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OPEN PEER REVIEW

Contrast-Enhanced Chest Computed Tomography (CT) Scan with Low Radiation and Total Iodine Dose for Lung Cancer Detection Using Adaptive Statistical Iterative Reconstruction

Xili Li, Shiyong Luo, Suping Chen, Du Wang, Yiqing Tan

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 24 Apr 2022

Editor-in-Chief

MINOR REVISION 24 Apr 2022

Dear authors,
Before starting the review process for your article, it is necessary to clarify the following items:

Given the importance of clarifying conflicts of interest, the corresponding author should fill out the “ICMJE form” and upload it during the submission process. (The form is available in the “conflict of interest” section of the site: https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).
Regards

2

Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor,

Thanks for your letter. We are sorry for our carelessness in the submission process of manuscript titled "***Chest CT enhancement with low radiation and total iodine dose for lung cancer detection using adaptive statistical iterative reconstruction***" (ID: 126572).

Contents below are our point by point replies (in normal text) to the comments (*red in italics font*).We hope this manuscript now allowable for review process.

Reviewers' Comments:

Associate Editor's Comments:

EIC decision:

Before starting the review processing of your article, it is necessary to clarify the following items:

Regarding the importance of "conflict of interest" clarification, the corresponding author should fill out the "ICMJE form" form and upload in the submission process. (The form exists in "conflict of interest" section of the site: https://brief.land/iranjradiol/knowledgebase/category/tree.html#conflicts_of_interest.html).

Reply: Thanks for your gentle suggestion. The corresponding author has filled out the "ICMJE form" for disclosure of potential conflict of interest and uploaded it in the submission process as "other files" (file name: coi disclosure_Yiqing Tan. pdf). The disclosure statements generated by the ICMJE form for each author were added in the revised manuscript with highlighted as follows:

Declaration of competing interest

Dr. Li reports grants from Foundation of Wuhan Municipal Health Commission, during the conduct of the study. Dr. Luo has nothing to disclose. Dr. Chen has nothing to disclose. Dr. Wang has nothing to disclose. Dr. Tan has nothing to disclose.

Details of Screening:

Control of Revised Files: FAILED

1) Highlight all revised parts in your word file. You need to highlight any change in

your word file.

Reply: Thanks for your gentle suggestion. We have modified the manuscript and the revision was highlighted.

2) You must reply to all reviewers' comments one by one with line number and numbering.

Reply: Thanks for your gentle suggestion. We have modified the “Reply to reviewers” and made one by one responses to the comments with line number and numbering.

3) Upload a new file for "Reply to Reviewers."

Reply: Thanks for your gentle suggestion. We have uploaded a new file for “Reply to Reviewers” named “Reply to reviewers. docx”.

2 Revision 1

2 comments · 5 Jul 2022 – 6 Jul 2022

Referee 1 Reviewer

MAJOR REVISION 5 Jul 2022

1-The title is unclear. Do you mean: “reduction of radiation dose and total iodine dosage in contrast enhanced chest computed tomography of patients with lung cancer using adaptive statistical iterative reconstruction”? In addition, the phrase “chest CT enhancement is useful” in the background of the abstract is unclear. Does it mean “contrast enhanced chest computed tomography”? If so, please change this phrase and all similar instances in the paper.
2-What is the meaning of ASIR 40% in line 12?
3-If the study is an RCT, the paper should be written according to the CONSORT guideline.
4-If the study is an RCT, it would be better for the authors to register it in a trial registry and mention the registration code.
5-Did the authors obtain ethics committee approval?
6-What was the method of randomization? Block randomization? Please explain.
7-What is the meaning of “The scope of the scan was”? Does it mean “The scanning field extended from . . ...”?
8-It is not stated in the methods section that all of the patients had confirmed lung cancer. It is also unclear how the authors confirmed the cancer.
9-What is the meaning of contrast in the 5-point visual scoring method? Does it refer to the contrast between the image and surrounding tissues, or does it refer to image quality due to the contrast agent?
10-The authors mentioned: “For images in the lung window, the following elements were evaluated: ① lung texture; ② bronchus; ③ proximal bronchus and adjacent vessels; ④ peripheral bronchus and adjacent vessels; and ⑤ clarity of the margins of lung lesions. For images in the mediastinal window, the following elements were evaluated: ① trachea and surrounding soft tissue at the level of the aortic arch; ② hilar protuberances and surrounding lymph nodes; ③ three different levels of the thoracic part of the esophagus; ④ pericardium at the level of the right ventricle; and ⑤ chest wall and muscle tissue.” Which of these evaluations assess the efficacy of the contrast agent and its role in image quality? One of the important parts of the study is related to assessing the role of contrast in CT imaging, so this should be measured clearly in the lesions. However, most of the assessments are performed in areas beyond the lesion [lung texture, bronchus, vessels, trachea, ...], and it is unclear how the effects of the contrast agent are evaluated in the images. In addition, it is unclear whether the authors can quantitatively assess the effect of the contrast agent on imaging [for example, by measuring HU in lesions].
11-Please add the manufacturer information for SPSS based on the IBM website.
12-Did you assess the normality of the data before the statistical analyses? [The type of statistical test depends on the normality of the data.] Please add this point in the statistical analysis section.
13-In line 143, please change “with an age” to “with a mean age”. Please follow this comment in other similar instances.
14-Please define the abbreviations used in the tables in their footnotes.
15-It would be better for the authors to delete >0.05 in table 2. Only the P-values are sufficient.
16-Please change P-values equal to 0.000 to <0.001.
17-Didn't the authors check the capability of the images for the general diagnosis of cancer? [If this is important and could be indicated.]
18-It is recommended that the authors add the following two parts to the analyses and results of the paper:
I-The authors mentioned: “Therein, the image with a score of 3-5 meets diagnosis, and the image quality of 1-2 points cannot be diagnosed.” So, for each of the 10 assessments in the lung and mediastinal windows, the authors can calculate the number of non-diagnostic cases in the case and control groups. It is recommended

