov statistical test was performed to assess the normality in all continuous variables. The sample t test or Mann-Whitney U test were performed to compare continuous variables. The Chi-square test was performed to compare qualitative data. The parameters AUC, optimal cutoff (if required), sensitivity, specificity, accuracy, positive likelihood ratio (PLR), negative likelihood ratio (NLR), positive predictive value (PPV), negative predicative value (NPV) of MRI T stage, thickness, maximum area and volume for differentiating T1a-T1b from T2 lesions were calculated. The Delong test was performed to compare the ROC curves. Kappa or weighted Kappa coefficient was estimated to assess the interobserver agreement in the qualitative data. Kappa values > 0.8 indicated excellent agreement, whereas those from 0.6 to 0.8, 0.4 to 0.6, 0.2 to 0.4 and 0.0 to 0.2 indicated substantial, moderate, fair and slight agreement, respectively. Kappa values < 0.0 indicated poor agreement (21). The intraclass correlation coefficient (ICC) was performed in continuous variables (ICC = 0 to 0.49, poor agreement; ICC = 0.50 to 0.75, moderate agreement; ICC = 0.76 to 0.90, good agreement; ICC = 0.91 to 1.00, excellent agreement) (22). P 0.05 was considered to indicate significant differences. The MedCalc software (version 19.6.1) was used to calculate the weighted Kappa coefficient, perform ROCs and compare them. The decision curve analysis (DCA) was performed with R (R version 3.3.3) and the SPSS software (version 20.0) was used to perform other statistical analyses.

Results

Patients

Among the 661 patients, 566 patients were excluded since they exhibited stage T3, T4a and T4b (n = 405) lesions. A part of these patients received preoperative therapy (n = 28) and some of them exhibited an artifact that influenced visualization of the lesion in CE MRI (n = 13). A total of 120 patients presented with lesions that were undetectable in CE MRI (n = 120). Finally, 95 patients were included (Fig. 2).

Clinical and pathological characteristics

All 95 patients (65 males, 30 females, mean age 62 ± 12 [standard deviation] years, range from 26 to 84 years) were treated with surgery and exhibited pathological data. A total of 8 lesions were present of T1a stage, whereas 31 lesions of T1b stage and 56 lesions of T2 stage were also noted. The mean BMI index of all patients was 23.1 ± 3.4 [standard deviation] kg/m^2, range from 16.5 to 32.4 kg/m^2. The data for the

tumor markers CEA, CA199 and CA724 were missing in two patients. A total of 18 patients were present whose CEA levels were > 5 ng/ml, whereas 75 patients exhibited CEA levels ≤ 5 ng/ml. A total of 5 patients were selected whose CA199 level was > 37 U/ml, whereas 88 patients exhibited CA199 levels ≤ 37 U/ml. There were 9 patients with CA724 levels > 9.8 U/ml and 84 patients with CA199 levels ≤ 9.8 U/ml. A total of 27 lesions were located at fundus, whereas 17 lesions were located at the body and 51 lesions at the antrum. All clinical and pathological characteristics of the T1a-T1b and T2 stage are shown in Table 1.

Table 1
Clinical characteristics in patients with T1a-T1b and T2 GC lesions

Variable	**T1a-T1b (*n* = 39)**	**T2 (*n* = 56)**	***P* value**
Age (y)	61 ± 13	63 ± 12	0.396
Sex			
Male	25	40	0.450
Female	14	16	
BMI index (kg/m^2)	23.2 ± 3.1	23.1 ± 3.6	0.880
CEA level			0.175
≤5 ng/ml	34	41	
5 ng/ml	5	13	
Missing		2	
CA199 level			0.137
≤37 U/ml	39	49	
37 U/ml	0	5	
Missing		2	
CA724 level			0.106
≤9.8 U/ml	38	46	
9.8 U/ml	1	8	
Missing		2	
Tumor location			0.850
fundus	11	16	
Body	8	9	
Antrum	20	31	

