Distinguishing Gastric Anisakiasis From Non-Anisakiasis using unenhanced CT.

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Abstruct

OBJECTIVE: The primary endpoint of this study was to assess the diagnostic performance of unenhanced computed tomography (CT) for distinguishing gastric anisakiasis from non-anisakiasis gastric conditions. Secondary endpoint was to assess the reproducibility of CT findings.

Methods: Fifty-six anisakiasis cases and 74 non-anisakiasis cases that had gastric wall thickening on urgent unenhanced CT were included. Two radiologists independently assessed reproducibility of the CT findings those were “circumferential gastric wall thickening”, “gastric wall thickening extended more than two segments”, “convex-shaped and low-density gastric wall thickening”, “increase of peri-gastric fat density” and “ascites” using κ analysis. To evaluate including all CT findings with numerical value, we applied anisakiasis diagnostic score (ADS). Further more, to evaluate the ADS alternatively, we defined anisakiasis diagnostic prediction (ADP) using appropriate cut off value. Two radiologists re-assessed in consensus them and evaluated the sensitivity, specificity, accuracy of these CT findings including ADP and area under the curve (AUC) of ADS.

Results: Assessment of reproducibility, all but “circumferential gastric wall thickening” ($\kappa=0.499$) was substantially agreed ($0.6<\kappa<0.8$) with κ analysis.

About diagnostic performance, all but ascites were more frequently observed on anisakiasis cases with statistically significant. “Convex-shaped and low-density gastric wall thickening” scored highest sensitivity (98.1%). “Gastric wall thickening extended more

than two segments" showed highest specificity (79.7%). Sensitivity and specificity, accuracy of the ADP were 91.1% and 83.8%, 87.0% respectively. AUC was 0.902 ($P<0.05$). **Conclusion**; Unenhanced CT findings is useful on distinguishing Anisakiasis from non-Anisakiasis condition and reproducibility of the CT findings was sufficient.

Background;

Gastrointestinal anisakiasis is a nematode infection caused by ingestion of larvae infected raw or undercooked seafood(1-3). Every year, approximately 20,000 cases of anisakiasis are reported worldwide, with more than 90% from Japan and most of the other cases from Spain, the Netherlands, and Germany, depending on the habits of raw fish consumption (4-8). Small number of case was reported in other countries(9-12). However the frequency of the disease could be underestimated in other countries where the consumption of these dishes is less frequent because it can be easily misdiagnosed as appendicitis, gastric ulcer, or other food allergies (7, 13, 14). Recently Japanese food culture, for example sushi and sashimi, are getting accepted in the western country and it is expected to increase the gastrointestinal anisakiasis (4, 6, 15, 16).

Now then computed tomography (CT) is becoming a major diagnostic tool for patient who has abdominal symptom due to easy access and exam speed. Familiarity with the CT appearance of urgent gastric condition is important and radiologist may be the first to recognize gastric disease(17-19).

On the CT findings of gastrointestinal anisakiasis, marked submucosal edema of the gastric wall, vanishing tumor, increased attenuation of adjacent fat, and ascites were

reported (4, 20, 21). In actual practice, in addition to these findings, circumferential and broad wall thickeness are often observed in gastric anisakiasis patient.

Some retrospective case reviews were reported about the CT findings of gastric anisakiasis (3, 4, 20). However there is no study that compared gastric anisakiasis with other gastric conditions using CT findings.

Therefore the present study aimed to examine the ability of unenhanced CT in distinguishing gastric anisakiasis from other gastric conditions.

