BMJ Open

Comparison of Approaches to Evaluating Inter-observer Variability in Computed Tomography Tumor Measurements of Cancer Lesions

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040096
Article Type:	Original research
Date Submitted by the Author:	05-May-2020
Complete List of Authors:	Woo, MinJae; Clemson University, Public Health Sciences Heo, Moonseong; Clemson University, Public Health Sciences Devane, Aron; Prisma Health Upstate, Radiology Lowe, Steven; Prisma Health Upstate, Radiology Gimbel, Ronald; Clemson, Public Health Sciences
Keywords:	Computed tomography < RADIOLOGY & IMAGING, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult oncology < ONCOLOGY

Comparison of Approaches to Evaluating Inter-observer Variability in Computed Tomography Tumor Measurements of Cancer Lesions

MinJae Woo, MS[1], Moonseong Heo, PhD[1], A. Michael Devane, MD[2], Steven L. Lowe, MD[2], Ronald W. Gimbel, PhD[1]

[1] Department of Public Health Sciences, Clemson University, Clemson, SC, USA
[2] Department of Radiology, Prisma Health System, Greenville, SC, USA

Work originated/research site:
Department of Radiology
Prisma Health System
200 Patewood Drive
Greenville, SC 29615

Corresponding author:
Ronald W. Gimbel, PhD
Chair, Department of Public Health Sciences
501 Edwards Hall
Clemson University
Clemson, SC 29634
(864) 656-1969 – *office*
(864) 656-6227 - *telefax*
rgimbel@clemson.edu

Manuscript type: Original Research

Keywords: Computed tomography, inter-observer variability, cancer lesions, decision making,

correlation coefficients, radiologists

Word count (excluding title, abstract, references, figures, and tables): 3,213

ABSTRACT

Background:

A growing number of research studies have reported inter-observer variability in sizes of tumors measured from computed tomography (CT) scans. It remains unclear whether the conventional statistical measures correctly evaluate the CT measurement consistency for optimal treatment management and decision making. We compared and evaluated the existing measures for evaluating inter-observer variability in CT measurement of cancer lesions.

Methods:

13 board-certified radiologists repeatedly reviewed 10 CT image sets of lung lesions and hepatic metastases selected through a randomization process. A total of 130 measurements under RECISTS 1.1 guidelines were collected for the demonstration. Intraclass correlation coefficient (ICC), Bland-Altman plotting, and outlier counting methods were selected for the comparison. Each selected measure was used to evaluate three cases with observed, increased, and decreased inter-observer variability.

Results:

The ICC score yielded a weak detection when evaluating different levels of the inter-observer variability among radiologists (increased: 0.912; observed: 0.962; decreased: 0.990). The outlier counting method using Bland-Altman plotting with 2 standard deviation yielded no detection at all with its number of outliers unchanging regardless of level of inter-observer variability. Outlier counting based on domain knowledge was more sensitized to different levels of the inter-observer variability compared to the conventional measures (increased: 0.756; observed: 0.923; improved: 1.000). Visualization of pairwise Bland-Altman bias was also sensitized to the inter-observer variability with its pattern rapidly changing in response to different levels of the inter-observer variability.

Conclusions:

Conventional measures may yield weak or no detection when evaluating different levels of the inter-observer variability among radiologists. We observed that the outlier counting based on domain knowledge was sensitized to the inter-observer variability in CT measurement of cancer lesions. Our study demonstrated that, under certain circumstances, the use of standard statistical correlation coefficients may be misleading and result in a sense of false security related to the consistency of measurement for optimal treatment management and decision making.

Strengths and weaknesses of study

- To the best of our knowledge, this manuscript is the first to compare performance of measures commonly used for evaluation of the inter-observer variability in radiologic measurements of cancer lesions.

- The Bland-Altman heat map of pairwise systematic discrepancy offered some useful insight on how the inter-observer variability can be addressed in interventional studies.

- Measurements were collected under a highly controlled environment which differs from the daily realities of clinical practice.

- The cancer lesion image selection process used in the study is potentially subjective, which may limit generalizability of the findings.

BACKGROUND

Clinical evaluation of cancer therapeutics is based on the assessment of change in tumor burden, which is an important surrogate marker reflecting the therapeutic efficacy of cancer treatments. A comprehensive evaluation of tumor burden often involves a series of measurements of multiple tumor diameters. Measurement accuracy and consistency are essential; a large inter-observer variability in measuring tumor size may interfere with precise assessment of cancer treatment response when serial measurements are performed by multiple radiologists. Some studies suggest there are radiologist-dependent factors (e.g. preferred guideline, measurement technique, years of clinical experience) that may contribute variability in the anatomic measurements.[1-6] A potentially heightened patient risk associated with the inter-observer variability may be present when a patient's repeat CT imaging is assigned to a radiologist different from the radiologist who originally measured the tumor. As a result, clinical disagreement due to the variability between the radiologists may result in an unnecessary change in treatment management.

Predominant methods for evaluation of the inter-observer variability in radiologic measurements typically include measures based on statistical correlation coefficient and Bland-Altman plot.[2 7-14] While these measures serve as useful assessment instruments in many other fields,[15-18] their use in evaluating the variability in radiologic measurements has not been adequately explored. There is a paucity of research investigating either the absolute or comparative effectiveness of these measures in evaluating inter-observer measurement variability among radiologists. Despite multiple statistical studies containing an explicit warning against the use of correlation-based measures and visualization in some cases,[19-24] it remains unclear whether the measures are sufficiently responsive to appropriately evaluate the inter-observer variability. Consequently, it is also not known whether these measures can be utilized for interventional studies aiming to reduce inter-observer variability in measurement.[6] Previous studies on inter-observer variability in radiologic measurement have reported correlation coefficient scores ranging from 0.860 to 0.999.[2 7-11 14] From a radiologist's perspective, these numbers offer little clinical insight on level of the inter-observer variability other than the fact that the scores are very high. The question of how high score is small inter-observer variability is open for further investigation.

In this paper using cases with different levels of inter-observer measurement variability, we compare sensitivity and clinical usefulness of different evaluation measures for inter-observer variability in CT lesion measurements. Additionally, cases were assessed using these measures to offer a better clinical insight for the question of how high the scores should be to achieve clinically acceptable measurement variability in daily clinical practice.

METHODS

Our demonstration is based on three cases with increased, observed, and decreased inter-observer measurement variability that were generated from real clinically observed data. Descriptions of how data were generated for each case are detailed below. The observed dataset was acquired from a single-site, double-blinded, observational study, conducted in the Department of Radiology, Prisma Health System, located within the Southeast United States. The study was conducted between July 2017 to December 2017. The Department of Radiology operates in an academic health center but does not train radiology residents.

Collecting observed data

Data were collected from 13 board-certified radiologists who regularly read CT examinations of lung lesions and hepatic metastasis. Each of the 5 lung lesions and 5 hepatic metastases samples were randomly selected from the Picture Archiving and Communication System (PACS) following two primary criteria: a) whether the lesions are measurable under the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 guideline, and b) whether the lesions are commonly encountered in clinical practice. See Supplementary Material 1, which are the selected images. These CT images contained normal anatomy cephalad and caudal to the lesion of interest. Each CT image set did not contain any recommendations regarding measurement. The 13 radiologists independently reviewed the same 10 CT image sets, which resulted in a total of 130 measurements (13×10). Individual radiologists adjusted the window level according to their preferences, as they would in their clinical practice. According to RECIST 1.1 criteria, only the longest CT axis of a tumor image and its corresponding measurement were collected.

Creating cases with different levels of inter-observer variability

The original observed data were used to generate cases with increased, observed, and decreased inter-observer measurement variability. The extent of variability classified as increased, observed, or decreased does not indicate the absolute level of measurement variability; the classifications were used to indicate different cases with relatively high or relatively low inter-observer variability. The original observed data served as the data representing the case with observed inter-observer measurement variability.

We generated data representing the case with increased inter-observer variability by moving each measurement in the observed data away from the nearest peer measurements. Specifically, we inflated the inter-observer variability by increasing the deviation of each measurement from the corresponding median by 40% for each case. Similarly, the deviation of each measurement from the corresponding median was decreased by 40% in the case with decreased inter-observer variability, Figure 1. The percent differences between each measurement and the corresponding median were visualized using scatter plots for all CT image sets, Figure 2. The raw data for each case can be found in Supplementary 2.

Description of Selected Measures for Comparison

We selected evaluation measures based on Intraclass correlation coefficient (ICC) and Bland-Altman plot, which are commonly used for the assessment of intra- and inter-observer variability in CT measurement.[2 7-14] While Bland-Altman plot is graphical method rather than statistical measure, some well-respected studies utilized the plotting for tracking a number of outlier measurement differences outside the 2SD upper and lower Limit of Agreement (LOA).[2 14 25] Accordingly, we quantified Bland-Altman plots using a number of data points exceeding the upper and lower LOA. The plotting compares two radiologists at a time; for each case, we performed a pairwise Bland-Altman analysis for all possible pairs within a group of radiologists and counted the total number of outliers from all pairs, Supplementary 3. If the number of outliers from Bland-Altman plot is sensitized to the different levels of inter-observer variability, more outliers (i.e. higher proportion of outlier measurement differences) would be observed in the case with increased inter-observer variability.

In the clinical context, this pairwise approach explores how safely a patient can be transferred from one radiologist to another within a group of radiologists. If two radiologists reviewed the same set of CT cases but suggested measurements largely different from each other, there may be concerns associated with the patient transfer between the radiologists. Similarly, if two radiologists reviewed the same set of CT cases and suggested measurements similar to each other, the concerns associated with the patient transfer may be marginal. Having more pairs with fewer outlier measurement differences may imply less concern for inter-observer variability when a patient is reviewed by multiple radiologists.

Statistical Analysis

We compared three evaluation measures for the comparison: (1) ICC, (2) Bland-Altman plot with 2SD LOA, (3) Bland-Altman plot with 20% fixed LOA. As for estimations of ICC scores, a two-way random-effects model that characterizes absolute agreement by incorporating both lesion-wise effect (target effect) and radiologist-wise effect (rater effect) was applied for both simulated and observed data.[2 17 26 27] The ICC scores were estimated based on all 130 measurements for each case (increased, observed, decreased).

While Bland-Altman plot allows data to be analyzed both as unit differences plot and as percentage differences plot,[28] we used percent difference plot as suggested by previous studies in the literature.[2 14 27] Bland-Altman plot with 2SD LOA was quantified into score value by calculating proportion of data points within the upper and lower LOA.

Bland-Altman plot with 20% fixed limits was also quantified into score value to compare with ICC and standard Bland-Altman plot with 2SD limits. There have been several clinical studies using Bland-Altman plot with fixed limits of agreement evidenced by relevant domain knowledge.[29 30] This essentially aligns with other studies that utilize clinical domain knowledge to define outliers.[31-34] We fixed the maximum acceptable LOA to assess the measurement interchangeability between radiologists at 20% evidenced by clinical guidelines. The predominant guideline for cancer treatment response evaluation, RECIST 1.1, heavily depends on percent difference in lesion diameter with a progression defined as a 20% increase in the sum of longest diameters.[35 36] The absolute inter-radiologist difference already exceeding 20% in CT measurements may interfere with the application of the 20% criterion from the guideline when a patient is reviewed by different radiologists. Thus, the 20% measurement difference was utilized as the fixed LOA for the Bland-Altman plot. In the context of radiologic measurement, this means that outlier measurement difference is explicitly defined as measurement difference exceeding 20% when a pair of radiologists reviewing the same image.

Bland-Altman plot also allows identification of any systematic difference (mean difference in measurements) between two observers. For each case of inter-observer variability, the mean difference in measurements was calculated for all possible pairs (n=78) and visualized in a heat map, Figure 3.

Patient and public involvement

No patients involved.

RESULTS

Characteristics of CT image sets included in the study

Each CT image set included in the study consisted of multiple CT slices with an average of 7.6 images, Table 1. The minimum and maximum size of the hepatic metastases ranged between 1.68 cm to 2.21 cm and 5.32 cm to 6.72 cm, respectively. The minimum and maximum size of lung lesions ranged between 1.27 cm to 1.68 cm and 3.69 cm to 5.02 cm, respectively. In the observed data, the largest lesion-wise percent difference in measurements was realized in Hepatic Metastasis 5 with 33.1% difference between the minimum and maximum measurements. The smallest lesion-wise percent difference in measurements was realized in Lung Lesion 2 with 14.5% difference between the minimum and maximum measurements.

Table 1. Descriptive statistics for the original observed data

CT image sets	Number of image slices	Median Measurements (S.D.)	Range	Min-Max Percent Difference
Hepatic Metastasis 1	9	4.46 (0.38)	(3.81–5.19)	30.7%
Hepatic Metastasis 2	5	2.68 (0.22)	(2.31–3.03)	27.0%
Hepatic Metastasis 3	5	1.91 (0.18)	(1.68–2.21)	27.2%
Hepatic Metastasis 4	13	6.14 (0.48)	(5.32–6.72)	23.3%
Hepatic Metastasis 5	6	2.68 (0.29)	(2.24–3.13)	33.1%
Lung Lesion 1	8	3.46 (0.24)	(3.10–3.86)	21.8%
Lung Lesion 2	10	4.18 (0.23)	(3.90–4.51)	14.5%
Lung Lesion 3	6	2.00 (0.17)	(1.71–2.37)	32.4%
Lung Lesion 4	10	4.29 (0.36)	(3.69–5.02)	30.5%
Lung Lesion 5	4	1.56 (0.11)	(1.27–1.68)	27.8%

Note: Average measurement and range are in centimeters (cm). S.D. denotes standard deviation. Min denotes minimum measurement for each lesion. Max denotes maximum measurement for each lesion. Percent difference between minimum and maximum values was calculated using the following formula: difference(min, max) / average(min, max). Range consists of (minimum observed value – maximum observed value).