that the authors compare the frequency of non-diagnostic subjects between the two groups in each of the 10 subjective assessments and add the data to the paper. [Please note that statistical similarity in mean subjective assessment scores does not necessarily mean similarity in the efficacy and proficiency of the two methods. Adding these data and analyses could improve the comparison of these two methods and make it more comprehensive.]
II-The authors could add the mean subjective score for each of the 10 assessments [5 in the lung and 5 in the mediastinum] separately in a table [in addition to the mean of all 10 assessments]. I mean that a comparison similar to that in table 1 could be performed for each of the 10 subjective assessments and added to the paper and table 1.
19-Was the Adaptive Statistical Reconstruction (ASIR) protocol performed on the main workstation of the CT machine? Or did the authors use separate software for this assessment on another computer? If you used another computer, please add information about the software, its manufacturer, and its validity to the paper.
20-To assess the real effect of Adaptive Statistical Reconstruction (ASIR) on improving the image quality of contrast-enhanced CT, it would have been better if the authors had included another group receiving iodixanol at a concentration of 270 mgI/L and a tube voltage of 100 kVp without the application of ASIR, but they did not follow this design in their study [the question could be raised whether, even without using the ASIR method, image quality is not reduced and the two methods are similar]. However, I believe that, in its current form, the study conveys an appropriate message in its findings: the reduced contrast dose and radiation dose with ASIR could yield a good result [regarding image quality and reduction of contrast and radiation dose]. So, I recommend that the authors add to their discussion the results of similar studies that reduced the contrast and radiation dose without applying ASIR, to show whether image quality without ASIR is reduced [to reach the conclusion that ASIR is needed to eliminate the reduction in image quality due to reduced contrast and radiation. This could show that ASIR is a necessary adjunct to reductions in contrast, radiation, and kVp].
21-If there are similar studies on the lung or other parts of the body, it would be better to mention them briefly in the discussion.

Editor-in-Chief MAJOR REVISION 6 Jul 2022

Dear authors,
Your article needs Major Revision.
Regards

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor,

Thanks for your letter and we are grateful for the comments made by editors and reviewers on our manuscript titled **"Contrast enhanced chest CT with low radiation and total iodine dose for lung cancer detection using adaptive statistical iterative reconstruction" (Manuscript ID: 126572)**. We also feel sorry for the insufficient and confusing descriptions in the previous manuscript. According to the reviewers' comments and questions, we have made extensive modification of the manuscript. The final revised manuscript as well as a version with revision highlighted were both uploaded. And the point-to-point responses were enclosed as follows. The Reviewers' comments are displayed in green italics, and responses are shown in black body.

We hope the revised manuscript would be allowed for further consideration and publication.

Dr. Yiqing Tan

Reviewer 1:
In terms of methodology, it can be said that this manuscript designed, conducted, and written appropriately; but it needs some minor editions as follows:

1. The design of study is parallel randomized clinical trial and it should be written in the abstract and full text of the method.
Reply: Thanks for your gentle advice. In fact, this study was not a randomized clinical trial but a prospective study. We are so sorry for our carelessness, and the related description was added in the abstract and method section.

2. The clinical trial registry code and the ethics code of study must be provided in the full-text method section.
Reply: Thanks for your gentle suggestion. Since this study was not a randomized clinical trial, the clinical trial registry code was not provided. We have added the ethics number in the method section. This study was approved by Wuhan Third Hospital Ethics Committee (Wuhan Third Hospital Ethics Approval No:2015-008).

3. Sentences should not start with a number.
Reply: Thanks for your gentle suggestion. We have modified the related sentences. The two groups hold statistically non-significant subjective scores on 5 structures observed in the lung window and 5 anatomies detected in mediastinal window as well as overall image (all P>0.05)..

4. In the abstract and full text of the results, it is better to use the term experience and comparison group to compare values between groups.
Reply: Thanks for your gentle suggestion. We have modified the whole manuscript, and the phrases "control group" and "experimental group" were replaced by "experience group" and

“comparison group”, respectively.

5. The same word in line 18 should be changed to non-significant.
Reply: Thanks for your gentle suggestion. We have modified the word.

6. The method of randomization and used tool must be explained in the method.
Reply: Thanks for your kind suggestion. We are sorry for our carelessness as the patients were not randomly divided. The patients were actually divided according to the time as other studies reported [1,2]. The scan data for the experience group were retrospectively selected from the hospital database before June 01, 2015. The scan data in the comparison group for patients diagnosed with lung nodules and needed contrast-enhanced chest CT were collected between February 2018 to October 2020. The related descriptions were revised and added in method section.
References:
[1].Jihang Sun , Haoyan Li, Jianying Li, et a1. Performance evaluation of using shorter contrast injection and 70 kVp with deep learning image reconstruction for reduced contrast medium dose and radiation dose in coronary CT angiography for children: a pilot study[J]. Quant Imaging Med Surg, 2021;11(9):4162-4171 | http://dx.doi.org/10.21037/qims-20-1159.

[2]. Jihang Sun, Haoyan Li, Jun Gao, et a1. Performance evaluation of a deep learning image reconstruction (DLIR) algorithm in “double low” chest CTA in children: a feasibility study[J].La radiologia medica, (2021) 126:1181–1188. https://doi.org/10.1007/s11547-021-01384-2.

