Peer review file

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Reviewer A

The purpose of this work was 'to develop and to validate a classification tree model based on contrast-enhanced CT characteristics of solid lung tumors to differentiate between the malignant or benign nature in clinical preoperative patients'.
It is well written, and the description of the model construction is detailed and clear.
In my opinion, apart from few limitations listed by the Authors, the work is of great scientific and practical value especially taking into account complicated process of lung nodules management.
I appreciate the Appendix 1 which shows the nodule features and appendix 2 with cases and analyses results by radiologists and CART model.

Please verify:
Comment 1: The threshold grades. ST2 range is mistakenly depicted as ST2= IF 20%< Malignant%<80%; Shouldn't it be 20% > ?
as ST1= IF Malignant%≤20%; (line 135, page 5; Figure 2 description, page 17; under Table 3 page 15).
Reply 1: Thank you for mentioning this important point. We are sorry for the misunderstanding. In page5, line 124-125, we describe the three threshold grades (ST1, ST2, and ST3), they were made to describe the malignancy probability in each child node (ST1= IF Malignant%≤20%; ST2= IF 20%< Malignant%<80%; ST3 = IF Malignant%≥80%). More specifically, ST1 is the malignancy probability less than 20%, ST2 is 20%-80%, while ST3 is higher than 80%. Therefore, the description in this paper should be correct.

Comment 2: Random division of nodules in two groups 2:1 (575 cases: 252 cases) is not exact.
Reply 2: Thank you for this comment. The ratio here is really inaccurate. We delete all the descriptions about 2:1 in Page2, line28 and Page 5, line 115.

Comment 3: According to TRIPOD Checklist

Reply 3: I sincerely thank the reviewer for your careful review. At the same time, thank you again for your recognition of my research.

Title

The title includes information about the type of the classification model, target population and the prediction outcome. It is not mentioned if the study concerns development and/or validation of the model however in my opinion it is sufficiently informative.

Abstract

The Abstract provides precise information about desired information (e.g., objectives, methods, results and conclusions).

Keywords are appropriate.

Introduction - background and objectives

The Authors describe the context of the lung nodules management and explain why it is very important and desired to develop multivariable validated classification model.

The objectives and existing guidelines have been mentioned (e.g., WHO, Lung-RADS, Fleischer Society; Ref. 3-6).

The Authors state that 'The use of difference in CT density between non-contrast and contrast CT may help to establish a classification model to effectively improve the diagnosis of pulmonary nodules'. It has been shown that the level of CT enhancement is different depending on the nodule nature.

Methods

The study has been approved by the Institutional Ethics Committee and its dates have been mentioned in the Abstract.

The study design and source of data have been described for the development and the validation data sets. Random division of nodules in two groups 2:1 (575 cases: 252 cases) is not exact.

The patient's group - sample size (total of 1789 patients form Tianjin Medical University Cancer Institute and Hospital) has been described.

The path and detailed characteristics of participants have been listed in Table 1 (clinical features, basic demographics).

Detailed parameters for inclusion criteria, examinations made (detailed parameters, exam evaluation – 'all contrast-enhanced CT scans were reviewed by two experienced radiologists blindly and independently at the time of CT acquisition, the final radiological characteristics-after a mutual consultation and assigned to one of five categories: 1. benign; 2. probably benign; 3. undetermined; 4. probably malignant; 5. high suspicion of malignancy') have been described in detail.

The outcome that is to be predicted by the prediction model is clearly defined and predictors have been listed.

Statistical analysis methods

The description of the predictors used in the analyses is included in the methods section where authors list 'three management groups defined by radiologist diagnosis risk thresholds based

on the malignancy probability of the five categories (observe = 1, indeterminate = 2 or 3 or 4, surgery = 5)'.

Statistical analysis is clear and shows random assignment in the training and testing group, and the methods used (Student's t-test, chi-square test, and Kolmogorov-Smirnov test were used to assess each indicator in the training and testing group). All steps are well described, and data analysis software has been mentioned.

Model development

The Authors describe the model that has been constructed to assess variables that might discriminate between benign and malignant tumors (Classification and regression tree (CART) method).

For the training group, 19 variables to be different between benign and malignant groups have been found (shown in Table 2).

In Figure 1 three categorical variables '[subjective enhancement (no /uniform,

heterogeneous); margin (smooth, lobulated/spiculated); shape (round/oval, irregular)]' which were automatically generated by the CART have been shown.
In Figure 2 the optimized classification diagram has been presented.