Characteristics of cases with different levels of inter-observer variability

The graph visualization of the data from each case suggested varying levels of inter-observer variability, Figure 2. The visualization of the original observed data suggested a substantial inter-observer variability with 31 (23.8%) measurements outside the light blue area representing plus or minus 10% interval from the average measurement value for each case. Additionally, a lesion-wise effect on inter-observer variability was observed with relatively high measurement variation in some CT image sets. The visualization of the case of decreased inter-observer variability illustrated a small number of measurements outside the threshold with 3 (2.3%) measurements locating outside the plus or minus 10% interval. With the decrease in the deviations of each measurement from the corresponding median, all measurements moved towards average and closer together as intended for demonstration. On the other hand, there was a relatively large number of measurements outside the threshold in the case of increased inter-observer variability with 50 (38.5%) measurements locating outside the plus or minus 10% interval.

Also, it was observed that all measurements were not only shifted away from median, but also moved further away from each other as intended.

Visualization of Bland-Altman Analysis

The heat map visualization of average percent measurement difference (fixed bias) for all pairs of radiologists suggested varying levels of the difference across all pairs, Figure 3. Some pairs of radiologists achieved a lower average percent difference than others. In the heat map of the original observed data, the smallest systematic difference in measurement was observed in the pair of Radiologist 11 and Radiologist 13; they maintained an average of 0.03% difference in their measurements when reviewing the same set of CT images. The largest systematic measurement difference was observed in the pair of Radiologist 1 and Radiologist 6. The systematic difference in their measurements was 13.6% when reviewing the same set of CT images. It was observed that some radiologists attributed more to inter-observer variability than others; Radiologist 1 and 10 generally overestimate lesion size compared to others while Radiologist 2 and 6 generally underestimated lesion size compared to others.

The heat map visualization from the case of increased inter-observer variability showed the increased systematic measurement differences between any two radiologists compared to other cases. Similarly, the heat map visualization from the case of decreased inter-observer variability showed the decreased systematic measurement differences compared to other cases. Overall, the cases with relatively high inter-observer variability tend to present the increased systematic measurement differences between any two radiologists as well as more pairs of radiologists with a systematic measurement difference close to 20% when reviewing the same CT image sets.

Comparison of the selected measures

The original observed data achieved the ICC score of 0.962. The ICC scores in the cases of increased and decreased inter-observer variability were 0.990 and 0.912, respectively. The percent increase in the deviation of each measurement from the corresponding median has a perfect linear relationship with the

ICC score (R-squared = 1.00), Figure 4. However, the magnitude of association was extremely low; 10 percent increase in the deviation was associated with 0.01 decrease in the ICC score. As a result, the graph representing a relationship between a percent increase in the deviation and the corresponding ICC score presented a virtually flat slope, which implies that the score is extremely insensitive to the changes in deviations.

The original observed data achieved the standard Bland-Altman score of 0.937, which indicates 93.7% of data points within lower and upper LOA along with 6.3% outlier data points. The score based on standard Bland-Altman presented flat slope with its score unchanging regardless of level of inter-observer variability (standard Bland-Altman score=0.937).

The presented Bland-Altman score with fixed limits was more responsive to the change in case than other measures. In the case with decreased inter-observer variability, all pairs were identified to have a percent difference less than 20% when reviewing the same CT image sets (fixed-limit Bland-Altman score=1.0). The original observed data suggested Bland-Altman score with fixed limits of 0.923 with 92.3% of all possible pairwise measurements having a percent difference less than 20%. In the case with increased inter-observer variability, 75.6% of measurements were identified to have a percent difference less than 20% when reviewing the same CT image sets. The Bland-Altman score with fixed limits changed by 0.167 (0.756 to 0.923) between increased case and observed data, and 0.077 (0.923 to 1.000) between observed data and increased case, Figure 4.

DISCUSSION

The importance of consistent measurement of cancer lesions in CT scans has been well documented.[10 35 36] We have performed an extensive simulation study using conventional evaluation measures and different cases with varying levels of inter-observer variability. Our study investigated precision of those measures and found that some measures are not sensitive enough to detect the difference between cases with clinically desirable and clinically unacceptable inter-observer variability in radiologic measurement.

The previous studies by McErlean et al and Zhao et al utilized statistical correlation coefficients and standard Bland-Altman plot as primary measures and concluded that serial CT measurements can be safely performed by different radiologists.[2 7] Our study indicated that the correlation-based measures may fail to serve as a true indicator of inter-observer variability. When the observed data were analyzed, the radiologists in our study achieved a high ICC score comparable to previous studies.[2 13] However, as demonstrated above, a high ICC score does not always guarantee low inter-observer variability in the context of radiologic measurement. Our analysis suggests that the statistical correlation-based measures may yield high scores regardless of level of the inter-observer variability among radiologists. Therefore, a group of radiologists who achieved a high ICC score within the group could fail to maintain clinically reasonable measurement consistency. For instance, an ICC score of 0.9 achieved by a group of readers is often considered to be excellent in many other fields.[36 37] However, in the case of cancer treatment response evaluation, the ICC score of 0.9 may raise serious patient safety concerns with radiologists always having at least 10% average percent difference in measurement to each other when reviewing the same CT image sets. In the presented case with increased inter-observer variability, the ICC score of 0.91 was still not high enough to achieve clinically acceptable inter-observer variability in CT measurement, as affirmed by the participating radiologists, Supplementary 2.

Another measure, outlier counts from standard Bland-Altman plotting with 2SD upper and lower LOA, presented no response to the varying levels of inter-observer variability in CT measurements. It was observed that its upper and lower limits increase proportionally to measurement variabilities. Our analysis suggested no evidence to support its use for the assessment of CT measurement variability or outlier detection.

While the standard Bland-Altman and ICC scores changed little across the different cases, the presented Bland-Altman score with 20% fixed limits rapidly changed between cases of increased, observed and decreased inter-observer variability. The presented score is also intuitive to interpret because of its self-descriptive nature; the decrease in the score from 0.923 to 0.756 means that the percentage of pairwise measurements having less than 20% difference has decreased from 92.3% to

75.6%. As documented, the predominant guideline for cancer treatment response evaluation defines a diameter increase of 20% as the cutoff for progression of cancer. If multiple pairs of measurements have 20% or higher measurement difference over the same CT image sets, this may interfere with the application of the 20% criterion from the guideline when a patient is reviewed by different radiologists. The Bland-Altman score with fixed limits demonstrated a potential to detect a decrease in the number of pairs having less than 20% measurement difference when reviewing the same image sets, which may better facilitate the application of guideline.

The Bland-Altman heat map of pairwise systematic discrepancy offered some useful insight on how the inter-observer variability can be addressed in interventional studies. The visualization identified radiologists who largely under- or over-measure compared to their peers, which can be a potential target for intervention to reduce the variability. Risk associated with inter-observer variability is realized when a patient is referred from one radiologist to another or reviewed by different radiologists. The pairwise approach to visualize systematic discrepancy may also be useful in addressing the risk by identifying pair of radiologists whose measurements typically differ greatly from each other.

A potential limitation of the study may result from the image selection process. Although the images were randomly selected from the health system PACS, the application of the selection criteria was performed by one senior radiologist. A selection criterion was whether or not images are commonly encountered in daily clinical practice, which may have introduced a bias in the image selection. Another limitation is that the measurements were collected under a highly controlled environment where the radiologists were rarely interrupted throughout the data collection. It is commonly believed that in real-world clinical practice, one's actual performance may be negatively affected by a heavy workload or various types of interruptions. Lastly, the suggested measure to evaluate dissimilarity between two radiologists is overly simple. There is a need for additional research to understand how the measurement similarity between two radiologists can be better measured in real-world clinical settings.

CONCLUSIONS

Conventional measures may yield weak or no detection when evaluating different levels of the inter-observer variability among radiologists. We observed that the outlier counting based on domain knowledge was sensitized to the inter-observer variability in CT measurement of cancer lesions. Our study demonstrated that, under certain circumstances, the use of standard statistical correlation coefficients may be misleading and result in a sense of false security related to the consistency of measurement. A visualization based on pairwise approach to identify systematic discrepancy may serve as a useful and practical tool for future efforts to reduce the inter-observer variability in radiologic measurement.

Acknowledgements: The authors acknowledge and appreciate the participating radiologists of the Prisma Health System. We also acknowledge and appreciate the logistics and regulatory support of Karen Edwards, MS of the Department of Public Health Sciences, Clemson University.

Authors' contributions: MW designed the study, analyzed the data, and developed the manuscript. MH made substantial contributions to the data analysis and critical revisions. SL and MD acted as Clinical Investigators and contributed substantially to study development and clinical data interpretation. RW served as co-PI and supervised preparation, conduct, and administration of the study. All authors developed, reviewed and approved the manuscript.

Funding statement: This work was supported by supported by Health Science Center, Prisma Health, Greenville, South Carolina (Grant number: Pro00065670).

Ethics approval: Institutional Review Board/Committee A, Greenville Health System (now Prisma Health System), Greenville, South Carolina, USA. Approval/ID# Pro00065670.

Patient consent for publication: Not required.

Disclaimer: The funders played no role in the conceptualisation or realisation of the research and no role in the decision to submit it for publication.

Competing interest statement: No competing interested declared by the authors.

Provenance and peer review: Not commissioned; externally peer reviewed.

Availability of data and materials: The raw data are available in Supplementary Material 2.

Figure legends

Figure 1. Example of increased and decrease inter-observer variability from observed data. To generate a case with increased inter-observer variability, the difference between each measurement and the median value was increased by 40% (right). The difference between each measurement and the median value was decreased by 40% in the case with decreased inter-observer variability (left)

Figure 2. Visualization of measurement distribution for each case. Each vertical line in the graphs represent different CT case and each point represent percent difference between a measurement and the corresponding median value. The light blue area represents plus and minus 10% interval from the median value.

Figure 3. Visualization of pairwise bias from Bland-Altman analysis. The systematic discrepancy (bias) was calculated using average percent differences and presented in decimal format. Darker red colors represent larger percent measurement differences. The positive values indicate that the radiologist on y-axis over-estimated compared to the radiologist on x-axis. The negative values indicate that the radiologist on y-axis under-estimated compared to the radiologist on x-axis.

Figure 4. Responsiveness comparison of Intraclass Correlation Coefficient and Bland-Altman outlier scores. Scaling factor *d* represents percent increase in the deviation of each measurement from the corresponding median. Horizontal axis corresponds to scaling factor *d* used to decrease or increase the inter-observer variability. Vertical axis represent ICC and Bland-Altman scores. Vertical dotted lines in red represent different datasets. *ICC score* – Intraclass Correlation Coefficient. *2SD* – 2 Standard Deviation.

REFERENCES

1. Jiang B, Zhou D, Sun Y, et al. Systematic analysis of measurement variability in lung cancer with multidetector computed tomography. *Ann Thorac Med* 2017;12(2):95-100. doi: 10.4103/1817-1737.203750

2. McErlean A, Panicek DM, Zabor EC, et al. Intra- and interobserver variability in CT measurements in oncology. *Radiology* 2013;269(2):451-9. doi: 10.1148/radiol.13122665

3. Oxnard GR, Zhao B, Sima CS, et al. Variability of lung tumor measurements on repeat computed tomography scans taken within 15 minutes. *J Clin Oncol* 2011;29(23):3114-9. doi: 10.1200/JCO.2010.33.7071

4. Singh S, Maxwell J, Baker JA, et al. Computer-aided classification of breast masses: performance and interobserver variability of expert radiologists versus residents. *Radiology* 2011;258(1):73-80. doi: 10.1148/radiol.10081308

5. Thiesse P, Ollivier L, Di Stefano-Louineau D, et al. Response rate accuracy in oncology trials: reasons for interobserver variability. Groupe Francais d'Immunotherapie of the Federation Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol* 1997;15(12):3507-14. doi: 10.1200/JCO.1997.15.12.3507

6. Woo M, Lowe SL, Devane AM, et al. Intervention to reduce inter-observer variability in CT measurement of cancer lesions among experienced radiologists. *Curr Probl Diagn Radiol* 2020 doi: 10.1067/j.cpradiol.2020.01.008 [published Online First: Jan 10]

7. Zhao B, James LP, Moskowitz CS, et al. Evaluating variability in tumor measurements from same-day repeat CT scans of patients with non-small cell lung cancer. *Radiology* 2009;252(1):263-72. doi: 10.1148/radiol.2522081593

8. Wormanns D, Diederich S, Lentschig MG, et al. Spiral CT of pulmonary nodules: interobserver variation in assessment of lesion size. *Eur Radiol* 2000;10(5):710-3. doi: 10.1007/s003300050990

9. Tyng CJ, Chojniak R, Pinto PN, et al. Conformal radiotherapy for lung cancer: interobservers' variability in the definition of gross tumor volume between radiologists and radiotherapists. *Radiat Oncol* 2009;4:28. doi: 10.1186/1748-717X-4-28

10. Nishino M, Jackman DM, Hatabu H, et al. New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for advanced non-small cell lung cancer: comparison with original RECIST and impact on assessment of tumor response to targeted therapy. *AJR Am J Roentgenol* 2010;195(3):W221-8. doi: 10.2214/AJR.09.3928

11. Chung MS, Cheng KL, Choi YJ, et al. Interobserver reproducibility of cervical lymph node measurements at CT in patients with head and neck squamous cell carcinoma. *Clin Radiol* 2016;71(12):1226-32. doi: 10.1016/j.crad.2016.07.014

12. Cornelis FH, Martin M, Saut O, et al. Precision of manual two-dimensional segmentations of lung and liver metastases and its impact on tumour response assessment using RECIST 1.1. *Eur Radiol Exp* 2017;1(1):16. doi: 10.1186/s41747-017-0015-4

13. Dinkel J, Khalilzadeh O, Hintze C, et al. Inter-observer reproducibility of semi-automatic tumor diameter measurement and volumetric analysis in patients with lung cancer. *Lung Cancer* 2013;82(1):76-82. doi: 10.1016/j.lungcan.2013.07.006

14. Krajewski KM, Nishino M, Franchetti Y, et al. Intraobserver and interobserver variability in computed tomography size and attenuation measurements in patients with renal cell carcinoma receiving antiangiogenic therapy: implications for alternative response criteria. *Cancer* 2014;120(5):711-21. doi: 10.1002/cncr.28493 [published Online First: 11/21]

15. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86(2):420-8.