Measurements

The median thickness of all patients was 5.650 mm [IQR, 4.400], ranging from 1.800 mm to 18.900 mm. The median maximum area of all patients was 149.500 mm^2 [IQR, 255.250], ranging from 10.600 mm^2 to 1788.100 mm^2. The median volume of all patients was 1680.600 mm^3 [IQR, 3437.250], ranging from 72.800 mm^3 to 50638.500 mm^3. The median thickness of T1a-T1b stage lesions (3.250mm, [IQR, 1.150]) was significantly lower than that of the T2 stage (6.650mm, [IQR, 5.300]) (p 0.0001) lesions (Fig. 1b). The median maximum area of the T1a-T1b stage (55.700mm^2, [IQR, 72.600]) lesions was significantly lower than that of the T2 stage (257.350mm^2, [IQR, 367.350]) (p 0.0001) lesions (Fig. 1c). The median volume of the T1a-T1b stage (471.600mm^3, [IQR, 806.100]) lesions was significantly lower than that of the T2 stage (3300.270mm^3, [IQR, 6387.980]) (p 0.0001) lesions. The MRI measurements in patients with T1a-T1b and T2 GC lesions are shown in Table 2.

Table 2
CE MRI measurements in patients with T1a-T1b and T2 GC lesions

Measurement	T1a-T1b (n = 39)	T2 (n = 56)	P value
Median thickness(mm)	3.250 (IQR, 1.150)	6.650 (IQR, 5.300)	0.0001
(range, mm)	1.800–7.000	2.650–18.850	
Median maximum area (mm^2)	55.700 (IQR, 72.600)	257.350 (IQR, 367.350)	0.0001
(range, mm^2)	10.600 -579.700	676.950–1788.050	
Median volume (mm^3)	471.600 (IQR, 806.100)	3300.270 (IQR, 6387.980)	0.0001
(range, mm^3)	72.750–6874.200	698.000–50639.000	

Observer agreement

The interobserver agreements between two radiologists are shown in Table 3. The agreement for the lesion location between the MRI and the pathology results was excellent (Kappa = 1.000, 95% CI: 1.000, 1.000). The interobserver agreements for the MRI T stage between the two radiologists was excellent (Kappa = 0.832, 95% CI 0.720, 0.943). The interobserver agreements for thickness, maximum area and volume were all excellent, with ICCs of 0.970 (95% CI 0.955, 0.980), 0.966 (95% CI 0.949, 0.977) and 0.958 (95% CI 0.938, 0.972), respectively.

Table 3
Interobserver agreements between two radiologists

Variable	Agreement (95%CI)
MRI T stage†	0.832 (0.720, 0.943)
Thickness*	0.970 (0.955, 0.980)
Maximum area*	0.966 (0.949, 0.977)
Volume*	0.958 (0.938, 0.972)
† kappa value	
* Intraclass correlation coefficient	

Diagnostic performance for differentiating T1a-T1b from T2 lesions

The comparison of the ROC curves (Fig. 3) indicated that the parameters thickness, maximum area and volume were all significantly higher than those at the MRI T stage in differentiating T1a-T1b from T2 lesions, with AUC values of 0.926 compared to 0.807 ($p = 0.004$), 0.902 compared to 0.807 ($p = 0.033$) and 0.897 compared to 0.807 ($p = 0.041$), respectively. No significant differences were noted with regard to the three ROC curves for the parameters thickness, maximum area and volume (thickness compared to maximum area, $p = 0.383$, thickness compared to volume, $p = 0.315$, maximum area compared to volume, $p = 0.315$). The optimal cut off values for thickness, maximum area and volume were 4.725 mm (Fig. 4), 132.625 mm^2 and 1343.850 mm^3, respectively. The values of the parameters sensitivity, specificity, accuracy, PPV and NPV in thickness were all higher than those in MRI T stage, maximum area and volume. The value of PLR in thickness was distinctly higher than that in the MRI T stage, maximum area and volume (12.205 compared to 3.645, 5.265 and 5.744). The NLR for the parameter thickness was lower than that noted for the parameters MRI T stage, maximum area and volume (0.14 versus 0.20, 0.183 and 0.209). The detailed data are shown in Table 4. The DCA curves indicated that thickness provided the most clinical benefit when the threshold probability was higher than 35% (Fig. 5).