Validation of the CART model and radiologist's diagnosis in the testing group has been described.

Performance of the CART prediction model and radiologist's nodule assessment have been described in detail showing the sensitivity specificity, PPV, NPV, and diagnostic accuracy to differentiate malignant from benign tumors in testing group (Table 3).
The Authors have shown that 'The CART model for solid tumors in studied clinical population resulted in a higher diagnostic accuracy compared to radiologist's diagnosis' and this suggests that contrast-enhanced CT characteristics can be the useful factor for discrimination between malignant and benign pulmonary lesions.

The limitations have been also mentioned (e.g., selection bias, retrospective single-center study, CART model should include more clinical information).
I agree with the Authors that 'This classification model could assist radiologists to make recommendations regarding follow-up or surgery in clinical patients with a solid lung tumor'.

I appreciate the Appendix 1 which shows the nodule features and appendix 2 with cases and analyses results by radiologists and CART model.
The source of funding has been provided.

The work opens the possibility for the use of described CART model which includes contrast-enhanced CT features except the traditional radiological characteristics. It is of great scientific and clinical value.

Reviewer B

The purpose of this study was to develop and internally validate a classification tree

model for distinguishing benign from malignant solid lung tumors using clinical and radiological characteristics.

My comments are as follows:

1. Title:

Comment 4: the title of this manuscript seems unclearly and unconcise.

Reply 4: Thank you for mentioning this. We revised our original title “A Contrast-Enhanced-CT-Based Classification Tree Model for Classifying Solid Lung Tumors in a Clinical Chinese Population as Malignant” to “A Contrast-Enhanced-CT-Based Classification Tree Model for Classifying malignancy of Solid Lung Tumors in a Chinese Clinical Population”, please see in Page 1, line 1-2.

2. Abstract:

Comment 5: please add the full name of IQR, PPV, NPV. The number of 98.6 should be 98.6%. This should be addressed in your content as well.

Reply 5: Thank you for this comment. We added the full name of IQR (interquartile range), PPV (positive predictive value), NPV (negative predictive value) in page 2, line 28 and 34, and Page 6, line 146.

3. Method.

Comment 6: 3.1 For the characteristic of location, it would be better using side and lobe together, such as, right upper lobe, right middle lobe….

Reply 6: We recalculated Table 2 as you suggested.

Please see table 2-R1 in the attachment.

Table 2: Characteristics of benign vs malignant tumors in the training group

Characteristics		Malignant (n=352)	Benign (n=223)	P
Patient age, mean (SD),		60.2±8.7	53.9±8.9	0.000[a]
Sex	Man	227(64.5%)	101(45.3%)	0.000[b]
	Woman	125(35.5%)	122(54.7%)	
Morphological				
Location	Left upper lobe	103(29.3%)	59(26.5%)	0.627[b]
	Left lower lobe	67(19.0%)	44(19.7%)	
	Right upper lobe	91(25.9%)	52(23.3%)	
	Right middle lobe	27(7.7%)	16(7.2%)	
	Right lower lobe	64(18.2%)	52(23.3%)	

Comment 7: 3.2 I guess all characteristics were evaluated by using RadiAnt DICOM Viewer that should be described in your manuscript.

Reply 7: Thank you for mentioning this important point. We added this description in Page 4, line 94. "All contrast-enhanced CT scans were reviewed by two experienced radiologists (6-year and 9 year reading experience in chest CT) blindly and independently by using the RadiAnt DICOM Viewer (version 2020.2).

Statistical analysis.

Comment 8:3.3 Why did you split training and validation dataset randomly?? This is not a recommendation for the checklist of TRIPOD you followed.

Reply 8: In order to avoid the data selection bias between the training and validation dataset, we chose to divide the data randomly. We do this to make the results more credible.

Comment 9: 3.4 Please add units in this sentence. 'The parent node stops splitting when the size is less than 15, and the child node stops splitting when the size is less than 5.'

Reply 9: Thank you for this comment. We revised this sentence in Page 5, line 121.

Comment 10: 3.5 "To show the accuracy of the classification tree model, ≥80% accuracy for each node was assumed as the cut-off value." Here, do you agree

probability is more appropriate than accuracy??