16. Hemphill JF. Interpreting the magnitudes of correlation coefficients. *Am Psychol* 2003;58(1):78-9.

17. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. *Malawi Med J* 2012;24(3):69-71.

18. Wolak ME, Fairbairn DJ, Paulsen YR. Guidelines for estimating repeatability. *Methods Ecol Evol* 2012;3(1):129-37. doi: 10.1111/j.2041-210X.2011.00125.x

19. Liljequist D, Elfving B, Skavberg Roaldsen K. Intraclass correlation – A discussion and demonstration of basic features. *PLoS One* 2019;14(7):e0219854. doi: 10.1371/journal.pone.0219854

20. Bobak CA, Barr PJ, O'Malley AJ. Estimation of an inter-rater intra-class correlation coefficient that overcomes common assumption violations in the assessment of health measurement scales. *BMC Med Res Methodol* 2018;18(1):93.

21. Shoukri M, Donner A. Efficiency considerations in the analysis of inter-observer agreement. *Biostatistics* 2001;2(3):323-36.

22. Weinberg R, Patel YC. Simulated intraclass correlation coefficients and their z transforms. *J Stat Comput Simul* 1981;13(1):13-26.

23. Ponzoni R, James J. Possible biases in heritability estimates from intraclass correlation. *Theor Appl Genet* 1978;53(1):25-27.

24. Ludbrook J. Confidence in Altman-Bland plots: a critical review of the method of differences. *Clin Exp Pharmacol Physiol* 2010;37(2):143-9. doi: 10.1111/j.1440-1681.2009.05288.x

25. Faria SL, Faria OP, Cardeal MDA, et al. Validation Study of Multi-Frequency Bioelectrical Impedance with Dual-Energy X-ray Absorptiometry Among Obese Patients. *Obesity Surgery* 2014;24(9):1476-80. doi: 10.1007/s11695-014-1190-5

26. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med* 2016;15(2):155-63.

27. Gutin B, Litaker M, Islam S, et al. Body-composition measurement in 9-11-y-old children by dual-energy X-ray absorptiometry, skinfold-thickness measurements, and bioimpedance analysis. *Am J Clin Nutr* 1996;63(3):287-92. doi: 10.1093/ajcn/63.3.287

28. Giavarina D. Understanding Bland Altman analysis. *Biochemia medica* 2015;25(2):141-51. doi: 10.11613/BM.2015.015

29. Bogui P, Balayssac-Siransy E, Connes P, et al. The PhysioFlow thoracic impedancemeter is not valid for the measurements of cardiac hemodynamic parameters in chronic anemic patients. *PLoS One* 2013;8(10):e79086-e86. doi: 10.1371/journal.pone.0079086

30. Vent-Schmidt J, Waltz X, Pichon A, et al. Indirect viscosimetric method is less accurate than ektacytometry for the measurement of red blood cell deformability. *Clin Hemorheol Microcirc* 2015;59(2):115-21. doi: 10.3233/CH-131727

31. Schold JD, Miller CM, Henry ML, et al. Evaluation of Flagging Criteria of United States Kidney Transplant Center Performance: How to Best Define Outliers? *Transplantation* 2017;101(6):1373-80. doi: 10.1097/TP.0000000000001373

32. Bergamin O, Anderson SC, Kardon RH. An objective method to define outlier optical coherence tomograms and repeatability of retinal nerve fibre layer measurements. *Acta Ophthalmol Scand* 2004;82(5):535-43. doi: 10.1111/j.1600-0420.2004.00316.x

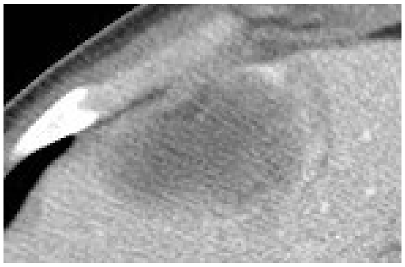
33. Montalbano A, Quinonez RA, Hall M, et al. Achievable Benchmarks of Care for Pediatric Readmissions. *J Hosp Med* 2019;14:E1-E7. doi: 10.12788/jhm.3201

34. Motulsky HJ, Brown RE. Detecting outliers when fitting data with nonlinear regression - a new method based on robust nonlinear regression and the false discovery rate. *BMC Bioinformatics* 2006;7:123. doi: 10.1186/1471-2105-7-123

35. Nishino M, Jagannathan JP, Ramaiya NH, et al. Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. *AJR Am J Roentgenol* 2010;195(2):281-9. doi: 10.2214/AJR.09.4110

36. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1: Update and clarification: From the RECIST committee. *Eur J Cancer* 2016;62:132-37. doi: 10.1016/j.ejca.2016.03.081

37. Gellhorn AC, Carlson MJ. Inter-rater, intra-rater, and inter-machine reliability of quantitative ultrasound measurements of the patellar tendon. *Ultrasound Med Biol* 2013;39(5):791-96.



Decreased Inter-observer Variability	
Radiologist	Measurement (cm)
7	5.65
6	5.68
2	5.85
8	5.96
13	6.02
9	6.15
3	6.18
4	6.34
5	6.34
12	6.37
11	6.41
10	6.44
1	6.49

Observed Inter-observer Variability	
Radiologist	Measurement (cm)
7	5.32
6	5.37
2	5.65
8	5.84
13	5.93
9	6.15
3	6.21
4	6.47
5	6.47
12	6.52
11	6.58
10	6.63
1	6.72

Increased Inter-observer Variability	
Radiologist	Measurement (cm)
7	4.99
6	5.06
2	5.45
8	5.72
13	5.84
9	6.15
3	6.24
4	6.6
5	6.6
12	6.67
11	6.75
10	6.82
1	6.95

Figure 1. Example of increased and decrease inter-observer variability from observed data. To generate a case with increased inter-observer variability, the difference between each measurement and the median value was increased by 40% (right). The difference between each measurement and the median value was decreased by 40% in the case with decreased inter-observer variability (left).

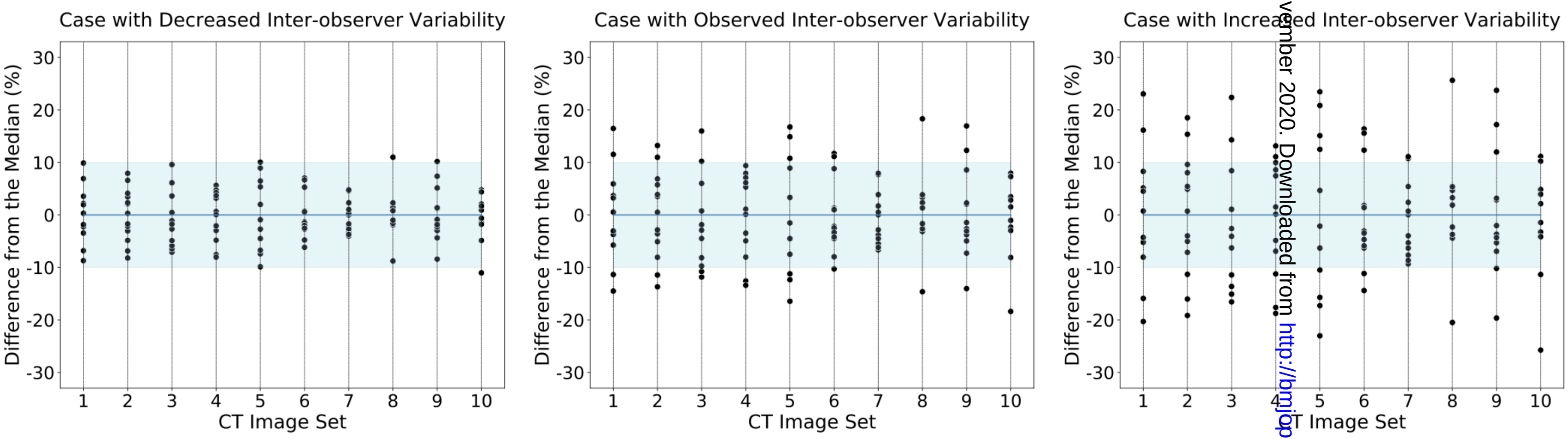
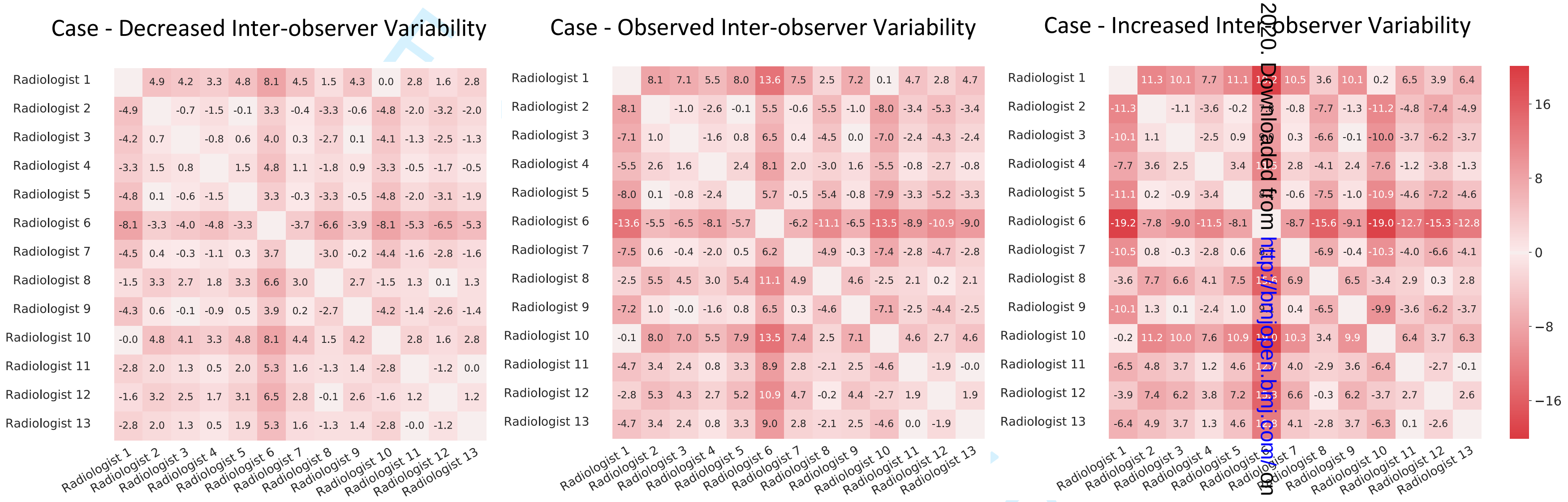


Figure 2. Visualization of measurement distribution for each case. Each vertical line in the graphs represent different CT case and each point represent percent difference between a measurement and the corresponding median value. The light blue area represents plus and minus 10% interval from the median value.