7. The full specifications of the statistical software version must be written in statistical analysis section.
Reply: Thanks for your gentle suggestion, we have added the full descriptions of SPSS version in revised manuscript. The statistical software we used was IBM SPSS Statistics 22.0.

8. The word measurement in line 135 must be replaced by continuous.
Reply: **Thanks for your gentle suggestion. The word “**measurement” was replaced by “continuous”.

9. Convert the (x ± s) term in line 136 to mean and standard deviation.
Reply: Thanks for your gentle suggestion. We have modified the related descriptions in revised manucript.

10. In line 137, the non-parametric Mann-Whitney test should be used to compare the mean rank of two groups.
Reply: Thanks for your gentle suggestion. We have added Mann-Whitney U result comparing subjective scores between two-group images in the revised manuscript.

11. In the full text of the results, the population part, for binary variables such as gender, only

one state should be reported and also the corresponding percentage should be presented in parentheses.

Reply: Thanks for your gentle suggestion. We have modified the description in revised manuscript. The modification content is as follows: there were 21 males（52.5%） and 19 females（47.5%） in comparison group；while 22 males（55%） and 18 females（45%） in experience group.

12. Delete the row of number samples from all tables.

Reply: Thanks for your gentle suggestion. We have deleted the row of number samples from all tables.

13.In Table 2, only the significance of the test must be reported.

Reply: Thanks for your gentle suggestion. We are sorry for the previous overkilled description including detail P value and significance. According to the latest articles published on IJR, we have revised the description and maintained the detail P value. For example: “00.812>0.05” was changed to"0.812”.

Table 1. The Study Variables Examined in Expired and Surviving Patients with Pulmonary Embolism (PE) [a]

	Groups		
Variables	Expired	Surviving	P-value
Sex			0.72
Male	4 (44.4)	28 (53.8)	
Female	5 (55.6)	24 (46.2)	
Age (y)	65.00 ± 13.18	59.85 ± 17.31	0.40
Location of PE			0.59
Central	6 (66.7)	33 (63.5)	
Peripheral	3 (33.3)	19 (36.5)	
Cardiopulmonary resuscitation and intubation	1 (11.1)	2 (3.8)	0.37
Thrombolytic therapy	2 (22.2)	9 (17.3)	0.66
Qanadli index	15.22 ± 5.36	15.48 ± 7.85	0.92
Interventricular septum			0.55 [b]
Normal	5 (55.6)	31 (59.6)	
Flattened	2 (22.2)	18 (34.6)	
Convex to the left	2 (22.2)	3 (5.8)	
Right to left ventricular diameter ratio	1.15 ± 0.30	1.04 ± 0.17	0.32
Contrast medium reflux into the inferior			0.72 [c]

References:

[1]. The Prognostic Significance of Pulmonary CT Angiography in Predicting the Outcomes of Acute Pulmonary Thromboembolism. Iran J Radiol. 2022;19(3):e121728. doi: 10.5812/iranjradiol-121728.

14. In Table 3, the significant level must be reported for total iodine.

Reply: Thanks for your gentle suggestion. We have added the statistical analysis for total iodine comparison in the revised manuscript.

Reviewer 2:
Dear authors,
1. Please rewrite the "conclusion section" of this manuscript.
Although your findings are valuable, but using some words such as "good news..." is not suitable for it.
Reply: Thanks for your gentle suggestion. We have modified the conclusion section and deleted the inappropriate descriptions as follows: In conclusion, ASIR maintained diagnostic CT image quality while significantly reduced the effective radiation dose by 36.59% and the total iodine contrast by 22.86% when comparing to FBP in enhanced chest CT for lung cancer detection.

Regards,
Reviewer 3:
Thanks to the authors for choosing the IJR for submitting their manuscript. I've two questions about this article:

1. Why did you use ASIR with 40% filtration due to reductions in patient radiation dose in CT? Given that this number (percent) is adjustable, what was your reason for choosing this?
Reply: Thanks for your positive question. ASIR technology can reduce image noise and improve image quality. The tube voltage decreases, the radiation dose decreases and the image noise increases. Image noise is one of the important factors affecting image quality. However, it is not higher the weight of ASIR, better the image quality. It is reported that an excessive ASIR weight (for example, more than 60%) would increase wax artifacts. Although the image noise can be further suppressed, the image contrast and subjective image quality were reduced, also the diagnostic confidence was damaged. Previous studies showed that image noise from chest and abdomen scans has decreased with increasing ASIR weights, and high image quality can be obtained by setting ASIR weights at 40% to 60%. Because lung tissue as gas-containing tissue has excellent contrast, a weight of 40% for ASIR was chosen in this study.

References：
[1].Yang Shangwen, He Jian, Yang Xianfeng,et a1.Studies on the application of adaptive statistical iterative reconstruction algorithm combined with automatic tube current modulation in chest low dose CT[J]. J Med Imaging，2012,22:58-61．

[2].Jia Nan,Wang Xinjiang, Hui Pig, et al. Radiation Dose Reduction in Chest CT Examination Using Adaptive Statistical Iterative Reconstruction Technique[J]. Chinese Journal of Medical Imaging, 2010, 18(6): 551-553.

[3].Naidich DP，Marshall CH，Gribbin C，et a1．Low—dose CT of the lungs：preliminary observations[J]．Radiology，1 990，175：739—731．

[4] Morgan DE. Dual-energy CT of the abdomen. Abdom Imaging, 2014, 39(1): 108-134.

