Peer Review File

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Reviewer A

Interesting paper

Questions:

Comment 1:

1) Most people get PET scans for gastric adenocarcinoma. Is this protocol for timing going to interfere with that.

Reply 1: We appreciate the reviewer for pointing out this important point. PET plays a crucial role in the preoperative assessment of gastric adenocarcinoma metabolism, metastasis, and postoperative recurrence, only approximately one-third of the patients with hepatoid adenocarcinoma of the stomach and conventional gastric adenocarcinoma included in this retrospective study underwent PET prior to surgery. However, all patients underwent unenhanced and enhanced CT scans. The preoperative differentiation between hepatoid adenocarcinoma of the stomach and conventional gastric adenocarcinoma in this study primarily relied on clinical, serum biochemical, and CT indicators. In the subsequent study, we will investigate the utility of PET in distinguishing and prognosticating hepatoid adenocarcinoma of the stomach from conventional gastric adenocarcinoma by expanding our sample size.

Changes in the text: Page 14, Line 283-284: “PET plays a crucial role in the preoperative assessment of gastric adenocarcinoma metabolism, metastasis, and postoperative recurrence.”

Comment 2:

2) What is the cost of this method v traditional CTs has HAS is so uncommon.

Reply 2: The reviewer's kind advice is greatly appreciated. The increased cost of CT-based radiomics nomogram, in comparison to traditional CT, primarily encompasses the expenses associated with serum biochemical examination (AFP) for patients and the time required for doctors to delineate lesions during clinical application. However, these additional costs do not

impose an excessive burden on patients. CT-based radiomics nomogram is recommended as an adjunctive tool for prediction, particularly when clinical, serum biochemical, and CT indicators suggest potential indications. However, it should be noted that pathological diagnosis remains the definitive standard.

Changes in the text: Page 13, Line 268-272: "The increased cost of CT-based radiomics nomogram, in comparison to traditional CT, primarily encompasses the expenses associated with serum biochemical examination (AFP) for patients and the time required for doctors to delineate lesions during clinical application. However, these additional costs do not impose an excessive burden on patients."

Comment 3:

3) You mention Tstage in the introduction. Can this method be used to predict Tstage similar to rectal MRI? I imagine not, but that would make it extremely clinically useful.

Reply 3: We appreciate the reviewer's kind advice and express our gratitude for the valuable insights. The present study aims to explore the potential of CT-based radiomics nomogram in distinguishing gastric adenocarcinoma from conventional gastric adenocarcinoma, as well as predicting T stage, which could serve as a promising avenue for future research endeavors for clinical diagnosis and treatment.

Changes in the text: Page 14, Line 284-287: "Eventually, with further exploration into the depth of infiltration prediction, postoperative long-term quality of life, and automated segmentation, radiomics analysis has the potential to yield more significant advancements in terms of HAS and CGA."

Reviewer B

This study aimed to develop predictive model for the diagnosis of hepatoid adenocarcinoma of the stomach compared with conventional gastric adenocarcinoma using CT-based radiomics nomogram.

Questions:

Comment 4:

Authors showed superior diagnostic performance of nomogram to those of AFP-only or radiomics score-only models in the diagnosis of hepatoid adenocarcinoma of the stomach (HAS). However, they did not explain why the radiomics (Radscore) showed significant differences and how the nomogram worked to differentiate the two tumor groups.

Reply 4: We greatly appreciate the valuable comments provided by the reviewer. The significant differences observed in the radiomics (Radscore) between hepatoid adenocarcinoma of the stomach and conventional gastric adenocarcinoma may be attributed to variations in pathological structures. The origin of hepatoid adenocarcinoma in the stomach is from the gastric mucosa. The hepatocellular differentiation area in HAS can coexist with the adenocarcinoma area, whereas CGA exclusively consists of the adenocarcinoma area. Radscore is derived from radiomics features that have been selected through a high-throughput radiomics feature selection process. In this study, it serves as an independent predictor for preoperative distinguishment between hepatoid adenocarcinoma of the stomach and conventional gastric adenocarcinoma, may suggesting the presence of hepatocellular differentiation area.

How the nomogram worked to distinguish the two groups is of great clinical significance. CT-based radiomics nomogram consisted of five components: Points, Radscore, AFP, Total Points, Predicted Probability. The initial "Points" scale was devised to assign scores for each predictor. The final predicted probability is determined by combining the scores derived from AFP and Radscore.