Materials and methods:

i) Patient population

The Institutional Review Board approved this retrospective study and waived the requirement to obtain informed consent from patients (Approved number: 27-356(8241)). Among 6,169 patients who underwent emergency gastro-duodenal endoscopy from October 2011 to December 2015, we selected patients with inclusion and exclusion criteria. Inclusion criterions were as follows; 1) Acute or subacute gastrointestinal symptom, for example abdominal pain, hematemesis, melena etc. 2) Examined whole abdominal unenhanced CT 3) Thickened gastric wall was recognized on unenhanced CT 4) Diagnosed as anisakiasis or other gastric conditions by gastro-duodenal endoscopy within before or after three days from CT acquisition. Exclusion criterions were as follows; 1) Esophageal or gastro-duodenal operation history 2) Gastro-duodenal perforation 3) Anisakiasis was suspected without anisakis larvae body 4) Foreign body placement (stenting, clipping) 5) Systemic edema caused by heart failure, hypoproteinemia, malnutrition 6) Hospitalized patients.

ii) CT acquisition:

All abdominal CT examinations were performed on 16 sections multi-detector raw CT system (Somatom Emotion, Siemens, Germany) featuring an automatic exposure control system (CareDose4D) in single institution. Scanning parameters included 1.2mm sectional collimation, pitch 0.8, effective tube current-time product 150 mAs and tube voltage 130 kVp. Axial images were reconstructed at 5mm slice thickness. All CT images were evaluated with only axial images.

iii) Image interpretation:

At first one abdominal radiologist (H.A 14 years of experience in abdominal imaging) preliminary evaluated the qualitative findings with knowing the clinical information and endoscopic results. Preliminary study was performed for the purpose of examines the usefulness of the CT findings. These CT findings were “circumferential gastric wall thickening”, “gastric wall thickening extended more than two segments”, “convex-shaped and low-density gastric wall thickening”, “increase of peri-gastric fat density”, “ascites” on unenhanced CT. Quantitative values were measured by the same radiologist in order to investigate whether numerical differences in thickened gastric wall were present between anisakiasis and non-anisakiasis patients. Those values were mean three-point CT value (Hounsfield unit: HU) on the thickened gastric wall and maximum diameter on that using the workstation (Synapse, Fuji film, Tokyo, Japan). These quantitative values were measured only this time. Mean three points CT values were selected in the mid depth region of the thickened gastric wall that did not include normal region nor mucosal nor

serosal surface. Maximum diameter of thickened gastric wall was measured the distance to the serosal surface from the mucosal surface on the maximum thickened wall portion. Univariate and multivariate statistical analysis were performed including all qualitative and quantitative data.

Blinded reading was conducted to assess the reproducibility of these qualitative CT findings. Another two radiologists (T.I 14 years and K.M 8 years of experience in the abdominal imaging) evaluated these five qualitative CT findings independently without knowing the clinical information and endoscopic result. Inter observer variability were evaluated with κ value. They re-assessed these CT findings in consensus to evaluate the diagnostic performance. In addition to these CT findings, we applied scoring method in order to evaluate including all these CT findings. Calculation of this score was aggregating one each point if the each CT finding was positive and 0 to 5 points were recorded for each cases. If there was a CT finding that demonstrated significantly large OR (odds ratio) on multivariate analysis in the preliminary study, one more point was added to the total score when that CT finding was positive at the stage of statistical processing. We defined this score as anisakiasis diagnostic score (ADS). Receiver operating characteristics (ROC) curve was created from ADS and the most appropriate cut off value was determined. To evaluate the ADS alternatively, anisakiasis diagnostic prediction (ADP) was determined as positive if anisakiasis diagnostic score was larger than or same as this cut off value. Area under the curve (AUC) of anisakiasis diagnostic score was calculated. Sensitivity, specificity, accuracy of these qualitative CT findings and ADP were evaluated with univariate analysis. And then these five CT findings were evaluated with multivariate

analysis.

Statistic analysis

Statistical analyses were performed by using Ekuseru-Toukei 2015 (SSRI, Tokyo, Japan). Mann-Whitney U test was used to compare the mean age, mean three points CT value, maximum diameter of thickened gastric wall because these data were not in accordance with the normal distribution. Qualitative CT findings were analyzed by using Fisher's exact test. For all analyses, $p < 0.05$ was considered statistically significant.

Binominal logistic regression analyses were used as multivariate analysis and examined the odds ratio for all CT findings including quantitative data on the preliminary study and two radiologist's consensus study evaluation for the qualitative CT findings.