[5] Singh S, Kalra MK, Hsieh J, et al. Abdominal CT: comparison of adaptive statistical iterative and filtered back projection reconstruction techniques. Radiology, 2010, 257(2): 373-383.

2. According to the new method, ASIR-V, represents the next generation of Adaptive Statistical Iterative Reconstruction, which has been broadly adopted on CT systems worldwide for its ability to help reduce patient dose while maintaining image quality. As well as, compared to ASIR, ASIR-V contains more advanced noise modeling and object modeling; what was the rationale for your use of the older generation (ASIR)?

Reply: Thanks for your gentle question. Indeed, ASIR-V is more advanced than ASIR, particularly in reconstruction speed and image quality. However, ASIR-V was not installed on all-type CT machines. On 16-row and some 64-row CT machines, ASIR was still applied and it would not updated to ASIR-V in a long time. In addition, for numerous hospitals, 16-row and 64-row machines still afforded heavy work to screen lung cancer. Thus, this study focused on patients who received contrast enhanced chest CT on those CT machines, and the number of these patients should be astonishing. Moreover, we tried to optimize the scan protocol using ASIR and hoped it would be beneficial for patients. In our study, results indicated that the use of ASIR maintained diagnostic CT image quality while significantly reduced the effective radiation dose by 36.59% and the total iodine contrast by 22.86% when comparing to FBP in contrast enhanced chest CT for lung cancer detection. We believe the sights gained from this study would help radiologist to optimize workflow and do better patient care.

Reviewer 4:

126572

1-the title is unclear. Do you mean: “reduction of radiation dose and total iodine dosage in contrast enhanced chest computed tomography of patients with lung cancer using adaptive statistical iterative reconstruction”? in addition, the part “chest CT enhancement is useful” in background of abstract is unclear. Does it mean “contrast enhanced chest computed tomography”? if yes, please change this part in all similar parts of paper.

Reply: Thanks for your gentle suggestion. We have modified the phrase “chest CT enhancement” into “contrast enhanced chest CT” in the title and whole manuscript.

2-what is the meaning of ASIR 40% in line 12?

Reply: Thanks for your gentle suggestion. ASIR 40% means ASIR with a blending ratio of 40% ASIR and 60% FBP (40%ASIR+60%FBP).

3-if the study is an RCT, the paper should be written as CONSORT guideline.

Reply: Thank you for your gentle advice, we are sorry for our carelessness, this study was a prospective study, and we have modified the manuscript to avoid confusion.

4-if the study is an RCT, it is better the authors register it in a trial registry and mention the registration code.

Reply: Thank you for your positive suggestion, this study was not an RCT.

5-did the authors get the ethics committee approval?

Reply: Thanks for your gentle suggestion. Our study was approved by Wuhan Third Hospital ethics committee. Wuhan Third Hospital Ethics Approval No:2015-008.

6-what was the method of randomization? Block randomization? Please explain.

Reply: Thanks for your kind suggestion. We are sorry for our carelessness. The patients were actually divided according to the time as other studies reported [1,2] but not randomized. The scan data for the experience group were retrospectively selected from the hospital database before June 01, 2015. The scan data in the comparison group for patients diagnosed with lung nodules and needed contrast-enhanced chest CT scan were collected between February 2018 to October 2020. The related descriptions were revised and added in method section.

References :

[1].Jihang Sun , Haoyan Li, Jianying Li, et a1. Performance evaluation of using shorter contrast injection and 70 kVp with deep learning image reconstruction for reduced contrast medium dose and radiation dose in coronary CT angiography for children: a pilot study[J]. Quant Imaging Med Surg, 2021;11(9):4162-4171 | http://dx.doi.org/10.21037/qims-20-1159.

[2]. Jihang Sun, Haoyan Li, Jun Gao, et a1. Performance evaluation of a deep learning image reconstruction (DLIR) algorithm in “double low” chest CTA in children: a feasibility study[J].La radiologia medica, (2021) 126:1181–1188. https://doi.org/10.1007/s11547-021-01384-2.

7-what is the meaning of “The scope of the scan was”? does it mean “The scanning field extended from …..”?

Reply: Thanks for your gentle question. Yes, “the scope of the scan” means scanning range, and we revised the related description according to your suggestion. “The scanning field extended from the tip of the lung to the below diaphragm.” CT plain scan first, scan ranged from the tip of the lung to the below diaphragm. Then enhanced scanning perform. Scan range is the same as plain scan.

8-it is not declared in method section that all of the patients had proved lung cancer. And it is questionable how did the authors approve the cancer?

Reply: Thanks for your gentle question. Actually, this study enrolled patients with pulmonary nodules and masses found in routine chest CT plain scan who needed contrast-enhanced chest CT examination to confirm lung cancer. In clinic, the diagnosis of lung cancer should take comprehensive consideration into CT images and pathological results.

9-what is the meaning of contrast in 5-point visual scoring method? Does it refer to contrast of image with surrounding tissues or it refers to imaging quality due to contrast agent?

Reply: Thanks for your questions. The aim of the 5-point visual scoring method is to subjectively score the display quality of the anatomy in the lung window and the mediastinal window, and to determine whether it meets the diagnostic requirements. The contrast in the scoring means image contrast between the structures of interest and surrounding tissue.