Changes in the text: Page 13, Line 259-265: “The hepatocellular differentiation area in HAS can coexist with the adenocarcinoma area, whereas CGA exclusively consists of the adenocarcinoma area. Radscore is derived from radiomics features that have been selected through a high-throughput radiomics feature selection process. In this study, it serves as an independent predictor for preoperative distinguishment between hepatoid adenocarcinoma of the stomach and conventional gastric adenocarcinoma, which may suggest the presence of hepatocellular differentiation area.”

Page 11, Line 215-219: “AFP and Radscore are integrated into the nomogram. CT-based radiomics nomogram consisted of five components: Points, Radscore, AFP, Total Points, Predicted Probability. The initial "Points" scale was devised to assign scores for each predictor.

The final predicted probability is determined by combining the scores derived from AFP and Radscore. Fig. 3 illustrates the CT-based radiomics nomogram."

Comment 5:
Introduction and discussion lack appropriate questions and problem statements; the rationale for preoperative prediction of HAS, and the analysis of the results in comparison with or in additional to other similar studies.

Reply 5: We appreciate the reviewer for pointing out this important point. Introduction and discussion sections are deficient in appropriate interrogations, formulations, as well as a comprehensive rationale for analyzing the results in comparison with or in addition to other studies. Relevant supplementary content has been added to the introduction and discussion sections.
Changes in the text: Page 3, Line 52-53, 58-59: "The clinical manifestations and imaging features of HAS and conventional gastric adenocarcinoma (CGA) are similar." "The preoperative identification of HAS from CGA holds significant clinical importance."
Page 4-5, Line 83-88: "CT-based radiomic analysis is hypothesized to be a valuable approach for augmenting the detection rate of HAS. Therefore, it is imperative to develop a reliable CT-based radiomics prediction model that encompasses both clinical predictors and radiomics signatures for the identification of HAS. The aim of this study is to establish a valuable noninvasive method for identifying HAS from CGA dependent on the construction of radiomics nomogram prior to surgery."
Page 12, Line 239-242: "The clinical manifestations and imaging features of HAS are similar to that of CGA. However, the surgical procedure for HAS is more complex and the prognosis is worse compared to CGA. The preoperative differentiation of HAS should be given immediate priority."

Comment 6:
Furthermore, the methods section lacks many aspects of detailed study design;
Patient selection- HAS is a very rare tumor compared to conventional gastric cancer (CGA), therefore inclusion & exclusion criteria should be elaborated in the manuscript including the

selection process of CGA group (time period, consecutiveness, total number of patients, random selection, etc.)

Reply 6: The reviewer's kind advice is greatly appreciated. Detailed information regarding the inclusion and exclusion criteria, including the process for selecting the CGA group (such as the time period, consecutiveness, total number of patients, random selection method, etc.) was illustrated in

Changes in the text: Page 5, Line 93-103: "The eligibility criteria for HAS were delineated as follows: (1) Surgical pathology diagnosis of HAS. (2) No history of other tumors. (3) Unenhanced and multiphase enhanced CT conducted one week before surgery. (4) Without neoadjuvant chemotherapy or radiotherapy. The exclusion criteria for HAS were outlined as follows: (1) Stomach with insufficient distension. (2) Pathological biopsy before CT examination. (3) Diameter of the tumor <5 mm. (4) Poor quality of CT images. Patients with CGA were systemically selected to ensure a match between HAS and CGA based on age, gender, and clinical T stage. The patients were randomly allocated in a 7:3 ratio. 59 patients with HAS and 122 patients with CGA enrolled in this study were divided into the training and test cohorts. The training cohort comprised 126 patients, and the test cohort encompassed 55 patients."

Comment 7:

CGA group was matched by age, gender, clinical T stage to those of HAS in the Fig.1 flow chart, then the T stage may not show difference between the two group in Table 1.

As for T stage, the authors included cT1-2 tumors, but these tumors are usually diagnosed in endoscopy, and not visible on CT scan. How did they assess and draw ROI on this early stage tumor?

Reply 7: We appreciate the reviewer's kind advice. Gastric tumors are typically diagnosed through endoscopy prior to surgery, primarily due to its efficacy in identifying clinical T stage. Early-stage tumors are typically imperceptible on unenhanced CT scans; however, their visibility can be enhanced through the administration of contrast medium. Supplementary Table 1 presenting clinical T stage on CT scan is attached below. In this study, endoscopy was performed

before operation for some patients, while all patients underwent both plain and enhanced CT scans. Consequently, the assessment of clinical T stage of lesions primarily relies on CT features.

Changes in the text: Supplementary Table 1.