For inter-observer variability assessment in terms of interpreting κ statistics were used to measure the degree of agreement. A value of up to 0.20 was interpreted as slight agreement, 0.21-0.40 fair agreement, 0.41-0.60 moderate agreement, 0.61-0.80 substantial agreement, and 0.81 or greater almost perfect agreement.

Result; Fifty six cases of gastric anisakiasis and 74 cases of non-anisakiasis gastric condition were included for this study. Patient demographics were shown on Table1. On the preliminary evaluation (Table2), circumferential gastric wall thickening, gastric wall thickening extended more than two segments, convex-shaped and low-density gastric wall thickening, increase of peri-gastric fat density, ascites were significantly observed more frequent in anisakiasis group on univariate analysis. Mean three points of CT value was significantly lower in akisakiasis (anisakiasis; 19.6 (4.4) HU vs non-anisakiasis 31.8 (8.3)

HU p<0.001) on univariate analysis. There was no significant difference between the two groups on maximum diameter of thieckened wall on univariate analysis (anisakiasis; 17.0 (3.1) mm vs non-anisakiasis 18.3 (10.2) mm p=0.79). There were also significant difference in Convex-shaped and low-density gastric wall thickening (OR; 105.7; P<0.001) and the mean three points of CT value (OR; 0.85; P=0.03) on multivariate analysis.

Inter observer variability, gastric wall thickening extended more than two segments (κ=0.607 P<0.001) and convex-shaped and low-density gastric wall thickening (κ=0.6969 P<0.001), increase of peri-gastric fat density (κ=0.633 P<0.001) and ascites (κ=0.724 P<0.001) were substantially agreed. Circumferential gastric wall thickening (κ= 0.449 P<0.001) was moderate agreement.

The result of two radiologist's consensus evaluation was given on Table3. Except for ascites, qualitative CT findings were observed more frequently in anisakiasis on univariate analysis (P<0.001). Convex-shaped and low-density gastric wall thickening showed the highest sensitivity (98.1%) and gastric wall thickening extended more than two segments showed the highest specificity (79.7%). ROC curve of anisakiasis diagnostic score was documented on Table4. Cut off point was decided as 4 because farthest point from diagonal line and the closest point from the upper left corner were matched in 4. AUC of anisakiasis diagnostic score was 0.902(P<0.001; 95% CI 0.847 – 0.958). Sensitivity and specificity, accuracy of ADP when cutt off value was set as 4 were 91.1% and 83.8%, 86.9% respectively. (Sensitivity and specificity, accuracy were 96.4% and 70.2%, 81.5% on cut off value 3, 75% and 87.8%, 82.3% on cut off value 5) . There were significant difference

in convex-shaped and low-density gastric wall thickening (OR: 86.0, 95%CI: 8.9-830.3 $p<0.001$) and gastric wall thickening extended more than two segments (OR: 6.2, 95%CI: 1.3-28.5, $p=0.02$) on multivariate analysis.

Discussion; Evaluated qualitative and quantitative CT findings of gastric anisakiasis were selected based on our experience and reports in previous literature(3, 4, 20). Each finding in preliminary study was statistically significant on univariate analyses and those were useful for diagnosis of gastric anisakiasis. Then two radiologists reviewed without clinical information and endoscopic result. Reproducibility of almost all CT findings in the blinded reading was substantially agreed. Unenhanced CT was sensitive for gastric anisakiasis especially the finding of convex-shaped and low-density gastric wall thickening. However, specificity of every CT finding was not enough high to rule out non-anisakiasis gastric conditions. ADP was helpful for distinguish from non-anisakiasis gastric conditions.

Almost all gastric anisakiasis expressed convex-shaped and low-density gastric wall thickening except for one case whose CT image was difficult to be recognized the thickened wall which was masked by fold redundancy because anisakis larvae protruded into esophago-cardial junction. High sensitivity of this finding was similar to the result that was reported on previous literature(20).