10-the authors mentioned: "For images in the lung window, the following elements were evaluated: ① lung texture; ② bronchus; ③ proximal bronchus and adjacent vessels; ④ peripheral bronchus and adjacent vessels; and ⑤ clarity of the margins of lung lesions. For images in the mediastinal window, the following elements were evaluated: ① trachea and surrounding soft tissue at the level of the aortic arch; ② hilar protuberances and surrounding lymph nodes; ③ three different levels of the thoracic part of the esophagus; ④ pericardium at the level of the right ventricle; and ⑤ chest wall and muscle tissue." What of these evaluations do assess the efficacy of contrast agent quality and role in imagings? One of important parts of the study is related to assessment of contrast role in CT imaging; so this point should be measured clearly in the lesions but most of assessments are done in parts beyond the lesion [lung texture, bronchus, vessels, trachea, …..] and it is unknown how are the effect of contrast agent evaluated in the images? In addition, it is questionable if the authors can assess quantitatively the effect of contrast agent in imaging [for example by measurement of HU in lesions]

Reply: Thank you for your gentle advice. According to previous literatures [1,2], we evaluated the contrast enhancement by measuring the CT value of the pulmonary arteries. Results indicated that CT attenuation of pulmonary arteries was not statistically different between the two-group images, thus the scanning and injection protocol did not influence enhancement. As for lesions, the enhancement effects relied on lesion types, therein, enhancement was not obvious for hypovascular lesions (such as benign) while vascular lesion (such as malignant) showed better enhancement (higher CT attenuation). However, the patients this study collected were just diagnosed with nodules/masses and without pathologic results (gold reference), thus the lesion types were not screened to be consistent. If evaluating lesion enhancement, the comparison between two groups would be greatly interpreted by the lesion types. This is a limitation of this study, thank you for your suggestion, and we have added this limitation in the revised manuscript. Moreover, in future, we would retrospectively collected patients with similar benign or malignant lesions (determined by pathological examination) and explore the impact of different scanning protocols on lesion enhancement.

References :

[1]. Heyer CM，Mohr PS，Lemlburg SP，et a1．Image quality and radiation exposure at pulmonary CT angiography with 100- or 120-kVp protocol：prospective randomized study[J]．Radiology, 2007, 245(2):577-583．

[2]. Cho ES，Chung JJ，Kim S，et a1．CT venography for deep vein thrombosis using a low tube voltage (100 kVp) setting could increase venous enhancement and reduce the amount of administered iodine[J]．Korean J Radiol, 2013, 14(2): 183-193.

11-please add the manufacturer data of SPSS based on IBM site.

Reply: Thank you for your gentle advice and we have added the manufacture data of SPSS in the revised manuscript.

12-did you assess the normality of data before statistical analyses? [the type of statistical test is dependent to normality of data]. Please add this point in statistical analysis section.

Reply: Thank you for your positive suggestion. We have added the normality analysis of continuous data in statistical analysis section.

13-in line 143, please change "with an age" to "with a mean age" please follow this comment in other similar instances.

Reply: Thanks for your gentle suggestion. We have rechecked the manuscript and modified the indicated phrases. For instance, "19 females, and their ages ranged from 34 to 86 years, with a mean age of (62.88±12.10) years.

14-please introduce the abbreviations of tables in their footnotes.

Reply: Thanks for your gentle suggestion. Has been added.

15-it is better the authors delete >0.05 in table 2. Only the value of P-values are sufficient.

Reply: Thanks for your gentle suggestion.

16-please change P-values equal to 0.000 to <0.001

Reply: Thanks for your gentle suggestion. Has been modified.

17-didn't the authors check the capability of images regarding general diagnosis of cancer? [if this is important and could be indicated]

Reply: Thanks for your positive question. Actually, the diagnosis of cancer not only rely on the results of contrast enhanced chest CT. CT images just provide morphological information and blood supply evaluation on lesions, and serve as assistant tools for pathological examination which was regarded as gold reference to diagnose lung cancer. The enhancement and size of lesions, nodule types (solid, ground glass) could be determined via CT imaging. During this process, diagnostic confidence would be influenced by CT image quality. Thus, this study mainly evaluated the image quality. Meanwhile, taking considerations into lesions found in various structures, this work also focused on the differences of subjective scores on 10 lung structures (both in lung window and mediastinal window) between the two groups. The results showed that dual-low protocol (comparison group) had statistically non-significant subjective image quality comparing with conventional protocol (experience group).

18-it is recommended the authors add two following parts in analyses and results of paper: I-the authors mentioned: "Therein, the image with a score of 3-5 meets diagnosis, and the image quality of 1-2 points cannot be diagnosed." So for each of 10 assessments in lung and mediastinal windows, the authors can calculate the number of non-diagnostic cases in case and control groups. It is recommended the authors compare frequency of non-diagnostic

subjects between two groups in each 10 subjective assessments and add the data to the paper. [Please note the point that statistical similarity of mean subjective scoring assessment does not necessarily mean the similarity of efficacy and proficiency of two methods. Adding this data and analysis could improve comparison of these two methods and makes comparison more comprehensive].

Reply: We're grateful for your constructive advice. We have analyzed the diagnostic images and non-diagnostic images and found all the images of both two groups were diagnostic (>3 points). Thus, to further compare the efficacy of two methods, we analyzed the subjective scoring distribution between two groups using Mann-Whitney U test, and the results were shown as Table 1. The results indicated that for whole image quality, the subjective score was not statistically different between two groups.

II-the authors could add mean subjective scoring for each of 10 assessments [5 in lung and 5 in mediastina] separately in a table. [in addition to mean of all 10 assessments] I mean similar comparison of table 1 could be done for each 10 subjective assessments and be added to paper and table 1.

Reply: Thanks for your advice. We have added the subjective scoring distribution comparison of each structure (sum to 10 structures) as shown in Table 1. The results suggested that the two methods did not make statistical differences in subjective image quality on each structure.