Case - Decreased Inter-observer Variability

	Radiologist 1	Radiologist 2	Radiologist 3	Radiologist 4	Radiologist 5	Radiologist 6	Radiologist 7	Radiologist 8	Radiologist 9	Radiologist 10	Radiologist 11	Radiologist 12	Radiologist 13
Radiologist 1		4.9	4.2	3.3	4.8	8.1	4.5	1.5	4.3	0.0	2.8	1.6	2.8
Radiologist 2	-4.9		-0.7	-1.5	-0.1	3.3	-0.4	-3.3	-0.6	-4.8	-2.0	-3.2	-2.0
Radiologist 3	-4.2	0.7		-0.8	0.6	4.0	0.3	-2.7	0.1	-4.1	-1.3	-2.5	-1.3
Radiologist 4	-3.3	1.5	0.8		1.5	4.8	1.1	-1.8	0.9	-3.3	-0.5	-1.7	-0.5
Radiologist 5	-4.8	0.1	-0.6	-1.5		3.3	-0.3	-3.3	-0.5	-4.8	-2.0	-3.1	-1.9
Radiologist 6	-8.1	-3.3	-4.0	-4.8	-3.3		-3.7	-6.6	-3.9	-8.1	-5.3	-6.5	-5.3
Radiologist 7	-4.5	0.4	-0.3	-1.1	0.3	3.7		-3.0	-0.2	-4.4	-1.6	-2.8	-1.6
Radiologist 8	-1.5	3.3	2.7	1.8	3.3	6.6	3.0		2.7	-1.5	1.3	0.1	1.3
Radiologist 9	-4.3	0.6	-0.1	-0.9	0.5	3.9	0.2	-2.7		-4.2	-1.4	-2.6	-1.4
Radiologist 10	-0.0	4.8	4.1	3.3	4.8	8.1	4.4	1.5	4.2		2.8	1.6	2.8
Radiologist 11	-2.8	2.0	1.3	0.5	2.0	5.3	1.6	-1.3	1.4	-2.8		-1.2	0.0
Radiologist 12	-1.6	3.2	2.5	1.7	3.1	6.5	2.8	-0.1	2.6	-1.6	1.2		1.2
Radiologist 13	-2.8	2.0	1.3	0.5	1.9	5.3	1.6	-1.3	1.4	-2.8	-0.0	-1.2	

Case - Observed Inter-observer Variability

	Radiologist 1	Radiologist 2	Radiologist 3	Radiologist 4	Radiologist 5	Radiologist 6	Radiologist 7	Radiologist 8	Radiologist 9	Radiologist 10	Radiologist 11	Radiologist 12	Radiologist 13
Radiologist 1		8.1	7.1	5.5	8.0	13.6	7.5	2.5	7.2	0.1	4.7	2.8	4.7
Radiologist 2	-8.1		-1.0	-2.6	-0.1	5.5	-0.6	-5.5	-1.0	-8.0	-3.4	-5.3	-3.4
Radiologist 3	-7.1	1.0		-1.6	0.8	6.5	0.4	-4.5	0.0	-7.0	-2.4	-4.3	-2.4
Radiologist 4	-5.5	2.6	1.6		2.4	8.1	2.0	-3.0	1.6	-5.5	-0.8	-2.7	-0.8
Radiologist 5	-8.0	0.1	-0.8	-2.4		5.7	-0.5	-5.4	-0.8	-7.9	-3.3	-5.2	-3.3
Radiologist 6	-13.6	-5.5	-6.5	-8.1	-5.7		-6.2	-11.1	-6.5	-13.5	-8.9	-10.9	-9.0
Radiologist 7	-7.5	0.6	-0.4	-2.0	0.5	6.2		-4.9	-0.3	-7.4	-2.8	-4.7	-2.8
Radiologist 8	-2.5	5.5	4.5	3.0	5.4	11.1	4.9		4.6	-2.5	2.1	0.2	2.1
Radiologist 9	-7.2	1.0	-0.0	-1.6	0.8	6.5	0.3	-4.6		-7.1	-2.5	-4.4	-2.5
Radiologist 10	-0.1	8.0	7.0	5.5	7.9	13.5	7.4	2.5	7.1		4.6	2.7	4.6
Radiologist 11	-4.7	3.4	2.4	0.8	3.3	8.9	2.8	-2.1	2.5	-4.6		-1.9	-0.0
Radiologist 12	-2.8	5.3	4.3	2.7	5.2	10.9	4.7	-0.2	4.4	-2.7	1.9		1.9
Radiologist 13	-4.7	3.4	2.4	0.8	3.3	9.0	2.8	-2.1	2.5	-4.6	0.0	-1.9	

Case - Increased Inter-observer Variability

	Radiologist 1	Radiologist 2	Radiologist 3	Radiologist 4	Radiologist 5	Radiologist 6	Radiologist 7	Radiologist 8	Radiologist 9	Radiologist 10	Radiologist 11	Radiologist 12	Radiologist 13
Radiologist 1		11.3	10.1	7.7	11.1	19.2	10.5	3.6	10.1	0.2	6.5	3.9	6.4
Radiologist 2	-11.3		-1.1	-3.6	-0.2	7.8	-0.8	-7.7	-1.3	-11.2	-4.8	-7.4	-4.9
Radiologist 3	-10.1	1.1		-2.5	0.9	9.0	0.3	-6.6	-0.1	-10.0	-3.7	-6.2	-3.7
Radiologist 4	-7.7	3.6	2.5		3.4	11.5	2.8	-4.1	2.4	-7.6	-1.2	-3.8	-1.3
Radiologist 5	-11.1	0.2	-0.9	-3.4		8.1	-0.6	-7.5	-1.0	-10.9	-4.6	-7.2	-4.6
Radiologist 6	-19.2	-7.8	-9.0	-11.5	-8.1		-8.7	-15.6	-9.1	-19.0	-12.7	-15.3	-12.8
Radiologist 7	-10.5	0.8	-0.3	-2.8	0.6	8.7		-6.9	-0.4	-10.3	-4.0	-6.6	-4.1
Radiologist 8	-3.6	7.7	6.6	4.1	7.5	15.6	6.9		6.5	-3.4	2.9	0.3	2.8
Radiologist 9	-10.1	1.3	0.1	-2.4	1.0	9.1	0.4	-6.5		-9.9	-3.6	-6.2	-3.7
Radiologist 10	-0.2	11.2	10.0	7.6	10.9	19.0	10.3	3.4	9.9		6.4	3.7	6.3
Radiologist 11	-6.5	4.8	3.7	1.2	4.6	12.7	4.0	-2.9	3.6	-6.4		-2.7	-0.1
Radiologist 12	-3.9	7.4	6.2	3.8	7.2	15.3	6.6	-0.3	6.2	-3.7	2.7		2.6
Radiologist 13	-6.4	4.9	3.7	1.3	4.6	12.8	4.1	-2.8	3.7	-6.3	0.1	-2.6	

Figure 3. Visualization of pairwise bias from Bland-Altman analysis. The systematic discrepancy (bias) was calculated using average percent differences and presented in decimal format. Darker red colors represent larger percent measurement differences. The positive values indicate that the radiologist on y-axis over-estimated compared to the radiologist on x-axis. The negative values indicate that the radiologist on y-axis under-estimated compared to the radiologist on x-axis.

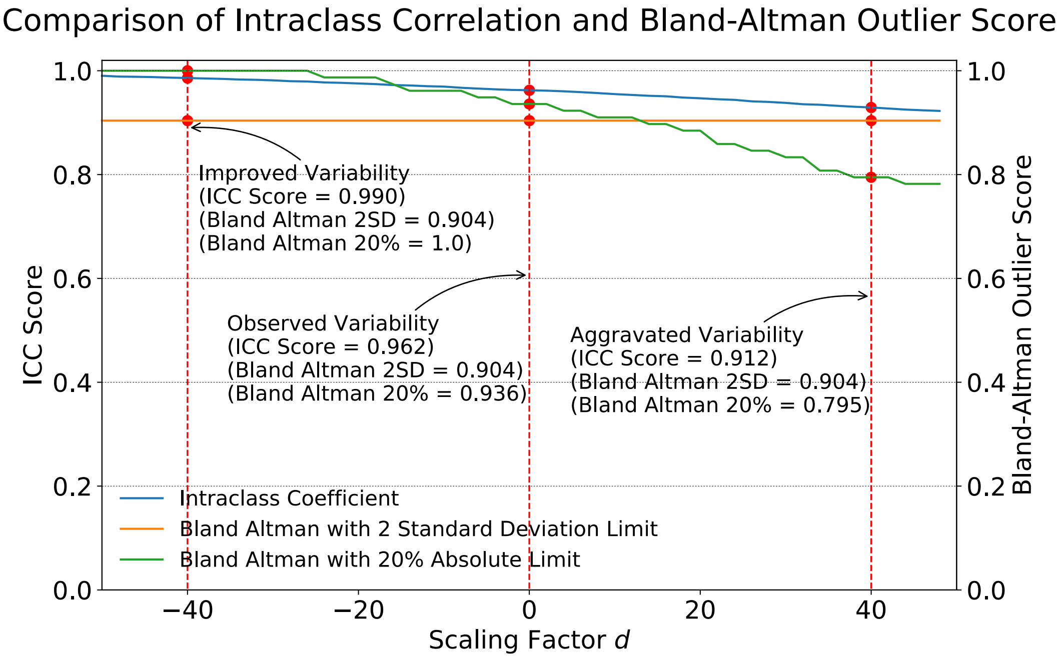
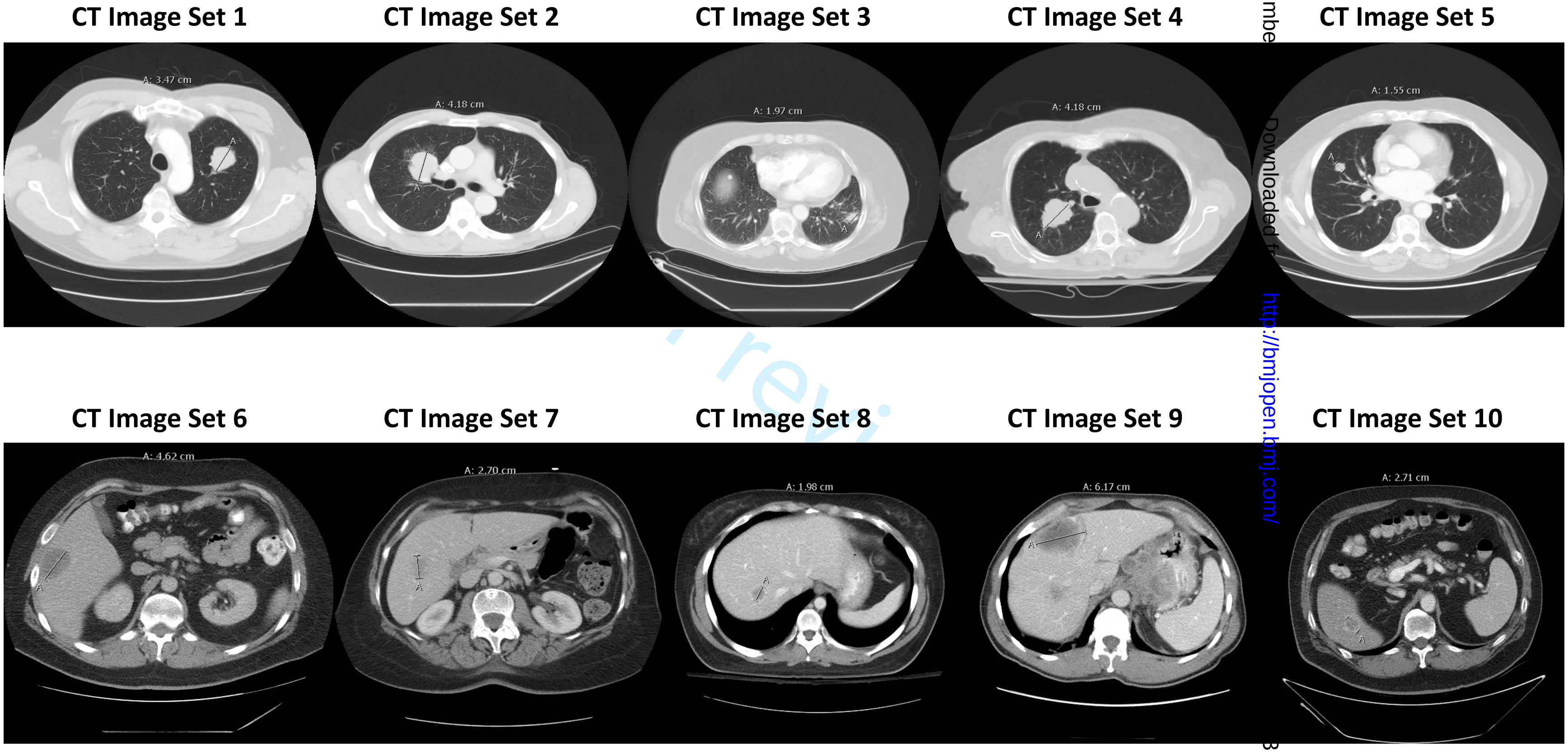


Figure 4. Responsiveness comparison of Intraclass Correlation Coefficient and Bland-Altman outlier scores. Scaling factor *d* represents percent increase in the deviation of each measurement from the corresponding median. Horizontal axis corresponds to scaling factor *d* used to decrease or increase the inter-observer variability. Vertical axis represent ICC and Bland-Altman scores. Vertical dotted lines in red represent different datasets. *ICC score* – Intraclass Correlation Coefficient. *2SD* – 2 Standard Deviation.

Supplementary 1.

Examples of measurement for all CT image sets used in this study.



Supplementary 2.