Table S1 Pathological manifestations and CT features of clinical T stage

clinical T stage	Pathological manifestations	CT features
cT1	Invasion of mucosa or submucosa	Continuous and hypo-density band between apparent enhanced tumor and slightly hyper-density muscle layer
cT2	Invasion of the musculi propria	Intermediate hypo-density stripes are interrupted and disappear, while the outer residual portion exhibits slightly hyper-density in the musculi propria
cT3	Penetration of the subserous connective tissue, without invading the visceral peritoneum	Apparent enhanced lesion invades the entire wall of the stomach, with the serosal surface being smooth or having only a few short fine cords
cT4a	Invasion of the visceral peritoneum but not adjacent structures	An irregular or nodular appearance on the serosal surface, with dense spicules or stripe-like infiltration in perivisceral adipose tissue
cT4b	Invasion of adjacent structures	Perivisceral adipose tissue adjacent to the surrounding structures disappear

Comment 8:

CT features- there are many additional imaging features to evaluate such as tumor size, depth of invasion, perigastric fat infiltration, enhancement pattern, degree of enhancement, presence of LN metastasis, hepatic metastasis, portal vein thrombosis etc. (several known + 3

imaging/clinicopathologic features of HAS should be considered in both radiologic assessment and nomogram generation)

Reply 8: We greatly appreciate the valuable comments provided by the reviewer. The comprehensive identification of HAS should encompass clinical, imaging, and pathological parameters. The imaging features include tumor size, depth of invasion, perigastric fat infiltration, enhancement pattern and degree, LN metastasis, hepatic metastasis, and portal vein thrombosis.

In our study, the maximum diameter serves as an indicator of tumor size, while clinical T stage provides insights into the depth of invasion and presence of perigastric fat infiltration. The enhancement pattern is classified into heterogeneous and homogeneous enhancement. To a certain extent, the CT density of lesions on unenhanced, arterial, portal, and delayed phases reflects the degree of enhancement. These parameters were analyzed in both the hepatoid adenocarcinoma of the stomach group and conventional gastric adenocarcinoma group. The construction of a CT-based radiomics nomogram involved the incorporation of AFP and Radscore, which exhibited a statistically significant P value (<0.05) in the multivariate analysis. Consequently, indicators that did not demonstrate any statistical difference in both univariate and multivariate analyses were excluded from the development of the nomogram.

The identification of LN metastasis requires pathological results, as multiple enlarged lymph nodes can occur in a patient due to inflammation and malignant transformation. Prior to surgery, accurate diagnosis of hepatic metastasis can be achieved through enhanced CT and MR scans. The incidence rate of portal vein thrombosis in gastric cancer is relatively low compared to that of hepatic cellular carcinoma. Computed tomography venography may be required for preoperative imaging diagnosis of portal vein thrombosis in the trunk and/or branches. The parameters of LN metastasis, hepatic metastasis, and portal vein thrombosis should be taken into consideration in our further study based on a comprehensive examination.

Changes in the text: Page 14, Line 277-287: “Secondly, the inclusion of supplementary imaging features may be necessary in subsequent investigations through a comprehensive imaging examination. The identification of LN and hepatic metastasis may necessitate enhanced CT and MR scans; however, an accurate diagnosis is contingent upon pathological findings. Computed tomography venography may need underwent for imaging diagnosis of portal vein thrombosis in

the trunk and/or branches. PET plays a crucial role in the preoperative assessment of gastric adenocarcinoma metabolism, metastasis, and postoperative recurrence. Eventually, with further exploration into the depth of infiltration prediction, postoperative long-term quality of life, and automated segmentation, radiomics analysis has the potential to yield more significant advancements in terms of HAS and CGA."

Comment 9:

Radiomics- example of ROI segmentation, radiomics features that studied and useful features selected can be presented with figures and tables.

Reply 9: We appreciate the reviewer's kind advice. The ROI segmentation example was illustrated in Figure 1b. Workflow of radiomics encompasses five sequential steps: (a) Imaging Delineation; (b) Feature Extraction; (c) Feature Selection; (d) Model Training; (e) Validation. The selection of radiomics features was illustrated in Figure 2 and useful radiomics features were presented in Table 2.