Table 1. Comparison of the subjective score between the experience (120 kVp) and comparison (100 kVp) groups

	Experience group (120 kVp)					Comparison group (100 kVp)					Z	P
	5	4	3	2	1	5	4	3	2	1		
Lung Window												
Lung texture	32	6	2	0	0	35	3	2	0	0	-0.855	0.508
Bronchus	31	7	2	0	0	35	3	2	0	0	-1.107	0.355
Proximal bronchus and Adjacent vessels	34	6	0	0	0	35	2	3	0	0	-0.177	1.000
Peripheral bronchus and adjacent vessels	32	7	1	0	0	34	3	3	0	0	-0.452	0.764
Clarity of the margins of lung lesions	37	7	1	0	0	34	4	2	0	0	-0.51	0.748
Mediastinal Window												
Trachea and surrounding soft tissue at the level of the aortic arch	32	7	1	0	0	34	5	1	0	0	-0.569	0.705
Hilar protuberances and surrounding lymph nodes	32	6	2	0	0	34	3	3	0	0	-0.495	0.745
Three levels of the thoracic part of the esophagus	31	5	4	0	0	34	4	2	0	0	-0.892	0.424
Pericardium at the level of the right ventricle	33	6	1	0	0	34	4	2	0	0	-0.24	0.968
Chest wall and muscle tissue	32	6	2	0	0	34	4	2	0	0	-0.553	0.701
Overall	32	7	1	0	0	34	4	2	0	0	-0.51	0.748

19-was the protocol of Adaptive Statistical Reconstruction (ASIR) done on the main work station of CT machine? Or did the authors use a separate software for this assessment on the other computer? If you used other computer, please add the data of software, manufacture and validity of the software in paper.

Reply: Thanks for your questions. The protocol of Adaptive Statistical Reconstruction (ASIR) was done on the main engine, and the reconstructed images were transferred to workstation（Advanced Workstation 4.6, GE Healthcare） for image quality evaluation. And the related information was added in the revised manuscript.

20-when we want to assess the real effect of Adaptive Statistical Reconstruction (ASIR) in improving the image quality of contrast enhanced CT, it would be better the authors had the other group who receive iodixanol with concentration of 270 mgI/L and a kVp of 100 for tube voltage without application of ASIR, but they did not follow this design in their study [this question could be proposed that even without using ASIR method, the imaging quality is not

reduced and two methods are similar]. However, I believe in the current form, the study bears an appropriate message in its findings that the reduced contrast dose and radiation dose with ASIR could yield a good result [regarding image quality and reduction of contrast and radiation dose]. So I recommend the authors can add in their discussion the results of similar studies without ASIR application which have reduced the contrast and radiation dose to show if the image quality without ASIR is reduced or not? [to reach this conclusion that ASIR is needed to eliminate the reduction of image quality due to reduction of contrast and radiation. This could show that the ASIR is a necessary adjunct to reduction of contrast and radiation and kVp]

Reply: Thanks for your gentle suggestion. The related discussion has been added in the revised manuscript. “There are several studies compared the image quality and radiation dose between low kVp CTA examinations with FBP and iterative algorithm utilized [1]. They found a lower kVp led to lower radiation dose, however with FBP utilized, the low kVp images had high noise and lower subjective scores, while the application of iterative algorithms led to diagnostic image quality. In addition, for double-low scanning [2], the images with different reconstruction algorithms utilized had different qualities, therein iterative reconstructed images were better than FBP images. Thus, the iterative algorithm could greatly reduce image noise, make up for the reduction on the image quality caused by the decreases of X-ray and contrast amount, which is not satisfactory obtained by FBP.”

References：

[1]. Wintersperger B, Jakobs T, Herzog P, et al . Aorto-iliac multidetector-row CT angiography with low KV settings: improved vessel enhancement and simultaneous reduction of radiation dose [J]. Eur Radiol, 2005,15(2):334-341. DOI: 10.1007/s00330-004-2575-y.

[2]. Liu Gang, Mao Xu, He Hui, et al. The effects of double low scanning combined with iterative reconstruction on the reduction for the risk of coronary CTA examination [J]. J Pract Radiol, 2014, 30(11): 1827-1838.

21-if there are similar studies on lung or other parts of body, it would be better to be mentioned in brief in discussion.

Reply: Thanks for your gentle suggestion. We have added the related description in the revised manuscript. “Hu Xuemei et al. applied ASIR iterative algorithm and explored the double-low feasibility in pulmonary artery imaging, Chen Hao, et al also applied IR algorithm from other vendor in enhanced chest CT and obtained acceptable CT images in dual-low way. Their research results are consistent with ours.”

3 Revision 2

5 comments · 3 Sep 2022 – 24 Sep 2022

Referee 2 Reviewer

ACCEPT 3 Sep 2022

Thanks for answering the questions.
Add the unavailability of ASIR-V, an advanced generation of Adaptive Statistical Iterative Reconstruction, in your CT system to the manuscript's limitations.
This paper is suitable for publication in IJR.

Referee 3 Reviewer

MINOR REVISION 5 Sep 2022

Thanks to the authors for the appropriate revision, but the following point should be reconsidered:
In the first section of the methods, the study design is described as prospective, but a later section states, "The scan data for the experience group were retrospectively selected from the hospital database before June 01, 2015. The scan data in the comparison group for patients diagnosed with pulmonary nodules or masses were collected between February 2018 to October 2020". How is it possible? It is important to separate study design from data timing. In epidemiology, it isn't logical to categorize study design according to calendar time because case-control and historical cohort studies use retrospective data but are methodologically completely different. If this study used retrospective data from a single point in time and compared some characteristics between two groups, the study design is case-control; if the two groups were also followed, the study design is retrospective cohort. Please revise the study design according to the above-mentioned points.