Table 4
Indices of MRI T stage, thickness, maximum area and volume for differentiating T1a-T1b from T2 lesions

	MRI T stage	Thickness (mm)	Maximum area (mm^2)	Volume (mm^3)
AUC	0.807 (0.713,0.881)	0.926 (0.853,0.969) *	0.902 (0.823,0.954) *	0.897 (0.818,0.950) *
Optimal cut off	NA	4.725	132.625	1343.850
Sensitivity	0.846 (33/39)	0.872 (34/39)	0.846 (33/39)	0.821 (32/39)
Specificity	0.768 (43/56)	0.929 (52/56)	0.839 (47/56)	0.857 (48/56)
Accuracy	0.800 (76/95)	0.905 (86/95)	0.842 (80/95)	0.842 (80/95)
PPV(%)	0.717 (33/46)	0.895 (34/38)	0.786 (33/42)	0.800 (32/40)
NPV(%)	0.878 (43/49)	0.912 (52/57)	0.887(47/53)	0.873 (48/55)
PLR	3.645	12.205	5.265	5.744
NLR	0.200	0.138	0.183	0.209
P value*	NA	0.004	0.034	0.041

* Compared to MRI T stage, respectively by the Delong test.

Discussion

The present study indicated that the CE T1W imaging values of the variables thickness, maximum area and volume were significantly higher than those of the MRI T stage in differentiating T1a-T1b from T2 lesions, with AUCs of 0.926 compared to 0.807 ($p = 0.004$), 0.902 compared to 0.807 ($p = 0.034$) and 0.897 compared to 0.807 ($p = 0.041$), respectively.

One meta-analysis demonstrated that MRI is a good diagnostic technology for preoperative T staging of GC (23). Due to the low sensitivity for detecting early GC (23), a limited number of studies have been reported that examined the ability to differentiate T1a-T1b from T2 GC lesions in MRI. Liu S et al. reported that the accuracy of differentiating Tis-T1 from T2-T4 in CE MRI was 96.1% (49/51). However, the study only included 20 cases of Tis-T2 GC lesions and mixed cases with T3 and T4 lesions. These factors may result in imprecise evaluation in differentiating T1 from T2 (16) lesions. To achieve optimal management for patient benefit, the accurate preoperative distinction of T1a-T1b from T2 stage is particularly important. The present study included 95 lesions of the T1a-T2 stage and revealed that the indices AUC, sensitivity, specificity and accuracy for differentiating T1a-T1b from T2 lesions in MRI T stage were 0.807, 0.846, 0.768 and 0.800, respectively.

Two previous studies (18–19) evaluated the CT volumetry correlation with T stage in GC and demonstrated that CT volumetry was capable of distinguishing T1 stage from higher T stages in GC, which was consistent with our findings. The accuracies of differentiating T1 stage from higher T stages of the two previous studies were 95% and 80.7%, respectively (18–19). The optimal cut off values of CT volumetry for differentiating T1 from higher stages derived from the two studies were 19.4 and 8.2 cm^3 (18–19), respectively, which were both distinctly higher than the cutoff value noted in the present study (1.34cm^3). This inconsistency may be caused by the predominance of T4 stages in the studies reported previously or by the different methods used. However, the diagnostic value of thickness and maximum area for differentiating T1a-T1b from T2 GC lesions in MRI has not been previously investigated in the literature. According to our findings, the parameters thickness, maximum area and volume, based on CE T1W imaging, were all significantly higher than those noted in the MRI T stage in differentiating T1a-T1b from T2 lesions. This finding is consistent with previous findings reporting that CT volumetry was significantly better than CT T-staging in predicting ≥ T2 (18). The key point of differentiating T1a-T1b from T2 lesions in the MRI T stage is based on whether the lesion exceeds the submucosal layer. *Ex vivo* MR imaging studies demonstrated that this method can clearly depict the gastric wall layers (24–26). However, in clinical practice, it was not possible to clearly distinguish each layer of the gastric wall, including the muscularis propria. Even though we could distinguish the muscularis propria from time to time, we were usually not able to evaluate the association between lesion and the muscularis propria precisely due to technical restriction. Therefore, the evaluation of MRI T stage was subjective. However, the measurements of the lesions are considered relatively objective. We can focus on the objective measurement based on the abnormal signal intensity without evaluating the status of muscularis propria subjectively. The variables thickness, maximum area and volume demonstrated excellent observer agreement. These measurements may be used for clinical practice in the future.