Increase of peri-gastric fat density showed high sensitivity (95%) and ascites showed not so high sensitivity (70%) on previous report (20). On the present study, increase of peri-gastric fat density showed high sensitivity (93%) similar to the previous study, however ascites showed very low sensitivity (41%). This difference occurred due to the

timing of CT acquisition or severity of inflammation. It is reported that ascites was feature of subserosal type in eosinophilic gastroenteritis correspond to mucosal or muscle layer type (22). Although there is difference in etiology between anisakiasis and eosinophlic gastroenteritis, however in terms of allergic gastroenteritis those eosinophils infiltrate, these pathological conditions were similar. On anisakiasis, different from eosinophilic gastroenteritis, at first larvae bite into mucosal surface and eosinophils emerge around larva body and infiltrate deeper in gastric wall. Ascites emerge when eosinophils came around serosal surface.

Mechanism of anisakis larvae invasion to gastric wall is documented that the larvae anchor to the stomach wall inducing direct damage and release the allergen ensue eosinophilic infiltration induce allergic reaction (23-26). Allergic reaction caused severe submucosal edema of gastric wall. This pathophysiology reflected the CT finding of convex-shaped and low-density gastric wall thickening. And this change became severe; the CT findings of gastric wall thickening extended more than two segments and circumferential gastric wall thickening may appear. More severe gastric anisakiasis was progressing, the more other findings such as increase of peri-gastric fat density and ascites would be emerged.

The specificity (75.7%) of convex-shaped and low-density gastric wall thickening was not enough higher than we expected. Submucosal edema is not specific for gastric anisakiasis, other gastric condition may cause submucosal edema if the disease was advanced or severe. The difference of pathophysiology between anisakiasis and non-anisakiasis is the presence of allergic reaction. That may induce vascular permeability and resulted in severe and wide

range edema. In non-anisakiasis gastric conditions, when inflammatory reaction or tumor invasion spread widely, gastric wall can mimic gastric anisakiasis on unenhanced CT. Specificity was increased up to 83.8% on ADP, however there was no appropriate CT finding combination with convex-shaped and low-density gastric wall thickening that can increase the specificity. Although ADP showed high specificity, it was difficult to completely exclude non-anisakiasis gastric condition.

Among non-anisakiasis conditions, the major gastric condition that represented the convex-shaped and low-density gastric wall thickening was gastric ulcer (n=12/18). The CT findings of gastric anisakiasis and gastric ulcer were overlapping (27). To distinguish these two conditions, gastric wall crater should be recognized. We reviewed CT images (Not applied to this study) of gastric ulcer cases with convex-shaped and low-density gastric wall thickening, crater was recognized on 50% (6/12) cases. Early investigation into the diagnosis of gastric and duodenal ulcers utilizing CT has suggested that ‘‘CT has no clinically useful role in detecting uncomplicated peptic ulcer disease’’(28). On the recent report, sensitivity of contrast enhanced CT for gastric ulcer is still low, however sensitivity was raised on contrast enhanced CT with multi planar reconstruction (MPR). And ulcer that was relatively large could be detected on enhanced CT (27). Although only axial unenhanced CT was evaluated on our study, detectability of ulcer crater could be raised up and distinguish gastric anisakiasis from non-anisakiasis condition more exactly with contrast enhanced CT with MPR.

About reproducibility of the CT findings, circumferential thickened wall showed lower κ value. It was difficult to evaluate around the gastric wall using only axial image.

Unfortunately MPR has not been created in all examination. Anterior and posterior wall can be easily evaluated accurately but evaluation of superior and inferior walls were difficult on the axial image. It is reported that MPR image on CT increased the sensitivity and accuracy for gastric ulcer(27).

Our study has several limitations. 1) Retrospective single institutional study. 2) The number of patients examined was relatively small. 3) We did not consider the physiological ascites of young women. It may cause that ascites did not show significant difference on this study. 4) Intravenous contrast enhancement and MPR should be used to evaluate gastric crater more exactly to distinguish gastric anisakiasis from gastric ulcer. Further evaluation is needed considering these factors.