To generate new data *M'ik* for the *i*-th radiologist measurement of the *k*-th case representing each case, we used the following formula with a function of a scaling factor *d* on a percent scale:

$$M'_{ik} = \overline{M_k} + (1 + d/100)(M_{ik} - \overline{M_k}).$$

Here, M_{ik} is the observed reading of the *i*-th radiologist *i* for the *k*-th case, and $\overline{M_k}$ is the median of measurements for the k-th case over all 13 radiologists. Specifically, we adjusted the inter-observer variability by assigning different values of the factor *d* to the deviation $M_{ik} - \overline{M_k}$ for each radiologist. We assigned *d* = 40, 0, and -40 so that the generated new *M'ik* measurement data represent those with increased, observed, and decreased inter-observer variability, respectively; the deviation of each radiologist-level measurement from the case-specific mean was increased, unchanged, or decreased by *d*%.

Case with Increased Inter-observer Variability													
Set	Radiologist												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1	5.14	4.20	3.52	3.71	4.46	4.06	4.65	4.19	4.62	4.23	4.46	5.45	4.79
2	2.87	2.47	2.79	2.91	2.23	2.14	2.52	3.07	2.80	3.15	2.35	2.68	2.55
3	2.23	1.84	1.98	1.91	1.88	1.64	1.67	2.38	2.38	2.12	1.70	1.98	1.74
4	6.86	5.36	6.14	6.51	6.51	4.97	4.90	5.63	6.06	6.73	6.66	6.58	5.75
5	3.14	2.27	2.12	2.57	2.86	2.46	2.32	3.30	2.86	3.07	2.57	3.37	2.68
6	3.46	3.44	4.13	3.62	3.40	3.34	4.10	3.61	3.06	3.36	3.99	3.18	3.61
7	4.40	3.95	4.63	4.01	3.79	3.86	4.63	4.18	3.91	4.21	4.64	3.81	4.28
8	2.03	2.48	2.06	1.88	2.03	1.56	1.89	1.92	1.56	2.00	2.07	2.00	2.07
9	4.15	4.29	4.96	5.19	4.15	4.01	4.22	4.36	3.61	5.47	4.57	4.26	4.59
10	1.70	1.47	1.12	1.46	1.35	1.60	1.60	1.50	1.56	1.68	1.50	1.58	1.68

Case with Observed Inter-observer Variability													
Set	Radiologist												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1	4.95	4.28	3.79	3.93	4.46	4.18	4.60	4.27	4.58	4.30	4.46	5.17	4.70
2	2.82	2.53	2.76	2.85	2.36	2.30	2.57	2.96	2.77	3.02	2.45	2.68	2.59
3	2.14	1.86	1.96	1.91	1.89	1.72	1.74	2.25	2.25	2.06	1.76	1.96	1.79
4	6.65	5.58	6.14	6.40	6.40	5.30	5.25	5.77	6.08	6.56	6.51	6.45	5.86
5	3.01	2.39	2.28	2.60	2.81	2.52	2.42	3.12	2.81	2.96	2.60	3.17	2.68
6	3.46	3.45	3.94	3.58	3.42	3.38	3.92	3.57	3.18	3.39	3.84	3.26	3.57
7	4.34	4.02	4.50	4.06	3.90	3.95	4.50	4.18	3.99	4.20	4.51	3.92	4.25
8	2.02	2.34	2.04	1.91	2.02	1.68	1.92	1.94	1.68	2.00	2.05	2.00	2.05
9	4.19	4.29	4.77	4.93	4.19	4.09	4.24	4.34	3.80	5.13	4.49	4.27	4.50
10	1.66	1.50	1.25	1.49	1.41	1.59	1.59	1.52	1.56	1.65	1.52	1.58	1.65

Case with Decreased Inter-observer Variability													
Set	Radiologist												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1	4.75	4.35	4.05	4.14	4.46	4.29	4.54	4.34	4.53	4.36	4.46	4.88	4.60
2	2.76	2.59	2.72	2.78	2.48	2.45	2.61	2.84	2.73	2.88	2.54	2.68	2.62
3	2.04	1.88	1.94	1.91	1.89	1.79	1.80	2.11	2.11	2.00	1.82	1.94	1.83
4	6.45	5.81	6.14	6.30	6.30	5.64	5.61	5.92	6.11	6.40	6.37	6.33	5.98
5	2.88	2.51	2.44	2.63	2.76	2.58	2.52	2.94	2.76	2.85	2.63	2.97	2.68
6	3.46	3.45	3.74	3.53	3.43	3.41	3.73	3.52	3.29	3.41	3.68	3.34	3.52
7	4.27	4.08	4.37	4.11	4.01	4.04	4.37	4.18	4.06	4.19	4.38	4.02	4.22
8	2.02	2.21	2.03	1.95	2.02	1.81	1.96	1.97	1.81	2.00	2.03	2.00	2.03
9	4.23	4.29	4.58	4.68	4.23	4.17	4.26	4.32	4.00	4.80	4.41	4.28	4.42
10	1.62	1.52	1.37	1.51	1.47	1.57	1.57	1.53	1.56	1.61	1.53	1.57	1.61

Supplementary 3.

Average percent systematic difference using pairwise approach

The pairwise average percent systematic difference δ_{ij} was calculated for Bland-Altman analysis. The measure is based on the average difference in measurement between any pair of the i-th and j-th radiologists for the k-th cases as follows.

$$\delta_{ij} = \frac{2}{K}\sum_{k=1}^{K}\frac{M_{ik} - M_{jk}}{M_{ik} + M_{jk}}$$

Here, K is the number of cases (in our study $K = 10$), and M_{ik} is a measurement value of the i-th radiologist for the k-th case.

Bland-Altman outlier scores with standard and fixed-limit

The standard Bland-Altman outlier scores Υ_{2SD} is reliant on the percentage of pairwise measurement difference less than 2 standard deviations. Similarly, the Bland-Altman scores $\Upsilon_{20\%}$ with 20% fixed limit is reliant on the percentage of pairwise measurement difference less than 20% and calculated as follows:

$$\Upsilon_{2\mathrm{SD}} = \frac{(N-2)!}{N!}\sum_{i=1}^{N}\sum_{j=1}^{N} 1\left(\frac{|\,M_{ik} - M_{jk}\,|}{M_{ik} + M_{jk}} < 2SD\right)$$

$$\Upsilon_{20\%} = \frac{(N-2)!}{N!}\sum_{i=1}^{N}\sum_{j=1}^{N} 1\left(\frac{|\,M_{ik} - M_{jk}\,|}{M_{ik} + M_{jk}} < 0.2\right)$$

Here, 1(A) is an indicator function whose value is 1 if A is true and 0 otherwise. N represents the number of radiologists. The fixed-limit Bland-Altman outlier scores were based on the percentage of pairs where a pair of radiologists reviewed the same CT image set and resulted in measurements that differ by less than 20%.

BMJ Open

Retrospective Comparison of Approaches to Evaluating Inter-observer Variability in CT Tumor Measurements in an Academic Health Center

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2020-040096.R1
Article Type:	Original research
Date Submitted by the Author:	13-Oct-2020
Complete List of Authors:	Woo, MinJae; Clemson University, Public Health Sciences Heo, Moonseong; Clemson University, Public Health Sciences Devane, Aron; Prisma Health Upstate, Radiology Lowe, Steven; Prisma Health Upstate, Radiology Gimbel, Ronald; Clemson, Public Health Sciences
<b>Primary Subject Heading</b>:	Radiology and imaging
Secondary Subject Heading:	Research methods
Keywords:	Computed tomography < RADIOLOGY & IMAGING, Quality in health care < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Adult oncology < ONCOLOGY

Retrospective Comparison of Approaches to Evaluating Inter-observer Variability in CT Tumor Measurements in an Academic Health Center

MinJae Woo, MS[1], Moonseong Heo, PhD[1], A. Michael Devane, MD[2], Steven L. Lowe, MD[2], Ronald W. Gimbel, PhD[1]

[1] Department of Public Health Sciences, Clemson University, Clemson, SC, USA
[2] Department of Radiology, Prisma Health System, Greenville, SC, USA

Work originated/research site:
Department of Radiology
Prisma Health System
200 Patewood Drive
Greenville, SC 29615

Corresponding author:
Ronald W. Gimbel, PhD
Chair, Department of Public Health Sciences
501 Edwards Hall
Clemson University
Clemson, SC 29634
(864) 656-1969 – *office*
(864) 656-6227 - *telefax*
rgimbel@clemson.edu

Manuscript type: Original Research

Keywords: Computed tomography, inter-observer variability, cancer lesions, decision making,

correlation coefficients, radiologists

Word count (excluding title, abstract, references, figures, and tables): 3,233

ABSTRACT

Background:

A growing number of research studies have reported inter-observer variability in sizes of tumors measured from computed tomography (CT) scans. It remains unclear whether the conventional statistical measures correctly evaluate the CT measurement consistency for optimal treatment management and decision making. We compared and evaluated the existing measures for evaluating inter-observer variability in CT measurement of cancer lesions.

Methods:

13 board-certified radiologists repeatedly reviewed 10 CT image sets of lung lesions and hepatic metastases selected through a randomization process. A total of 130 measurements under RECISTS 1.1 guidelines were collected for the demonstration. Intraclass correlation coefficient (ICC), Bland-Altman plotting, and outlier counting methods were selected for the comparison. The each selected measure was used to evaluate three cases with observed, increased, and decreased inter-observer variability.

Results:

The ICC score yielded a weak detection when evaluating different levels of the inter-observer variability among radiologists (increased: 0.912; observed: 0.962; decreased: 0.990). The outlier counting method using Bland-Altman plotting with 2 standard deviation yielded no detection at all with its number of outliers unchanging regardless of level of inter-observer variability. Outlier counting based on domain knowledge was more sensitized to different levels of the inter-observer variability compared to the conventional measures (increased: 0.756; observed: 0.923; improved: 1.000). Visualization of pairwise Bland-Altman bias was also sensitized to the inter-observer variability with its pattern rapidly changing in response to different levels of the inter-observer variability.

Conclusions:

Conventional measures may yield weak or no detection when evaluating different levels of the inter-observer variability among radiologists. We observed that the outlier counting based on domain knowledge was sensitized to the inter-observer variability in CT measurement of cancer lesions. Our study demonstrated that, under certain circumstances, the use of standard statistical correlation coefficients may be misleading and result in a sense of false security related to the consistency of measurement for optimal treatment management and decision making.

Article summary

Strengths and limitations of this study

- While several conventional statistical measures are frequently used to evaluate inter-observer variability in radiologic measurement, very few comparative studies have been performed to quantify the relative merits of the measures.
- The study demonstrated there is no evidence to support the use of statistical correlation coefficient for the assessment of inter-observer measurement variability.
- This is a retrospective study conducted in a single academic health center.
- Another limitation may be the measurements collected under a highly controlled environment where the radiologists were rarely interrupted throughout the data collection.

BACKGROUND

Clinical evaluation of cancer therapeutics is based on the assessment of change in tumor burden, which is an important surrogate marker reflecting the therapeutic efficacy of cancer treatments. A comprehensive evaluation of tumor burden often involves a series of measurements of multiple tumor diameters. Measurement accuracy and consistency are essential; a large inter-observer variability in measuring tumor size may interfere with precise assessment of cancer treatment response when serial measurements are performed by multiple radiologists. Some studies suggest there are radiologist-dependent factors (e.g. preferred guideline, measurement technique, years of clinical experience) that may contribute variability in the anatomic measurements.[1-6] A potentially heightened patient risk associated with the inter-observer variability may be present when a patient's repeat CT imaging is assigned to a radiologist different from the radiologist who originally measured the tumor. As a result, clinical disagreement due to the variability between the radiologists may result in an unnecessary change in treatment management.

Predominant methods for evaluation of the inter-observer variability in radiologic measurements typically include measures based on statistical correlation coefficient and Bland-Altman plot.[2 7-14] Intraclass correlation coefficient (ICC) is a widely used reliability measure comparing the variability of different ratings by the same raters to the total variation across all ratings and all raters.[15] This reliability measure can be used for test-retest, intra-rater, and inter-rater reliability analyses when the rating scale is continuous or ordinal. The Bland-Altman plotting is another popular exploratory analysis approach for intra-rater, and inter-rater reliability when two paired measurements use the same scale.[16]

While these measures serve as useful assessment instruments in many other fields,[17-20] their use in evaluating the variability in radiologic measurements has not been adequately explored. There is a paucity of research investigating either the absolute or comparative effectiveness of these measures in evaluating inter-observer measurement variability among radiologists. Despite multiple statistical studies containing an explicit warning against the use of correlation-based measures and visualization in some cases,[15 21-25] it remains unclear whether the measures are sufficiently responsive to appropriately evaluate the inter-observer variability. Consequently, it is also not known whether these measures can be utilized for interventional studies aiming to reduce inter-observer variability in measurement.[6] Previous studies on inter-observer variability in radiologic measurement have reported correlation coefficient scores ranging from 0.860 to 0.999.[2 7-11 14] From a radiologist's perspective, these numbers offer little clinical insight on level of the inter-observer variability other than the fact that the scores are very high. The question of how high score is small inter-observer variability is open for further investigation.