Referee 1 Reviewer

MINOR REVISION 10 Sep 2022

The authors have corrected many points, but some points should be addressed in the paper as follows:
1-Please add this sentence to the method section of the paper: [it has been mentioned in the abstract but not in the paper]
“This prospective study collected a total of 80 patients diagnosed with nodules or masses who needed contrast enhanced chest CT scanning”

2-Please cite SPSS based on this page: https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss
3-Please add to the discussion the limitation that the study is not a randomized trial.
4-The authors replied in response to a question: “we evaluated the contrast enhancement by measuring the CT value of the pulmonary arteries. Results indicated that CT attenuation of pulmonary arteries was not statistically different between the two-group images, thus the scanning and injection protocol did not influence enhancement. As for lesions, the enhancement effects relied on lesion types, therein, enhancement was not obvious for hypovascular lesions (such as benign) while vascular lesion (such as malignant) showed better enhancement (higher CT attenuation). However, the patients this study collected were just diagnosed with nodules/masses and without pathologic results (gold reference), thus the lesion types were not screened to be consistent. If evaluating lesion enhancement, the comparison between two groups would be greatly interpreted by the lesion types. This is a limitation of this study, thank you for your suggestion, and we have added this limitation in the revised manuscript. Moreover, in future, we would retrospectively collected

References :
[1]. Heyer CM， Mohr PS， Lemlburg SP， et a1. Image quality and radiation exposure at pulmonary CT angiography with 100- or 120-kVp protocol ： prospective randomized study[J]. Radiology, 2007, 245(2):577-583.
[2]. Cho ES， Chung JJ， Kim S， et a1. CT venography for deep vein thrombosis using a low tube voltage (100 kVp) setting could increase venous enhancement and reduce the amount of administered iodine[J]. Korean J Radiol, 2013, 14(2): 183-193."
As these points are useful, I recommend that the authors add the important points from this part to the paper; in particular, the following should be noted in the paper: "we evaluated the contrast enhancement by measuring the CT value of the pulmonary arteries. Results indicated that CT attenuation of pulmonary arteries was not statistically different between the two-group images, thus the scanning and injection protocol did not influence enhancement" [of course, it would be very good if the authors supported this part with numerical data; i.e., they can add the mean HU of the pulmonary arteries to show that the mean HU values for both methods are similar].

Associate Editor

MINOR REVISION 22 Sep 2022

Dear authors
Thank you for considering the Iranian Journal of Radiology. The manuscript needs minor revision based on the reviewers' comments.
Best regards

Editor-in-Chief

MINOR REVISION 24 Sep 2022

Dear authors,
Your article needs Minor Revision.
Regards

4

Revision 3

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear editor,

Thanks for your letter and we are grateful for the comments made by editors and reviewers on our manuscript titled **“Contrast enhanced chest CT with low radiation and total iodine dose for lung cancer detection using adaptive statistical iterative reconstruction” (Manuscript ID: 126572)**. We also feel sorry for the insufficient description in the previous manuscript. According to the reviewers’ comments and questions, we have made modification of the manuscript again. The final revised manuscript with revision highlighted was uploaded. And the point-to-point responses were enclosed as follows. The Reviewers’ comments are displayed in green italics, and responses are shown in black body.

We hope the revised manuscript would be allowed for further consideration and publication.

Dr. Yiqing Tan

Reviewer 1:
Thanks for answering the questions.
Add unavailability to ASIR-V in your's CT system as an advanced generation of Adaptive Statistical Iterative Reconstruction in the limitation manuscript.
This paper is suitable for publication in IJR.
Reply: Thanks for your support for this paper. We have added related description in the limitation section as follows: “⑥ Advanced generation of adaptive statistical iterative reconstruction (ASIR-V) was not applied in this study and further exploration should be conducted with ASIR-V by which lower radiation and iodine dose than ASIR might be reached.” (line 292 on page17).

Reviewer 2:
Thanks to the authors for appropriate revision; but the following point should be reconsidered:
In the first section of method, study design mentioned prospective, but in the later section mentioned "The scan data for the experience group were retrospectively selected from the hospital database before June 01, 2015. The scan data in the comparison group for patients diagnosed with pulmonary nodules or masses were collected between February 2018 to October 2020". How is it possible? It is important to separate study design from data time. In epidemiology it isn't logical to categorize study design according to calendar time. Because, case-control and historical cohort studies used retrospective

data; but methodologically are completely different. If, in this study used of retrospective data in a point of time, and some characteristics compared between two groups the study design is case-control, if also two groups followed the study design is retrospective cohort. Please revised study design according to above mentioned points.

Reply: Thanks for your gentle advice. We apologized for the confusing description such as “the patients were actually divided according to the time” and we have corrected the manuscript. Actually, this study was a prospective study which collected data comprising prospective data and retrospective data. For a prospective study, scientists often observe the endpoints by prospectively setting different exposure factors. For this study, we explored the influence of designed factor on image quality as well as radiation and iodine dose by setting two-group populations who experienced different scan and image reconstruction protocols. The comparison group conducted with designed factors was prospectively selected, and the experience group with conventional settings as control group was retrospectively collected. A prospective study comprising prospective and retrospective data was reported in numerous previous studies [Ref. 1, 2], and we performed our study in accordance with these studies. If we do a retrospective study, we should collect two-group data with similar image quality as well as distinguishing radiation and iodine dose, and to retrospectively find the factors (might be scan protocols and image reconstruction, also BMI and so on) which lead to the endpoints. We apologized again for our insufficient description in the previous studies and we really hope to discuss with you if there is still some confusions.