No significant differences were noted between the three ROC curves corresponding to thickness, maximum area and volume. However, all the indices (containing sensitivity, specificity, accuracy, PLR, NLR, PPV, NPV) of thickness examined, exhibited the highest efficacy among these three approaches. PLR (value = 12.21) is a comprehensive indicator that exhibits more meaningful diagnostic value compared to other indicators when the value is higher than 10. According to the DCA curves, thickness may provide the best clinical benefit for differentiating T1a-T1b from T2 lesions compared to the other two indices (maximum area and volume) when the threshold probability is above 35%.

The present study exhibited certain limitations. Firstly, it was a retrospective study with inevitable selection bias and the sample size was not large. Secondly, we only used CE T1W imaging for evaluation and the values of other sequences, such as T2W imaging (27) and DW imaging (28) require further investigation. Thirdly, this was a single-center research study and additional centers are required to further confirm our findings.

Conclusions

In conclusion, all the three approaches, namely thickness, maximum area and volume that were based on CE T1W imaging provided better diagnostic performance than MRI T stage in differentiating T1a-T1b from T2 GC lesions. Thickness may provide the most efficient approach and gain the best clinical benefit among these three measurement approaches.

Abbreviations

GC	gastric cancer
MRI	magnetic resonance imaging
ROC	receiver operating characteristic curve
AUC	area under the curve
T1W	T1-weighted
CE	contrast-enhanced
T2W	T2-weighted
DW	diffusion-weighted
NCCN	National Comprehensive Cancer Network
CT	computed tomography
ROI	region of interest
AJCC	American Joint Committee on Cancer
ICC	intraclass correlation coefficient
PLR	positive likelihood ratio
NLR	negative likelihood ratio
PPV	positive predictive value
NPV	negative predicative value
DCA	decision curve analysis
IQR	interquartile range

Declarations

Ethics approval and consent to participate

This study was approved by Biomedical Research Ethics Committee of the Navy Military Medical University of the Chinese People ' s Liberation Army.

Consent for publication

Written informed consent was waived from each patient due to this retrospective study.

Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no conflict of interest.

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Authors' contributions

QH and SF conceived of the present idea. YY and SR designed the study. Data acquisition was performed by SR and TW. YY and SR performed the statistical analysis. YY, TW and contributed to the data analysis and interpretation. YY and SR were major contributors and contributed equally to writing the manuscript. All the authors read and approved the final manuscript.