In this paper using cases with different levels of inter-observer measurement variability, we compare sensitivity and clinical usefulness of different evaluation measures for inter-observer variability in CT lesion measurements. Additionally, cases were assessed using these measures to offer a better clinical insight for the question of how high the scores should be to achieve clinically acceptable measurement variability in daily clinical practice.

METHODS

Our demonstration is based on three cases with increased, observed, and decreased inter-observer measurement variability that were generated from real clinically observed data. Descriptions of how data were generated for each case are detailed below. The observed dataset was acquired from a single-site, double-blinded, observational study, conducted in the Department of Radiology, Prisma Health System, located within the Southeast United States. The study was conducted between July 2017 to December 2017. The Department of Radiology operates in an academic health center but does not train radiology residents.

Collecting observed data

Data were collected from 13 board-certified radiologists who regularly read CT examinations of lung lesions and hepatic metastasis. Each of the 5 lung lesions and 5 hepatic metastases samples were randomly selected from the Picture Archiving and Communication System (PACS) following two primary criteria: a) whether the lesions are measurable under the Response Evaluation Criteria in Solid

Tumors (RECIST) 1.1 guideline, and b) whether the lesions are commonly encountered in clinical practice. See Supplementary Material 1, which are the selected images. These CT images contained normal anatomy cephalad and caudal to the lesion of interest. Each CT image set did not contain any recommendations regarding measurement. The 13 radiologists independently reviewed the same 10 CT image sets, which resulted in a total of 130 measurements (13×10). Individual radiologists adjusted the window level according to their preferences, as they would in their clinical practice. According to RECIST 1.1 criteria, only the longest CT axis of a tumor image and its corresponding measurement were collected.

Creating cases with different levels of inter-observer variability

The original observed data were used to generate cases with increased, observed, and decreased inter-observer measurement variability. The extent of variability classified as increased, observed, or decreased does not indicate the absolute level of measurement variability; the classifications were used to indicate different cases with relatively high or relatively low inter-observer variability. The original observed data served as the data representing the case with observed inter-observer measurement variability.

We generated data representing the case with increased inter-observer variability by moving each measurement in the observed data away from the nearest peer measurements. Specifically, we inflated the inter-observer variability by increasing the deviation of each measurement from the corresponding median by 40% to create a case with evidently unacceptable measurement variability. Similarly, the deviation of each measurement from the corresponding median was decreased by 40% in the case with decreased inter-observer variability, Figure 1. The percent differences between each measurement and the corresponding median were visualized using scatter plots for all CT image sets, Figure 2. The raw data for each case can be found in Supplementary 2.

Description of Selected Measures for Comparison

We selected evaluation measures based on Intraclass correlation coefficient (ICC) and Bland-Altman plot, which are commonly used for the assessment of intra- and inter-observer variability in CT measurement.[2 7-14] While Bland-Altman plot is graphical method rather than statistical measure, some well-respected studies utilized the plotting for tracking a number of outlier measurement differences outside the 2SD upper and lower Limit of Agreement (LOA).[2 14 26] Accordingly, we quantified Bland-Altman plots using a number of data points exceeding the upper and lower LOA. The plotting compares two radiologists at a time; for each case, we performed a pairwise Bland-Altman analysis for all possible pairs within a group of radiologists and counted the total number of outliers from all pairs, Supplementary 3. If the number of outliers from Bland-Altman plot is sensitized to the different levels of inter-observer variability, more outliers (i.e. higher proportion of outlier measurement differences) would be observed in the case with increased inter-observer variability.

In the clinical context, this pairwise approach explores how safely a patient can be transferred from one radiologist to another within a group of radiologists. If two radiologists reviewed the same set of CT cases but suggested measurements largely different from each other, there may be concerns associated with the patient transfer between the radiologists. Similarly, if two radiologists reviewed the same set of CT cases and suggested measurements similar to each other, the concerns associated with the patient transfer may be marginal. Having more pairs with fewer outlier measurement differences may imply less concern for inter-observer variability when a patient is reviewed by multiple radiologists.

Statistical Analysis

We compared three evaluation measures for the comparison: (1) ICC, (2) Bland-Altman plot with 2SD LOA, (3) Bland-Altman plot with 20% fixed LOA. As for estimations of ICC scores, a two-way random-effects model that characterizes absolute agreement by incorporating both lesion-wise effect (target effect) and radiologist-wise effect (rater effect) was applied for both simulated and observed data.[2 19 27 28] The ICC scores were estimated based on all 130 measurements for each case (increased, observed, decreased).

While Bland-Altman plot allows data to be analyzed both as unit differences plot and as percentage differences plot,[16] we used percent difference plot as suggested by previous studies in the literature.[2 14 28] Bland-Altman plot with 2SD LOA was quantified into score value by calculating proportion of data points within the upper and lower LOA.

Bland-Altman plot with 20% fixed limits was also quantified into score value to compare with ICC and standard Bland-Altman plot with 2SD limits. There have been several clinical studies using Bland-Altman plot with fixed limits of agreement evidenced by relevant domain knowledge.[29 30] This essentially aligns with other studies that utilize clinical domain knowledge to define outliers.[31-34] We fixed the maximum acceptable LOA to assess the measurement interchangeability between radiologists at 20% evidenced by clinical guidelines. The predominant guideline for cancer treatment response evaluation, RECIST 1.1, heavily depends on percent difference in lesion diameter with a progression defined as a 20% increase in the sum of longest diameters.[35 36] The absolute inter-radiologist difference already exceeding 20% in CT measurements may interfere with the application of the 20% criterion from the guideline when a patient is reviewed by different radiologists. Thus, the 20% measurement difference was utilized as the fixed LOA for the Bland-Altman plot. In the context of radiologic measurement, this means that outlier measurement difference is explicitly defined as measurement difference exceeding 20% when a pair of radiologists reviewing the same image.

Bland-Altman plot also allows identification of any systematic difference (mean difference in measurements) between two observers. For each case of inter-observer variability, the mean difference in measurements was calculated for all possible pairs (n=78) and visualized in a heat map, Figure 3.

Patient and Public Involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Characteristics of CT image sets included in the study

Each CT image set included in the study consisted of multiple CT slices with an average of 7.6 images, Table 1. The minimum and maximum size of the hepatic metastases ranged between 1.68 cm to 2.21 cm and 5.32 cm to 6.72 cm, respectively. The minimum and maximum size of lung lesions ranged between 1.27 cm to 1.68 cm and 3.69 cm to 5.02 cm, respectively. In the observed data, the largest lesion-wise percent difference in measurements was realized in Hepatic Metastasis 5 with 33.1% difference between the minimum and maximum measurements. The smallest lesion-wise percent difference in measurements was realized in Lung Lesion 2 with 14.5% difference between the minimum and maximum measurements.

Table 1. Descriptive statistics for the original observed data

CT image sets	Number of image slices	Median Measurements (S.D.)	Range	Min-Max Percent Difference
Hepatic Metastasis 1	9	4.46 (0.38)	(3.81–5.19)	30.7%
Hepatic Metastasis 2	5	2.68 (0.22)	(2.31–3.03)	27.0%
Hepatic Metastasis 3	5	1.91 (0.18)	(1.68–2.21)	27.2%
Hepatic Metastasis 4	13	6.14 (0.48)	(5.32–6.72)	23.3%
Hepatic Metastasis 5	6	2.68 (0.29)	(2.24–3.13)	33.1%
Lung Lesion 1	8	3.46 (0.24)	(3.10–3.86)	21.8%
Lung Lesion 2	10	4.18 (0.23)	(3.90–4.51)	14.5%
Lung Lesion 3	6	2.00 (0.17)	(1.71–2.37)	32.4%
Lung Lesion 4	10	4.29 (0.36)	(3.69–5.02)	30.5%
Lung Lesion 5	4	1.56 (0.11)	(1.27–1.68)	27.8%

Note: Average measurement and range are in centimeters (cm). S.D. denotes standard deviation. Min denotes minimum measurement for each lesion. Max denotes maximum measurement for each lesion. Percent difference between minimum and maximum values was calculated using the following formula: difference(min, max) / average(min, max). Range consists of (minimum observed value – maximum observed value).

Characteristics of cases with different levels of inter-observer variability

The graph visualization of the data from each case suggested varying levels of inter-observer variability, Figure 2. The visualization of the original observed data suggested a substantial inter-observer variability with 31 (23.8%) measurements outside the light blue area representing plus or minus 10% interval from the average measurement value for each case. Additionally, a lesion-wise effect on inter-observer variability was observed with relatively high measurement variation in some CT image sets. The visualization of the case of decreased inter-observer variability illustrated a small number of measurements outside the threshold with 3 (2.3%) measurements locating outside the plus or minus 10% interval. With the decrease in the deviations of each measurement from the corresponding median, all measurements moved towards average and closer together as intended for demonstration. On the other hand, there was a relatively large number of measurements outside the threshold in the case of increased inter-observer variability with 50 (38.5%) measurements locating outside the plus or minus 10% interval. Also, it was observed that all measurements were not only shifted away from median, but also moved further away from each other as intended.

Visualization of Bland-Altman Analysis

The heat map visualization of average percent measurement difference (fixed bias) for all pairs of radiologists suggested varying levels of the difference across all pairs, Figure 3. Some pairs of radiologists achieved a lower average percent difference than others. In the heat map of the original observed data, the smallest systematic difference in measurement was observed in the pair of Radiologist 11 and Radiologist 13; they maintained an average of 0.03% difference in their measurements when reviewing the same set of CT images. The largest systematic measurement difference was observed in the pair of Radiologist 1 and Radiologist 6. The systematic difference in their measurements was 13.6% when reviewing the same set of CT images. It was observed that some radiologists attributed more to inter-observer variability than others; Radiologist 1 and 10 generally overestimate lesion size compared to others while Radiologist 2 and 6 generally underestimated lesion size compared to others.

The heat map visualization from the case of increased inter-observer variability showed the increased systematic measurement differences between any two radiologists compared to other cases. Similarly, the heat map visualization from the case of decreased inter-observer variability showed the decreased systematic measurement differences compared to other cases. Overall, the cases with relatively high inter-observer variability tend to present the increased systematic measurement differences between any two radiologists as well as more pairs of radiologists with a systematic measurement difference close to 20% when reviewing the same CT image sets.

Comparison of the selected measures

The original observed data achieved the ICC score of 0.962. The ICC scores in the cases of increased and decreased inter-observer variability were 0.990 and 0.912, respectively. The percent increase in the deviation of each measurement from the corresponding median has a perfect linear relationship with the ICC score (R-squared = 1.00), Figure 4. However, the magnitude of association was extremely low; 10 percent increase in the deviation was associated with 0.01 decrease in the ICC score. As a result, the graph representing a relationship between a percent increase in the deviation and the corresponding ICC score presented a virtually flat slope, which implies that the score is extremely insensitive to the changes in deviations.

The original observed data achieved the standard Bland-Altman score of 0.937, which indicates 93.7% of data points within lower and upper LOA along with 6.3% outlier data points. The score based on standard Bland-Altman presented flat slope with its score unchanging regardless of level of inter-observer variability (standard Bland-Altman score=0.937).

The presented Bland-Altman score with fixed limits was more responsive to the change in case than other measures. In the case with decreased inter-observer variability, all pairs were identified to have a percent difference less than 20% when reviewing the same CT image sets (fixed-limit Bland-Altman score=1.0). The original observed data suggested Bland-Altman score with fixed limits of 0.923 with 92.3% of all possible pairwise measurements having a percent difference less than 20%. In the case with increased inter-observer variability, 75.6% of measurements were identified to have a percent difference less than 20% when reviewing the same CT image sets. The Bland-Altman score with fixed limits changed by 0.167 (0.756 to 0.923) between increased case and observed data, and 0.077 (0.923 to 1.000) between observed data and increased case, Figure 4.

DISCUSSION

The importance of consistent measurement of cancer lesions in CT scans has been well documented.[10 35 36] We have performed an extensive simulation study using conventional evaluation measures and different cases with varying levels of inter-observer variability. Our study investigated precision of those measures and found that some measures are not sensitive enough to detect the difference between cases with clinically desirable and clinically unacceptable inter-observer variability in radiologic measurement.

The previous studies by McErlean et al and Zhao et al utilized statistical correlation coefficients and standard Bland-Altman plot as primary measures and concluded that serial CT measurements can be safely performed by different radiologists.[2 7] Our study indicated that the correlation-based measures may fail to serve as a true indicator of inter-observer variability. When the observed data were analyzed, the radiologists in our study achieved a high ICC score comparable to previous studies.[2 13] However, as demonstrated above, a high ICC score does not always guarantee low inter-observer variability in the context of radiologic measurement. Our analysis suggests that the statistical correlation-based measures may yield high scores regardless of level of the inter-observer variability among radiologists. Therefore, a group of radiologists who achieved a high ICC score within the group could fail to maintain clinically reasonable measurement consistency. For instance, an ICC score of 0.9 achieved by a group of readers is often considered to be excellent in many other fields.[36 37] However, in the case of cancer treatment response evaluation, the ICC score of 0.9 may raise serious patient safety concerns with radiologists always having at least 10% average percent difference in measurement to each other when reviewing the same CT image sets. In the presented case with increased inter-observer variability, the ICC score of 0.91 was still not high enough to achieve clinically acceptable inter-observer variability in CT measurement, as affirmed by the participating radiologists, Supplementary 2. Despite the unrealistically high increase in the variability observed in the case with increased inter-observer variability, the ICC score failed to provide an adequate warning.