Reply 10: Thank you for your suggestion. I agree probability is more appropriate. We revised it in Page 5, line 122.

Comment 11: 3.6 Please provide parameters of tree model.

Reply 11: The blew table showed the parameters of tree model. About the CART model we also describe it in the Page 5, line 118-122.

Model Summary

Specifications	Growing Method	CRT
	Dependent Variable	1=M 0=B
	Independent Variables	0=Peripheral ，1=Central, 0=round/oval 1 irregular, 0=smooth;1=Lobulate; 2=Spiculate, Calcification, Fat;No=0; Have=1（min-50）, Necrosis, 0=none;1=yes, Air_Bronchograms, Pleural_indentation, Vascular_invasion, Satellite_Nodules, Lymph_nodes, Postobstructive_pneumonia, diameter(mm), 0=No enhancement 1=Uniform enhancement 2=Heterogeneous enhancement, gender
	Validation	None
	Maximum Tree Depth	3
	Minimum Cases in Parent Node	15
	Minimum Cases in Child Node	5

Results	Independent Variables Included	0=No enhancement 1=Uniform enhancement 2=Heterogeneous enhancement, diameter(mm), 0=smooth;1=Lobulate; 2=Spiculate, Fat;No=0; Have=1（min-50）, Satellite_Nodules, 0=round/oval 1 irregular, Postobstructive_pneumonia, Vascular_invasion, 0=none;1=yes, Necrosis
	Number of Nodes	9
	Number of Terminal Nodes	5
	Depth	3

4. Results

Comment 12: 4.1 Why did not you use other clinical variables such as smoking status, COPD?

Reply 12: Thank you for this great comment. A good model should contain more clinical information. Unfortunately, we lack this part of clinical information in this batch of data. We also describe it in the lamination section, page 8, line 202-204. In the future research, we will further add more clinical information and improve the model.

Comment 13: 4.2 Is it possible to compare your model with Brock model? Brock model is a famous model for estimating the risk of lung cancer.

Reply 13: As we explained in comment 12, we lack the clinical information (like the smoking history and family cancer history). So, it is hard to use Brock model without this information. In the Page 7, line 165-174, we describe our previous study about the comparing between the three models (VA, Mayo, Brock) and radiologist diagnosis. The radiologist's diagnosis showed higher performance contrast to the three classification models. However, our CART model is more accurate than radiologist diagnosis in solid tumor. In the future, we will collect more data to further compare

our CART model and Brock model.

Comment 14&15: 4.3 How did you reduce and select variables? Feature importance? Add more details please.

4.4 Please add more explanation for figure 1.

Reply 14&15: In Statistical analysis section (Page 5, line 115-118), we describe the selection of variables. First, we used student's t-test, chi-square test, and Kolmogorov-Smirnov test to assess each variable in the train group was significantly different between benign and malignant tumors. Second, variables (p-value < 0.05 in univariable analysis) were selected to CART model. After setting parameters of the tree model, a decision model was automatically generated (show in Figure1). To simplify the classification tree diagram, we made concise tables in Figure 2. The detail description in Page 5, line 122-127.