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Figures

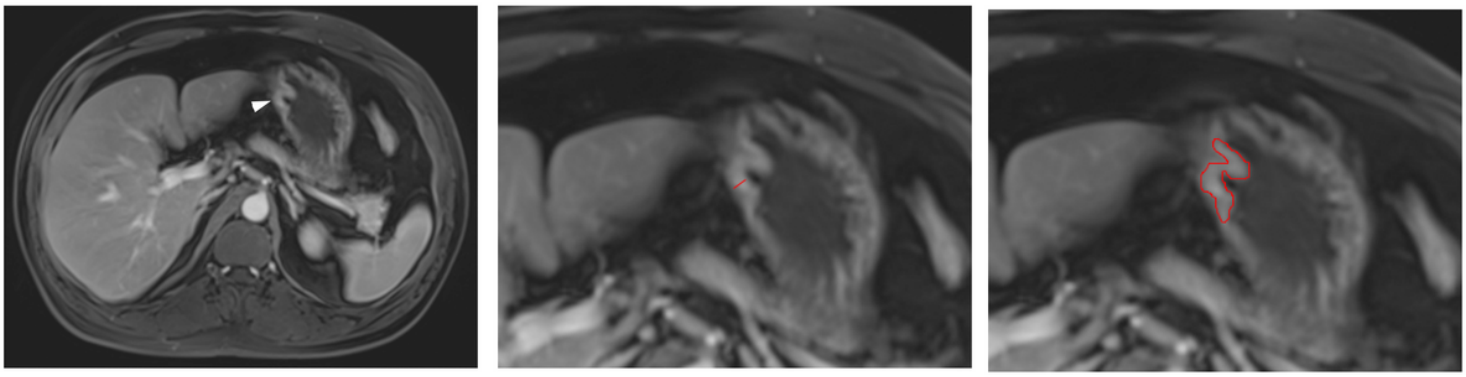

Figure 1

(a - c) A 58 year-old man with gastric body cancer (a, white arrowhead), with measurements of thickness 5.45 mm (b, red line), maximum area 174.15 mm2 (c, red ROI) and volume 2193.75 mm3, was grouped into T2 stage according to the optimal cut off values of thickness 4.725 mm, maximum area 132.625 mm2 and volume 1343.850 mm3.