In conclusion, the finding of convex-shaped and low-density gastric wall thickening on unenhanced CT for diagnosis of gastric anisakiasis was sensitive. ADP was useful for differentiating from gastric ulcer. Even thought gastric ulcer is most difficult differentiation of gastric anisakiasis on unenhanced CT image only, however these can be distinguished more exactly with contrast enhanced CT using MPR image.

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Table1. Patient demographics

	Anisakiasis group	Non-anisakiasis group	p-value
Patient number	56	74	
Sex, male	40	46	0.27
Age(years), mean(range)	42.8(28-74)	65.9(28-96)	p<0.001
Symptom	Chest pain 2	Abdominal pain 35	
	Abdominal pain 54	Melena 24	
		Hematoemesis 6	
		Other 9	
Diagnosis	Gastric anisakiasis 56	Gastric ulcer 46	
		Gastric cancer 13	
		Gastritis 12	
		SMT 1	
		Metastatic gastric tumor 1	
		Lymphoma 1	

SMT submucosal tumor

Table2. Result of preliminary study

			Univariate	Multivariate	
	Anisakiasis	Non-anisakiasis	p-value	p-value	OR (95%CI)
Maximum diameter of thickened wall (mm) Mean(SD)	17(3.1)	18.3(10.2)	0.34	0.0502	
3 point of CT (HU) Mean (SD)	19.6(4.4)	31.8(8.3)	<0.001	0.03	0.85(0.73-0.98)
Circumferential gastric wall thickening			<0.001	0.95	0.94(0.14-6.4)
Positive	41	31			
Negative	15	43			
Gastric wall thickening extended more than two segments			<0.001	0.84	1.3(0.13-12.7)
Positive	49	15			
Negative	7	59			
Convex-shaped and low-density gastric wall thickening			<0.001	<0.001	105.7(9.2-1209.2)
Positive	55	18			
Negative	1	56			
Increase of peri-gastric fat density			<0.001	0.86	5.4(0.79-37.5)
Positive	52	31			
Negative	4	43			
Ascites			0.09	0.13	6.1(0.6-62.1)
Positive	23	19			
Negative	33	55			

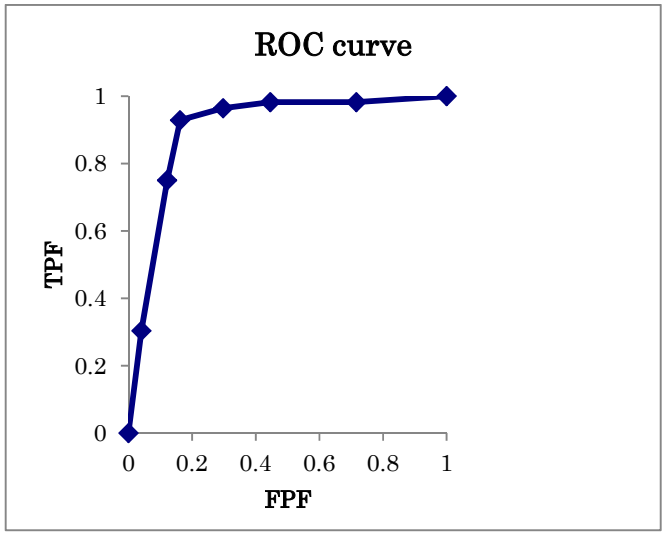
HU housefield unit, OR odds ratio, SD standard deviation

Table3. Diagnostic performance for gastric anisakiasis on consensus evaluation

				Univariate	Multivariate	
	Sensitivity	Specificity	Accuracy	p-value	p-value	OR (95%CI)
Circumferential gastric wall thickening	73%	58%	64%	<0.001	0.29	0.46 (0.11-1.93)
Gastric wall thickening extended more than two segments	87%	80%	83%	<0.001	0.02	6.16 (1.33-28.49)
Convex-shaped and low-density gastric wall thickening	98%	76%	85%	<0.001	<0.001	85.89 (8.88-830.29)
Increase of peri-gastric fat density	93%	58%	73%	<0.001	0.49	1.85 (0.32-10.6)
Ascites	41%	74%	60%	0.09	0.88	0.91 (0.28-2.96)