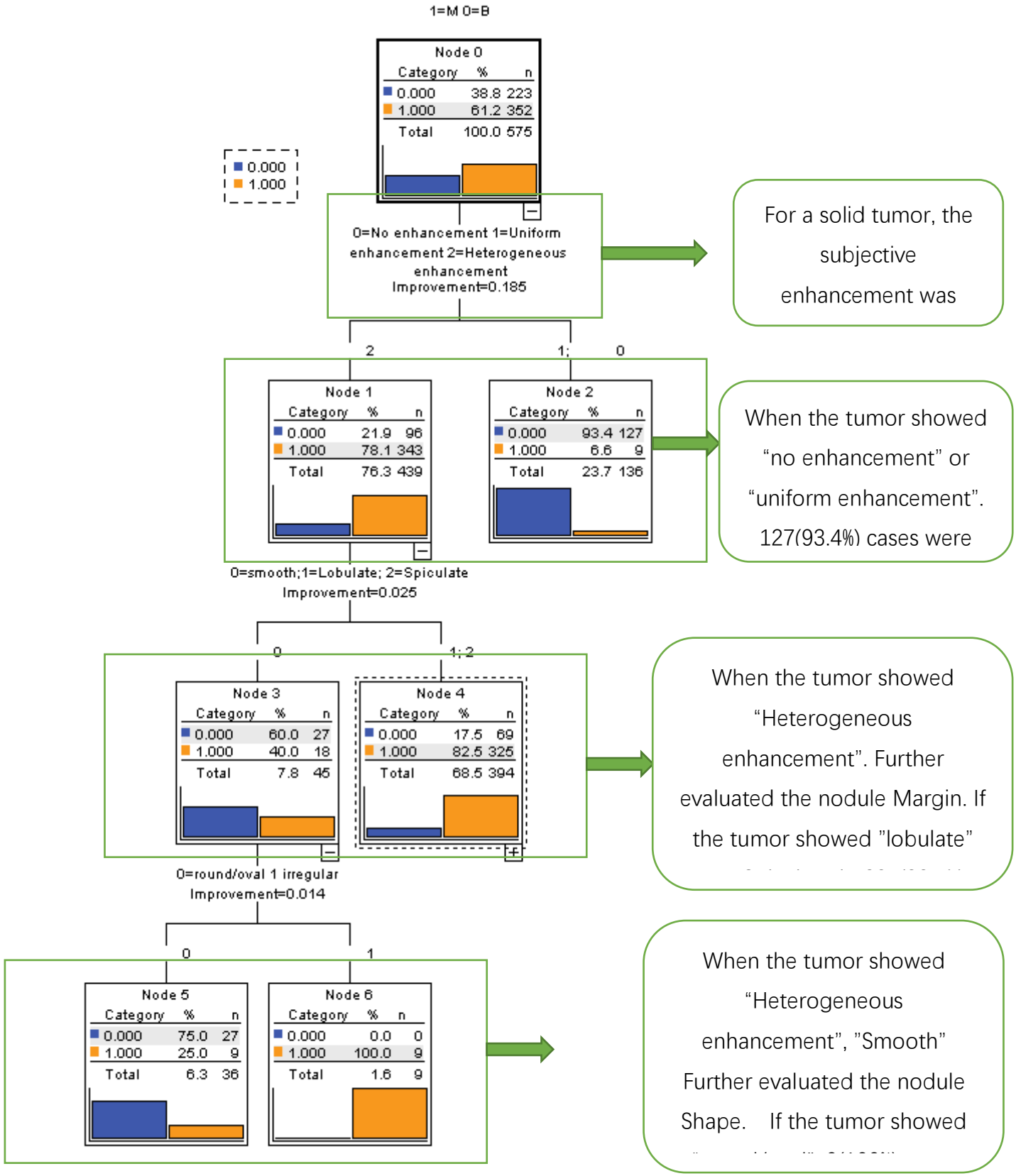
1=M 0=B
Node 0
Category % n
0.000 38.8 223
1.000 61.2 352
Total 100.0 575
0.000
1.000
0=No enhancement 1=Uniform enhancement 2=Heterogeneous enhancement
Improvement=0.185
For a solid tumor, the subjective enhancement was
2
1; 0
Node 1
Category % n
0.000 21.9 96
1.000 78.1 343
Total 76.3 439
Node 2
Category % n
0.000 93.4 127
1.000 6.6 9
Total 23.7 136
When the tumor showed "no enhancement" or "uniform enhancement". 127(93.4%) cases were
0=smooth;1=Lobulate; 2=Spiculate
Improvement=0.025
0
1; 2
Node 3
Category % n
0.000 60.0 27
1.000 40.0 18
Total 7.8 45
Node 4
Category % n
0.000 17.5 69
1.000 82.5 325
Total 68.5 394
When the tumor showed "Heterogeneous enhancement". Further evaluated the nodule Margin. If the tumor showed "lobulate"
0=round/oval 1 irregular
Improvement=0.014
0
1
Node 5
Category % n
0.000 75.0 27
1.000 25.0 9
Total 6.3 36
Node 6
Category % n
0.000 0.0 0
1.000 100.0 9
Total 1.6 9
When the tumor showed "Heterogeneous enhancement", "Smooth" Further evaluated the nodule Shape. If the tumor showed

Figure 1

Shape	No/Uniform enhancement		Heterogeneous enhancement	
			Smooth	Lobulated/Spiculated
Round/oval	ST1	ST1	ST2	ST3
Irregular	ST1	ST1	ST3	ST3

Figure 2

Reviewer C

Comment : Well written.

Reply: Thank you very much for your recognition of my research results.