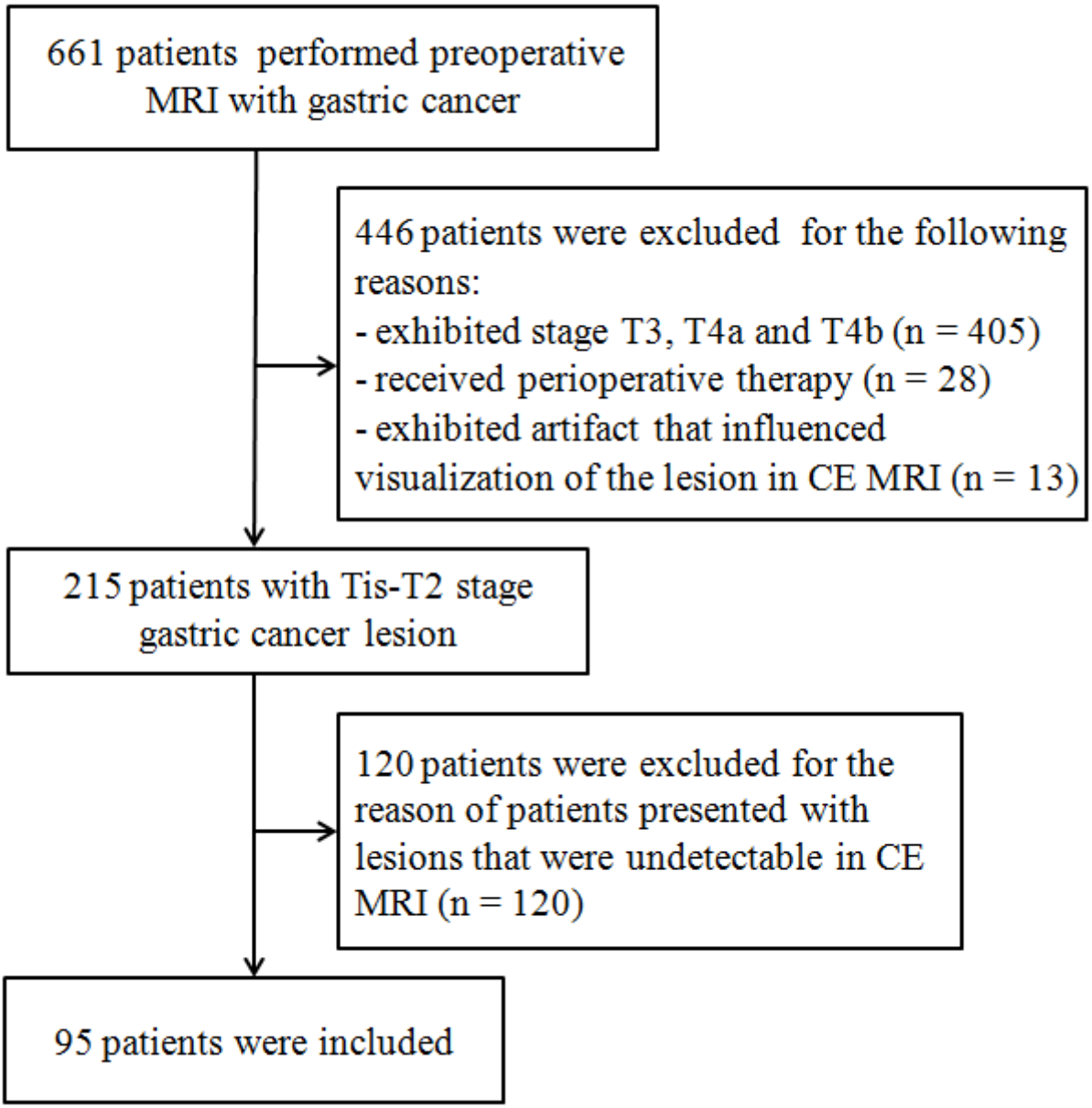

Figure 2

Flowchart shows the inclusion and exclusion criteria

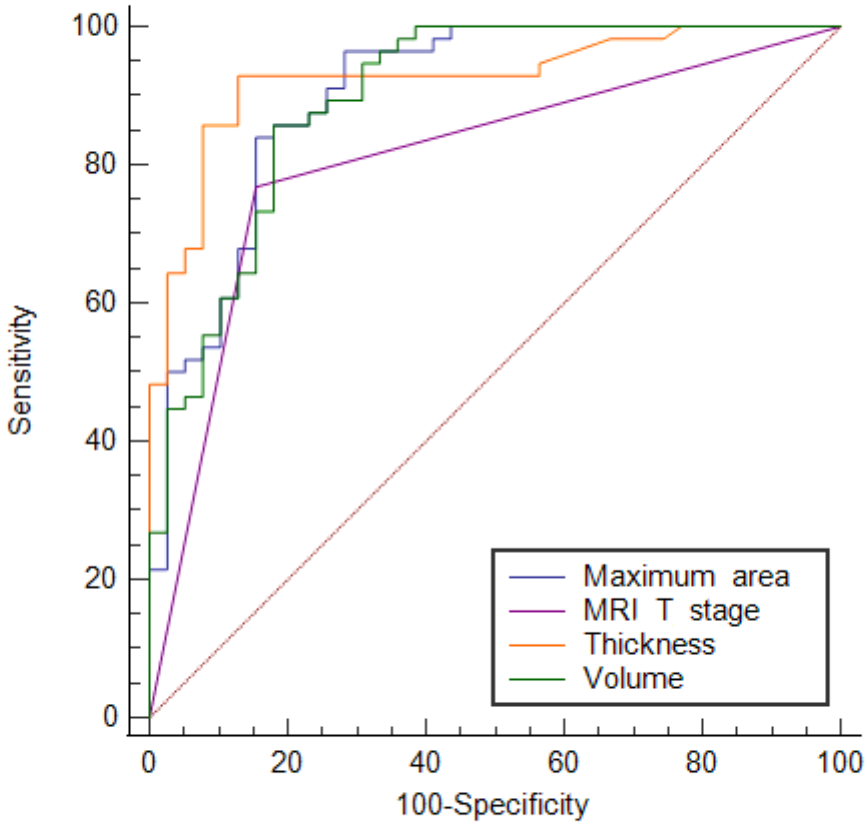

Figure 3

The ROC curves of MRI T stage, thickness, maximum area and volume for differentiating T1a-T1b from T2 lesions