Related revisions:

This prospective study collected a total of 80 patients diagnosed with nodules or masses who needed contrast enhanced chest CT scanning, 40 in the experience group (using conventional dose, hypertonic contrast medium) and 40 in the comparison group (using low dose, isotonic low-concentration contrast medium). Similar to previous studies [Ref. 1,2], the scan data comprised of retrospective data and prospective data. The scan data for the experience group were retrospectively selected from the hospital database before June 01, 2015. The scan data in the comparison group for patients were collected between February 2018 to October 2020. --in line 86 on page 5.

References:

[1].Jihang Sun , Haoyan Li, Jianying Li, et a1. Performance evaluation of using shorter contrast injection and 70 kVp with deep learning image reconstruction for reduced contrast medium dose and radiation dose in coronary CT angiography for children: a pilot study[J].Quant Imaging Med Surg, 2021;11(9):4162-4171. http://dx.doi.org/10.21037/qims-20-1159.

[2]. Jihang Sun, Haoyan Li, Jun Gao, et a1. Performance evaluation of a deep learning image reconstruction (DLIR) algorithm in “double low” chest CTA in children: a feasibility study[J].La radiologia medica, (2021) 126:1181–1188. https://doi.org/10.1007/s11547-021-01384-2.

Reviewer 3:
Dear editor in-chief,
I read the revised file of manuscript, and In my view, this study is acceptable.
Reply: Thanks for your support for this paper.

Sincerely;
Reviewer 4:
the authors have corrected many points but some points should be addressed in paper as follows:
1-Please add this sentence in method section of paper: [it has been mentioned in abstract but not in paper]
“This prospective study collected a total of 80 patients diagnosed with nodules or masses who needed contrast enhanced chest CT scanning”
Reply: Thanks for your gentle advice. We have added this sentence in method section of paper: “This prospective study collected a total of 80 patients diagnosed with nodules or masses who needed contrast enhanced chest CT scanning”.--in line 86 on page 5.

2-please cite SPSS based on this page:
https://www.ibm.com/support/pages/how-cite-ibm-spss-statistics-or-earlier-versions-spss
Reply: Thank you for your gentle advice and we have added the manufacture data of SPSS in the revised manuscript. “SPSS (IBM Corp. Released 2013. IBM SPSS Statistics for Windows, Version 22.0 Armonk, NY: IBM Corp.) was used for statistical analysis. ” --in line 161 on page 9.

3-please add this limitation in discussion that the study is not a randomized trial.
Reply: Thanks for your gentle advice. We have added this sentence in discussion section of paper: “⑦ The study was not a randomized trial.” ---in line 295 on page 17.

4-the authors replied in response to a question: “we evaluated the contrast enhancement by measuring the CT value of the pulmonary arteries. Results indicated that CT attenuation of pulmonary arteries was not statistically different between the two-group

images, thus the scanning and injection protocol did not influence enhancement. As for lesions, the enhancement effects relied on lesion types, therein, enhancement was not obvious for hypovascular lesions (such as benign) while vascular lesion (such as malignant) showed better enhancement (higher CT attenuation). However, the patients this study collected were just diagnosed with nodules/masses and without pathologic results (gold reference), thus the lesion types were not screened to be consistent. If evaluating lesion enhancement, the comparison between two groups would be greatly interpreted by the lesion types. This is a limitation of this study, thank you for your suggestion, and we have added this limitation in the revised manuscript. Moreover, in future, we would retrospectively collected patients with similar benign or malignant lesions (determined by pathological examination) and explore the impact of different scanning protocols on lesion enhancement.

References :

[1]. Heyer CM，Mohr PS，Lemlburg SP，et a1．Image quality and radiation exposure at
pulmonary CT angiography with 100- or 120-kVp protocol：prospective randomized study[J]．Radiology, 2007, 245(2):577-583．
[2]. Cho ES，Chung JJ，Kim S，et a1．CT venography for deep vein thrombosis using a low tube voltage (100 kVp) setting could increase venous enhancement and reduce the amount of administered iodine[J]．Korean J Radiol, 2013, 14(2): 183-193.”

As these points are useful, I recommend the authors add important points of this part to the paper; especially, this part is important to be noted in paper: “we evaluated the contrast enhancement by measuring the CT value of the pulmonary arteries. Results indicated that CT attenuation of pulmonary arteries was not statistically different between the two-group images, thus the scanning and injection protocol did not influence enhancement” [of course, it would be very good if the authors document this part by numerical profile; i.e. they can add mean HU of pulmonary arteries to show that mean HU in both methods are similar]

Reply: Thanks for your gentle advice. We have added these important points in discussion section of revised paper: “Besides for the image quality, enhancement was important index for diagnosis, thus we evaluated the contrast enhancement by measuring the CT value of the pulmonary arteries. Results indicated that CT attenuation of pulmonary arteries was not statistically different between the two-group images (314.90±23.42 HU for comparison group vs. 308.93±21.40 HU for experience group, P>0.05) (Table 2), thus the scanning and injection protocol did not influence contrast enhancement.” --in line 246 on page 14.

4 Revision 3

3 comments · 8 Oct 2022 – 21 Oct 2022

Referee 3 Reviewer

ACCEPT 8 Oct 2022

Currently, this manuscript is acceptable and ready for publication in IJR from a methodological perspective.

Associate Editor

ACCEPT 20 Oct 2022

Dear authors
Thank you for considering our journal. The manuscript could be accepted for publication.
Best regards

Editor-in-Chief

ACCEPT 21 Oct 2022

Based on the reviewer's and AE's decisions, this article is now suitable for publication.