Another measure, outlier counts from standard Bland-Altman plotting with 2SD upper and lower LOA, presented no response to the varying levels of inter-observer variability in CT measurements. It was observed that its upper and lower limits increase proportionally to measurement variabilities, Figure 5. Our analysis suggested no evidence to support its use for the assessment of CT measurement variability or outlier detection.

While the standard Bland-Altman and ICC scores changed little across the different cases, the presented Bland-Altman score with 20% fixed limits rapidly changed between cases of increased, observed and decreased inter-observer variability. The presented score is also intuitive to interpret because of its self-descriptive nature; the decrease in the score from 0.923 to 0.756 means that the percentage of pairwise measurements having less than 20% difference has decreased from 92.3% to 75.6%. As documented, the predominant guideline for cancer treatment response evaluation defines a diameter increase of 20% as the cutoff for progression of cancer. If multiple pairs of measurements have 20% or higher measurement difference over the same CT image sets, this may interfere with the application of the 20% criterion from the guideline when a patient is reviewed by different radiologists. The Bland-Altman score with fixed limits demonstrated a potential to detect a decrease in the number of pairs having less than 20% measurement difference when reviewing the same image sets, which may better facilitate the application of guideline.

The Bland-Altman heat map of pairwise systematic discrepancy offered some useful insight on how the inter-observer variability can be addressed in interventional studies. The visualization identified radiologists who largely under- or over-measure compared to their peers, which can be a potential target for intervention to reduce the variability. Risk associated with inter-observer variability is realized when a patient is referred from one radiologist to another or reviewed by different radiologists. The pairwise approach to visualize systematic discrepancy may also be useful in addressing the risk by identifying pair of radiologists whose measurements typically differ greatly from each other.

This was a retrospective study conducted in a single academic health center. Future study may extend our approach to more measurements with various respond evaluation criteria utilized by radiologists from multiple institutions. A potential limitation of the study may result from the image selection process. Although the images were randomly selected from the health system PACS, the application of the selection criteria was performed by one senior radiologist. A selection criterion was whether or not images are commonly encountered in daily clinical practice, which may have introduced a bias in the image selection. Another limitation is that the measurements were collected under a highly controlled environment where the radiologists were rarely interrupted throughout the data collection. It is commonly believed that in real-world clinical practice, one's actual performance may be negatively affected by a heavy workload or various types of interruptions. Lastly, future studies are warranted to explore other existing evaluation approaches. For example, although the reliability of the estimated regression line depends on the sample size, the homoscedasticity and normality of the distribution of the differences, the regression of the mean on the difference could reveal whether the extend of disagreement depends on the mean of two measurements.

CONCLUSIONS

Conventional measures may yield weak or no detection when evaluating different levels of the inter-observer variability among radiologists. We observed that the outlier counting based on domain knowledge was sensitized to the inter-observer variability in CT measurement of cancer lesions. Our study demonstrated that, under certain circumstances, the use of standard statistical correlation coefficients may be misleading and result in a sense of false security related to the consistency of measurement. A visualization based on pairwise approach to identify systematic discrepancy may serve as a useful and practical tool for future efforts to reduce the inter-observer variability in radiologic measurement.

Acknowledgements: The authors acknowledge and appreciate the participating radiologists of the Prisma Health System. We also acknowledge and appreciate the logistics and regulatory support of Karen Edwards, MS of the Department of Public Health Sciences, Clemson University.

Authors' contributions: MW designed the study, analyzed the data, and developed the manuscript. MH made substantial contributions to the data analysis and critical revisions. SL and MD acted as Clinical Investigators and contributed substantially to study development and clinical data interpretation. RW served as co-PI and supervised preparation, conduct, and administration of the study. All authors developed, reviewed and approved the manuscript.

Funding statement: This work was supported by supported by Health Science Center, Prisma Health, Greenville, South Carolina (Grant number: Pro00065670).

Ethics approval: Institutional Review Board, Prisma Health System, Greenville, South Carolina

Patient consent for publication: Not required.

Disclaimer: The funders played no role in the conceptualisation or realisation of the research and no role in the decision to submit it for publication.

Competing interest statement: No competing interested declared by the authors.

Provenance and peer review: Not commissioned; externally peer reviewed.

Availability of data and materials: The raw data are available in Supplementary Material 2.

Figure legends

Figure 1. Example of increased and decrease inter-observer variability from observed data. To generate a case with increased inter-observer variability, the difference between each measurement and the median value was increased by 40% (right). The difference between each measurement and the median value was decreased by 40% in the case with decreased inter-observer variability (left)

Figure 2. Visualization of measurement distribution for each case. Each vertical line in the graphs represent different CT case and each point represent percent difference between a measurement and the corresponding median value. The light blue area represents plus and minus 10% interval from the median value.

Figure 3. Visualization of pairwise bias from Bland-Altman analysis. The systematic discrepancy (bias) was calculated using average percent differences and presented in decimal format. Darker red colors represent larger percent measurement differences. The positive values indicate that the radiologist on y-axis over-estimated compared to the radiologist on x-axis. The negative values indicate that the radiologist on y-axis under-estimated compared to the radiologist on x-axis.

Figure 4. Responsiveness comparison of Intraclass Correlation Coefficient and Bland-Altman outlier scores. Scaling factor *d* represents percent increase in the deviation of each measurement from the corresponding median. Horizontal axis corresponds to scaling factor *d* used to decrease or increase the inter-observer variability. Vertical axis represents ICC and Bland-Altman scores. Vertical dotted lines in red represent different datasets. *ICC score* – Intraclass Correlation Coefficient. *2SD* – 2 Standard Deviation.

Figure 5. Standard Bland-Altman plotting for the selected pairs. The upper and lower Limit of Agreement (LOA) were calculated using 2 standard deviations. The dotted and solid lines represent LOA and mean difference, respectively. Different colors represent different radiologist pairs. While there were a total 78 possible pairs, the plotting included 6 selected pairs for visualization purposes. The total number of outliers was unchanging across the different cases, regardless of the number of pairs in the plotting.

REFERENCES

1. Jiang B, Zhou D, Sun Y, et al. Systematic analysis of measurement variability in lung cancer with multidetector computed tomography. *Ann Thorac Med* 2017;12(2):95-100. doi: 10.4103/1817-1737.203750
2. McErlean A, Panicek DM, Zabor EC, et al. Intra- and interobserver variability in CT measurements in oncology. *Radiology* 2013;269(2):451-9. doi: 10.1148/radiol.13122665
3. Oxnard GR, Zhao B, Sima CS, et al. Variability of lung tumor measurements on repeat computed tomography scans taken within 15 minutes. *J Clin Oncol* 2011;29(23):3114-9. doi: 10.1200/JCO.2010.33.7071
4. Singh S, Maxwell J, Baker JA, et al. Computer-aided classification of breast masses: performance and interobserver variability of expert radiologists versus residents. *Radiology* 2011;258(1):73-80. doi: 10.1148/radiol.10081308
5. Thiesse P, Ollivier L, Di Stefano-Louineau D, et al. Response rate accuracy in oncology trials: reasons for interobserver variability. Groupe Francais d'Immunotherapie of the Federation Nationale des Centres de Lutte Contre le Cancer. *J Clin Oncol* 1997;15(12):3507-14. doi: 10.1200/JCO.1997.15.12.3507
6. Woo M, Lowe SL, Devane AM, et al. Intervention to reduce inter-observer variability in CT measurement of cancer lesions among experienced radiologists. *Curr Probl Diagn Radiol* 2020 doi: 10.1067/j.cpradiol.2020.01.008 [published Online First: Jan 10]
7. Zhao B, James LP, Moskowitz CS, et al. Evaluating variability in tumor measurements from same-day repeat CT scans of patients with non-small cell lung cancer. *Radiology* 2009;252(1):263-72. doi: 10.1148/radiol.2522081593

8. Wormanns D, Diederich S, Lentschig MG, et al. Spiral CT of pulmonary nodules: interobserver variation in assessment of lesion size. *Eur Radiol* 2000;10(5):710-3. doi: 10.1007/s003300050990

9. Tyng CJ, Chojniak R, Pinto PN, et al. Conformal radiotherapy for lung cancer: interobservers' variability in the definition of gross tumor volume between radiologists and radiotherapists. *Radiat Oncol* 2009;4:28. doi: 10.1186/1748-717X-4-28

10. Nishino M, Jackman DM, Hatabu H, et al. New Response Evaluation Criteria in Solid Tumors (RECIST) guidelines for advanced non-small cell lung cancer: comparison with original RECIST and impact on assessment of tumor response to targeted therapy. *AJR Am J Roentgenol* 2010;195(3):W221-8. doi: 10.2214/AJR.09.3928

11. Chung MS, Cheng KL, Choi YJ, et al. Interobserver reproducibility of cervical lymph node measurements at CT in patients with head and neck squamous cell carcinoma. *Clin Radiol* 2016;71(12):1226-32. doi: 10.1016/j.crad.2016.07.014

12. Cornelis FH, Martin M, Saut O, et al. Precision of manual two-dimensional segmentations of lung and liver metastases and its impact on tumour response assessment using RECIST 1.1. *Eur Radiol Exp* 2017;1(1):16. doi: 10.1186/s41747-017-0015-4

13. Dinkel J, Khalilzadeh O, Hintze C, et al. Inter-observer reproducibility of semi-automatic tumor diameter measurement and volumetric analysis in patients with lung cancer. *Lung Cancer* 2013;82(1):76-82. doi: 10.1016/j.lungcan.2013.07.006

14. Krajewski KM, Nishino M, Franchetti Y, et al. Intraobserver and interobserver variability in computed tomography size and attenuation measurements in patients with renal cell carcinoma receiving antiangiogenic therapy: implications for alternative response criteria. *Cancer* 2014;120(5):711-21. doi: 10.1002/cncr.28493 [published Online First: 11/21]

15. Liljequist D, Elfving B, Skavberg Roaldsen K. Intraclass correlation – A discussion and demonstration of basic features. *PLOS ONE* 2019;14(7):e0219854. doi: 10.1371/journal.pone.0219854

16. Giavarina D. Understanding Bland Altman analysis. *Biochem Med (Zagreb)* 2015;25(2):141-51. doi: 10.11613/BM.2015.015

17. Shrout PE, Fleiss JL. Intraclass correlations: uses in assessing rater reliability. *Psychol Bull* 1979;86(2):420-8.

18. Hemphill JF. Interpreting the magnitudes of correlation coefficients. *Am Psychol* 2003;58(1):78-9.

19. Mukaka MM. Statistics corner: A guide to appropriate use of correlation coefficient in medical research. *Malawi Med J* 2012;24(3):69-71.

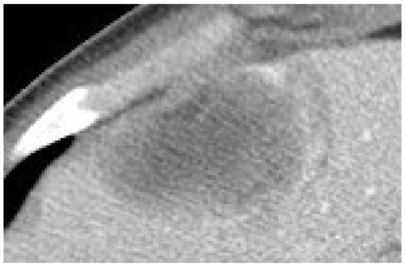
20. Wolak ME, Fairbairn DJ, Paulsen YR. Guidelines for estimating repeatability. *Methods Ecol Evol* 2012;3(1):129-37. doi: 10.1111/j.2041-210X.2011.00125.x

21. Bobak CA, Barr PJ, O'Malley AJ. Estimation of an inter-rater intra-class correlation coefficient that overcomes common assumption violations in the assessment of health measurement scales. *BMC Med Res Methodol* 2018;18(1):93.

22. Shoukri M, Donner A. Efficiency considerations in the analysis of inter-observer agreement. *Biostatistics* 2001;2(3):323-36.

23. Weinberg R, Patel YC. Simulated intraclass correlation coefficients and their z transforms. *J Stat Comput Simul* 1981;13(1):13-26.