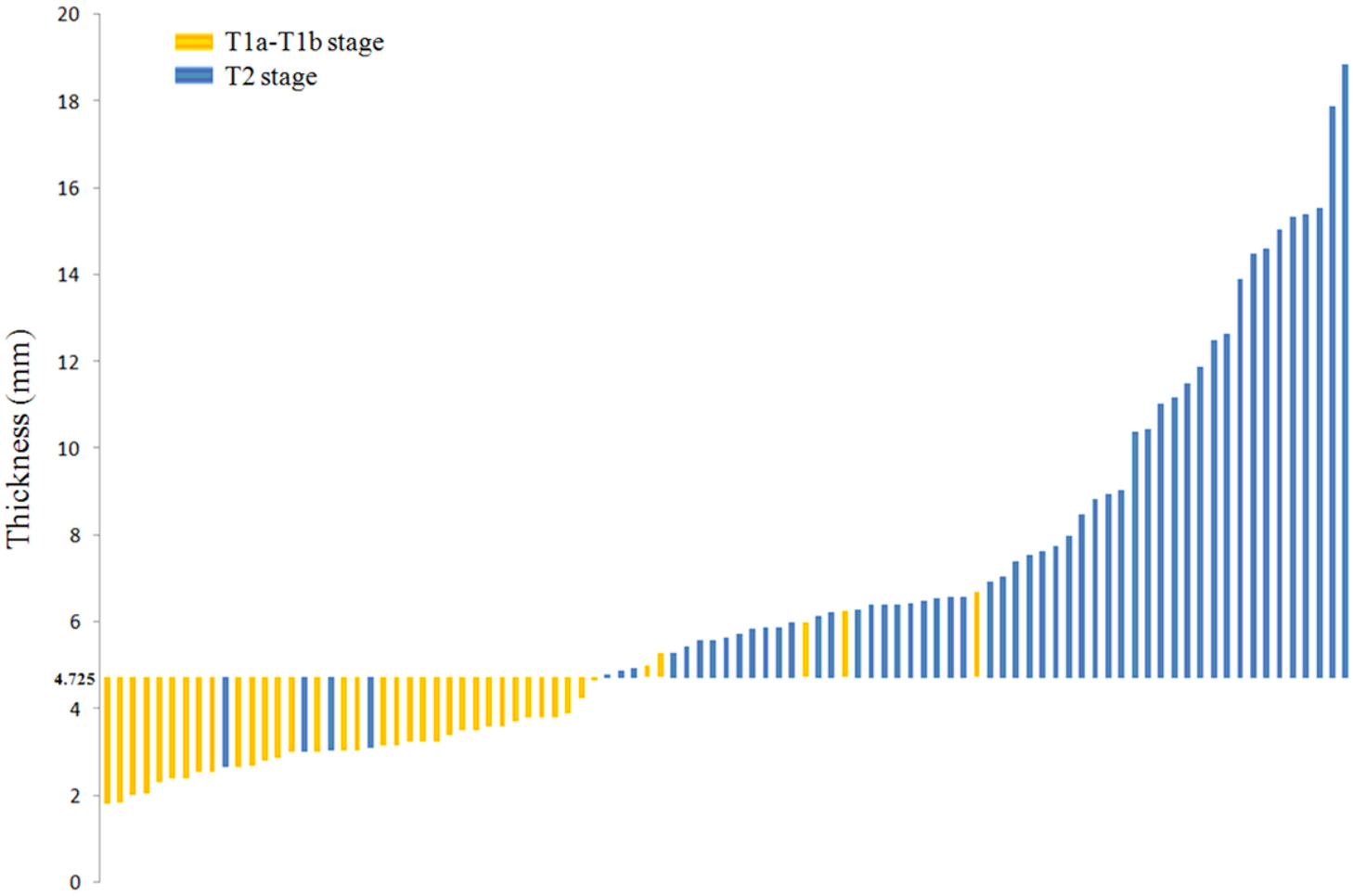

Figure 4

The thickness values for each lesion. The blue bars indicate the thickness value for T2 stages and the orange bars indicate the thickness value for T1a- T1b stages.