Changes in the text:

Figure 1

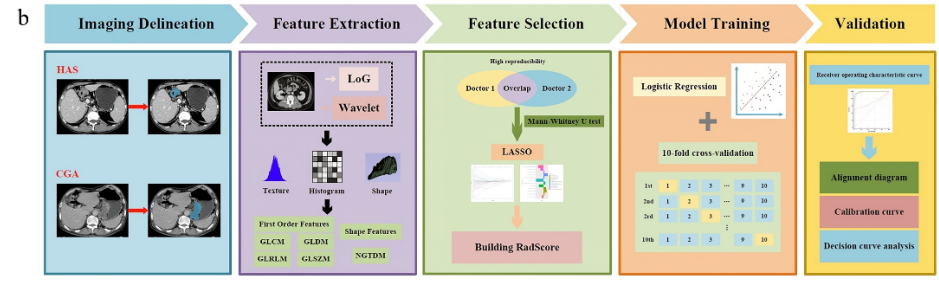

Fig.1 **a** Flowchart of patient enrolled process. **b** Workflow of radiomics encompasses five sequential steps: (a) Imaging Delineation; (b) Feature Extraction; (c) Feature Selection; (d) Model Training; (e) Validation.

Figure 2

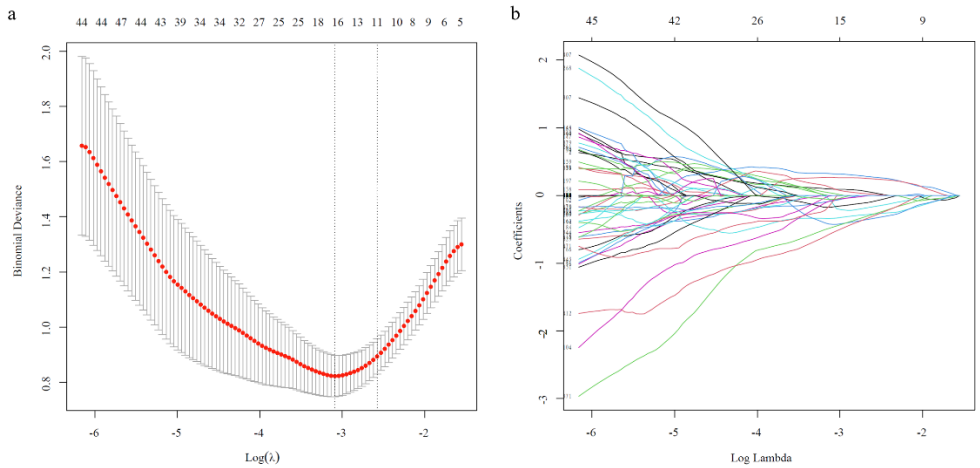

Fig. 2 Radiomic features selection through the LASSO regression. **a** The multinomial deviance was plotted against the logarithm of λ, with red dots representing the average deviance values for each model at a given λ and a vertical line indicating optimal values determined by using minimum criteria where 15 features had non-zero coefficients. **b** LASSO coefficient profiles depicted the coefficients of radiomic features, with each colored line representing a feature.

Table 2. Useful_features after LASSO in the training cohort

Useful_features after LASSO	Coefficients
(Intercept)	-0.947607813
wavelet.HHH_firstorder_Maximum	-0.548949393
wavelet.HHL_glcm_Imc2	-0.468042456
wavelet.HLH_glcm_InverseVariance	-0.42637156
log.sigma.3.0.mm.3D_firstorder_Skewness	-0.337821351
log.sigma.3.0.mm.3D_glszm_ZoneEntropy	0.320295709
wavelet.LLH_glcm_Imc2	0.266089709
log.sigma.3.0.mm.3D_glcm_ClusterShade	-0.169327246
original_firstorder_90Percentile	-0.112368092
wavelet.HHL_glcm_Correlation	0.107557756

wavelet.LLL_firstorder_90Percentile	-0.09326564
original_shape_MajorAxisLength	0.092442496
original_shape_Sphericity	-0.079912906
log.sigma.4.0.mm.3D_glcm_ClusterShade	-0.070496245
wavelet.LLL_firstorder_Mean	-0.054802644
original_shape_Maximum2DDiameterRow	0.032665275

Comment 10:

The nomogram is too simple, consisting of only two factors, and in addition, the clinical significance of this nomogram is poorly understood, although it showed good diagnostic performance.

Reply 10: We greatly appreciate the valuable comments provided by the reviewer. The indicators that showed statistically significant differences in the univariate analysis of the training cohort were included in a binary multivariate logistic regression analysis, and those with a P value less than 0.05 for AFP and Radscore were utilized to construct a CT-based radiomics nomogram. The result was supplemented with an illustration of a nomogram.

Changes in the text: Page 11, Line 215-219: “AFP and Radscore are integrated into the nomogram. CT-based radiomics nomogram consisted of five components: Points, Radscore, AFP, Total Points, Predicted Probability. The initial "Points" scale was devised to assign scores for each predictor. The final predicted probability is determined by combining the scores derived from AFP and Radscore. Fig. 3 illustrates the CT-based radiomics nomogram.”