OR: odds ratio

Table4.ROC curve of ADS



TPF: true positive fraction, FPF: false positive fraction.
AD: Anisakiasis diagnostic score.
ROC: Receiver operating characteristics.
AUC (area under the curve): 0.9 (95% CI; 0.85-0.96, p<0.001).
Farthest point from diagonal line was 4.
Closest point from the upper left corner was 4.

a. b.

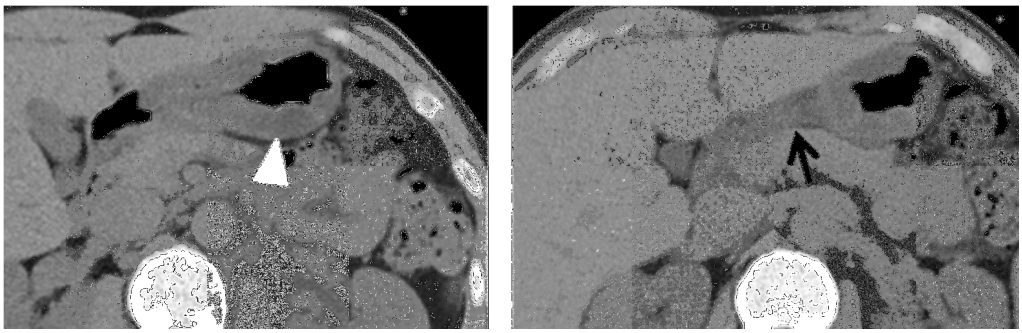


Fig 1. 40years old male who complaint acute abdominal pain, anisakis larve was removed by gastro-duodenal endoscopy. a) Convex-shaped and low-density gastric wall thickening (white arrow head) with the finding of gastric wall thickening extended more than two segments and circumferential gastric wall thickening was seen on unenhanced CT. b) Increase of peri-gastric fat density (arrow) was identified more cephalad level of the same CT series.

a b

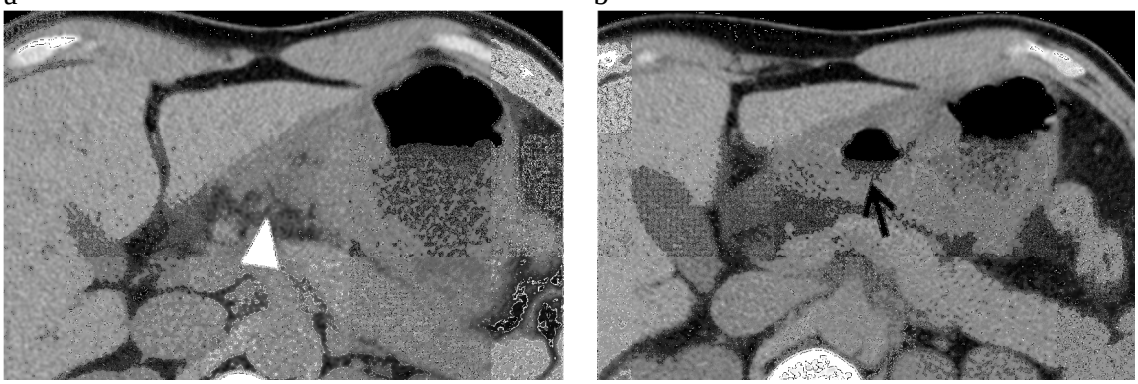


Fig 2 A 42 years old male patient who complaint acute abdominal pain revealed gastric ulcer by gastro-duodenal endoscopy. a) Increase of peri-gastric fat density (white arrowhead) was seen on unenhanced CT. b) Convex-shaped and low-density gastric wall thickening with large crater (arrow) was identified on the lower level of the same CT series.