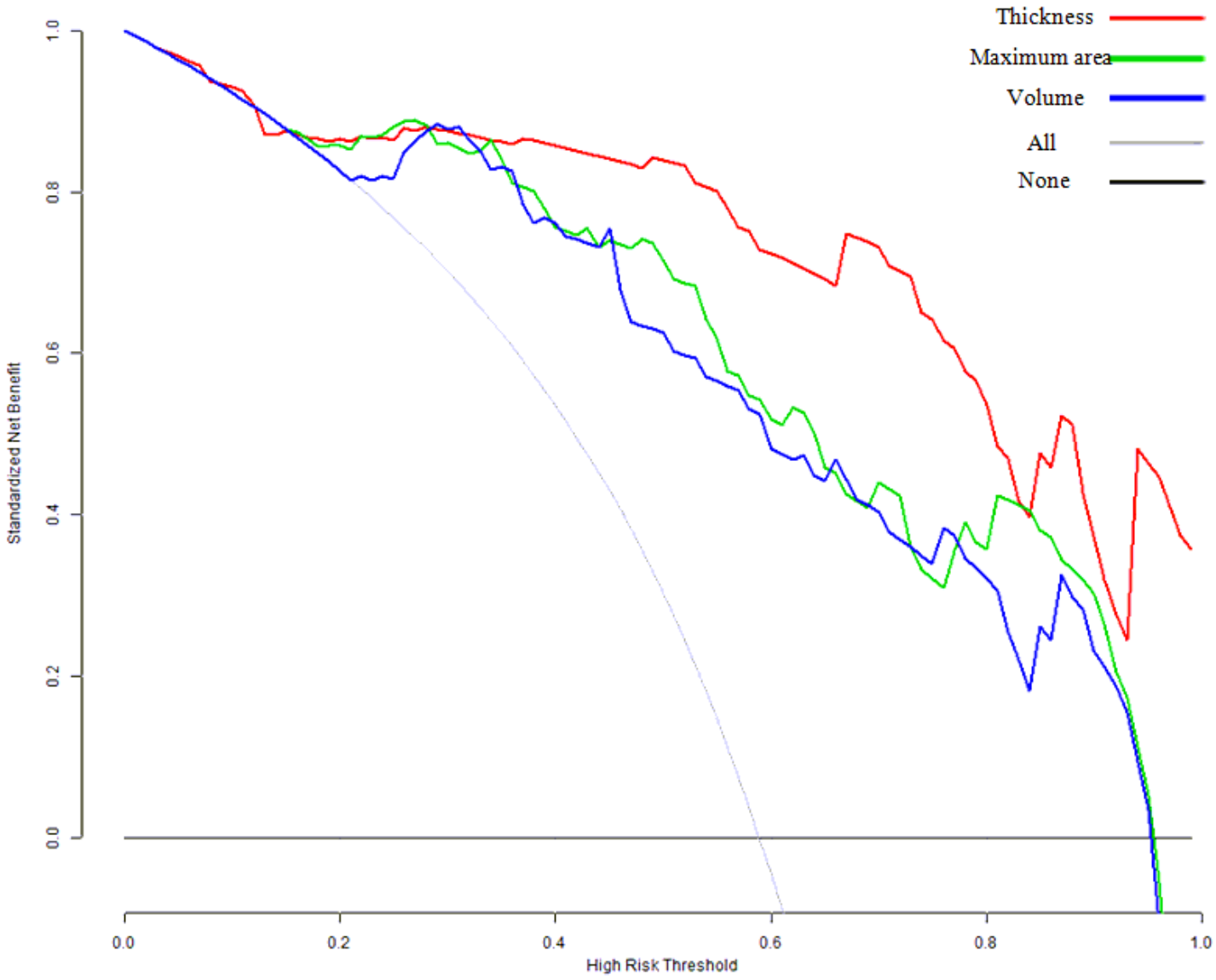

Figure 5

Decision curve analysis (DCA) for thickness, maximum area and volume in differentiating T1a-T1b from T2 lesions.