24. Ponzoni R, James J. Possible biases in heritability estimates from intraclass correlation. *Theor Appl Genet* 1978;53(1):25-27.
25. Ludbrook J. Confidence in Altman-Bland plots: a critical review of the method of differences. *Clin Exp Pharmacol Physiol* 2010;37(2):143-9. doi: 10.1111/j.1440-1681.2009.05288.x
26. Faria SL, Faria OP, Cardeal MDA, et al. Validation Study of Multi-Frequency Bioelectrical Impedance with Dual-Energy X-ray Absorptiometry Among Obese Patients. *Obesity Surgery* 2014;24(9):1476-80. doi: 10.1007/s11695-014-1190-5
27. Koo TK, Li MY. A guideline of selecting and reporting intraclass correlation coefficients for reliability research. *J Chiropr Med* 2016;15(2):155-63.
28. Gutin B, Litaker M, Islam S, et al. Body-composition measurement in 9-11-y-old children by dual-energy X-ray absorptiometry, skinfold-thickness measurements, and bioimpedance analysis. *Am J Clin Nutr* 1996;63(3):287-92. doi: 10.1093/ajcn/63.3.287
29. Bogui P, Balayssac-Siransy E, Connes P, et al. The PhysioFlow thoracic impedancemeter is not valid for the measurements of cardiac hemodynamic parameters in chronic anemic patients. *PloS one* 2013;8(10):e79086-e86. doi: 10.1371/journal.pone.0079086
30. Vent-Schmidt J, Waltz X, Pichon A, et al. Indirect viscosimetric method is less accurate than ektacytometry for the measurement of red blood cell deformability. *Clin Hemorheol Microcirc* 2015;59(2):115-21. doi: 10.3233/CH-131727
31. Schold JD, Miller CM, Henry ML, et al. Evaluation of Flagging Criteria of United States Kidney Transplant Center Performance: How to Best Define Outliers? *Transplantation* 2017;101(6):1373-80. doi: 10.1097/TP.0000000000001373
32. Bergamin O, Anderson SC, Kardon RH. An objective method to define outlier optical coherence tomograms and repeatability of retinal nerve fibre layer measurements. *Acta Ophthalmol Scand* 2004;82(5):535-43. doi: 10.1111/j.1600-0420.2004.00316.x
33. Montalbano A, Quinonez RA, Hall M, et al. Achievable Benchmarks of Care for Pediatric Readmissions. *J Hosp Med* 2019;14:E1-E7. doi: 10.12788/jhm.3201
34. Motulsky HJ, Brown RE. Detecting outliers when fitting data with nonlinear regression - a new method based on robust nonlinear regression and the false discovery rate. *BMC Bioinformatics* 2006;7:123. doi: 10.1186/1471-2105-7-123
35. Nishino M, Jagannathan JP, Ramaiya NH, et al. Revised RECIST guideline version 1.1: What oncologists want to know and what radiologists need to know. *AJR Am J Roentgenol* 2010;195(2):281-9. doi: 10.2214/AJR.09.4110
36. Schwartz LH, Litière S, de Vries E, et al. RECIST 1.1: Update and clarification: From the RECIST committee. *Eur J Cancer* 2016;62:132-37. doi: 10.1016/j.ejca.2016.03.081
37. Gellhorn AC, Carlson MJ. Inter-rater, intra-rater, and inter-machine reliability of quantitative ultrasound measurements of the patellar tendon. *Ultrasound Med Biol* 2013;39(5):791-96.



Decreased Inter-observer Variability	
Radiologist	Measurement (cm)
7	5.65
6	5.68
2	5.85
8	5.96
13	6.02
9	6.15
3	6.18
4	6.34
5	6.34
12	6.37
11	6.41
10	6.44
1	6.49

Observed Inter-observer Variability	
Radiologist	Measurement (cm)
7	5.32
6	5.37
2	5.65
8	5.84
13	5.93
9	6.15
3	6.21
4	6.47
5	6.47
12	6.52
11	6.58
10	6.63
1	6.72

Increased Inter-observer Variability	
Radiologist	Measurement (cm)
7	4.99
6	5.06
2	5.45
8	5.72
13	5.84
9	6.15
3	6.24
4	6.6
5	6.6
12	6.67
11	6.75
10	6.82
1	6.95

Figure 1. Example of increased and decrease inter-observer variability from observed data. To generate a case with increased inter-observer variability, the difference between each measurement and the median value was increased by 40% (right). The difference between each measurement and the median value was decreased by 40% in the case with decreased inter-observer variability (left).

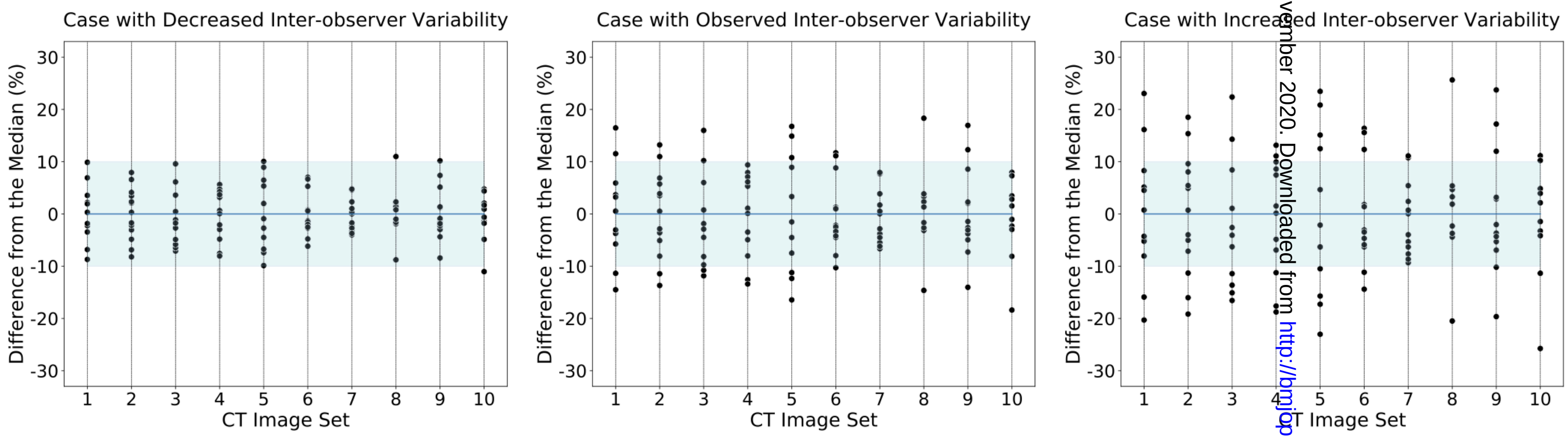


Figure 2. Visualization of measurement distribution for each case. Each vertical line in the graphs represent different CT case and each point represent percent difference between a measurement and the corresponding median value. The light blue area represents plus and minus 10% interval from the median value.

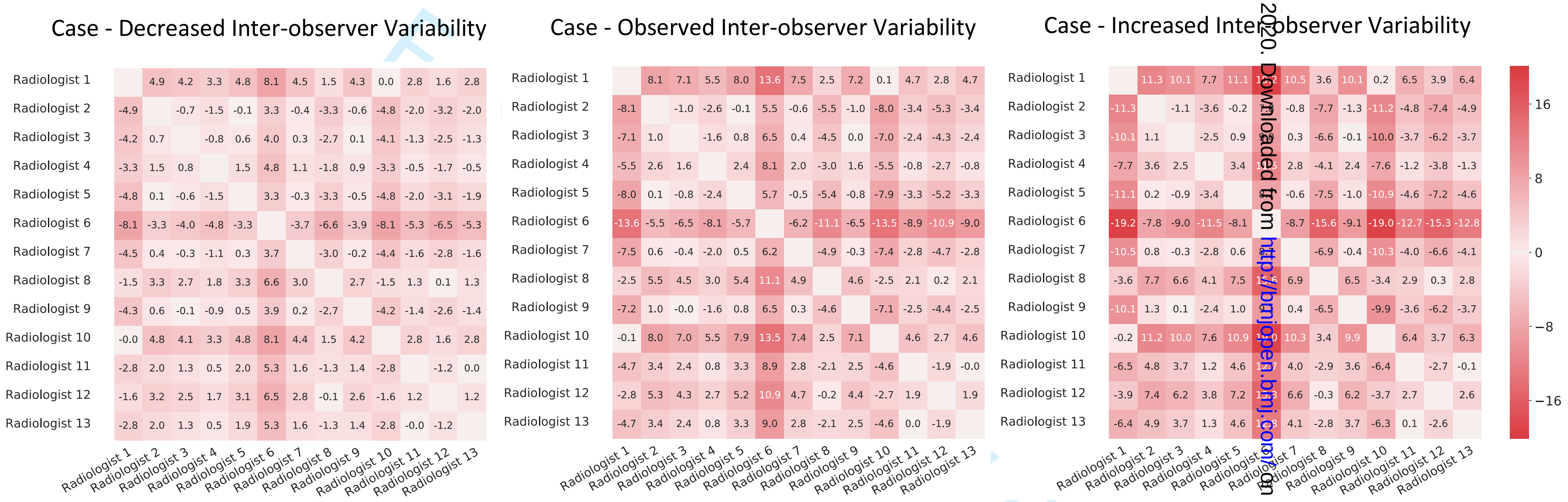


Figure 3. Visualization of pairwise bias from Bland-Altman analysis. The systematic discrepancy (bias) was calculated using average percent differences and presented in decimal format. Darker red colors represent larger percent measurement differences. The positive values indicate that the radiologist on y-axis over-estimated compared to the radiologist on x-axis. The negative values indicate that the radiologist on y-axis under-estimated compared to the radiologist on x-axis.

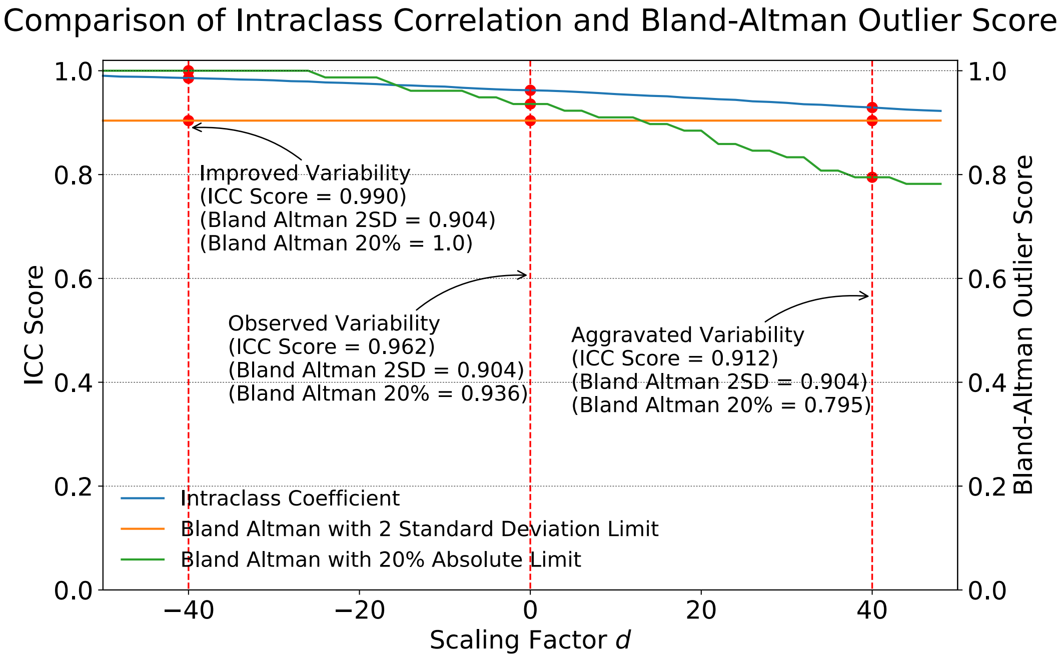


Figure 4. Responsiveness comparison of Intraclass Correlation Coefficient and Bland-Altman outlier scores. Scaling factor *d* represents percent increase in the deviation of each measurement from the corresponding median. Horizontal axis corresponds to scaling factor *d* used to decrease or increase the inter-observer variability. Vertical axis represent ICC and Bland-Altman scores. Vertical dotted lines in red represent different datasets. *ICC score* – Intraclass Correlation Coefficient. *2SD* – 2 Standard Deviation.

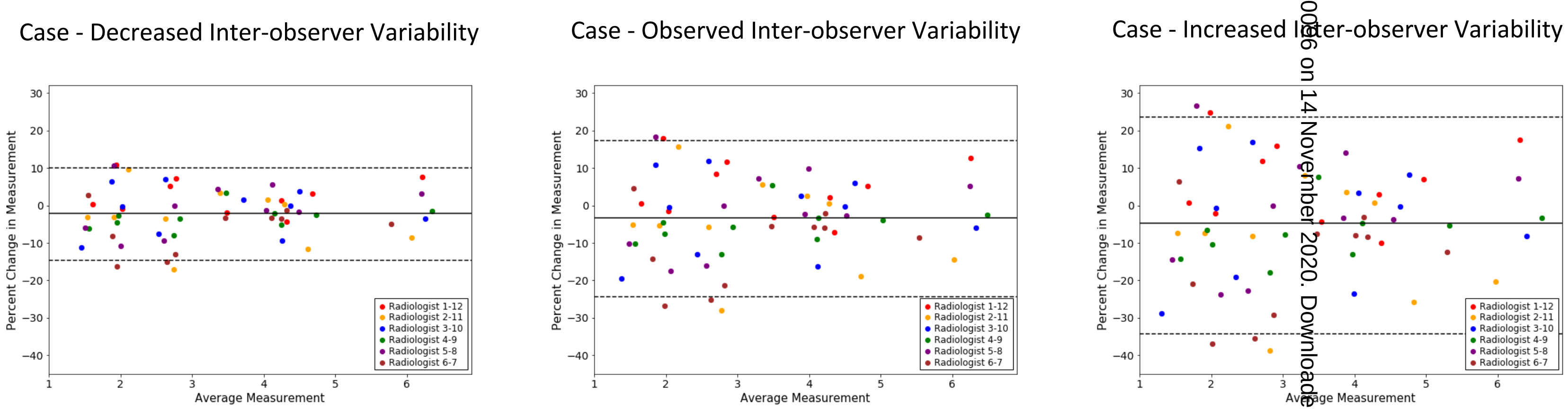
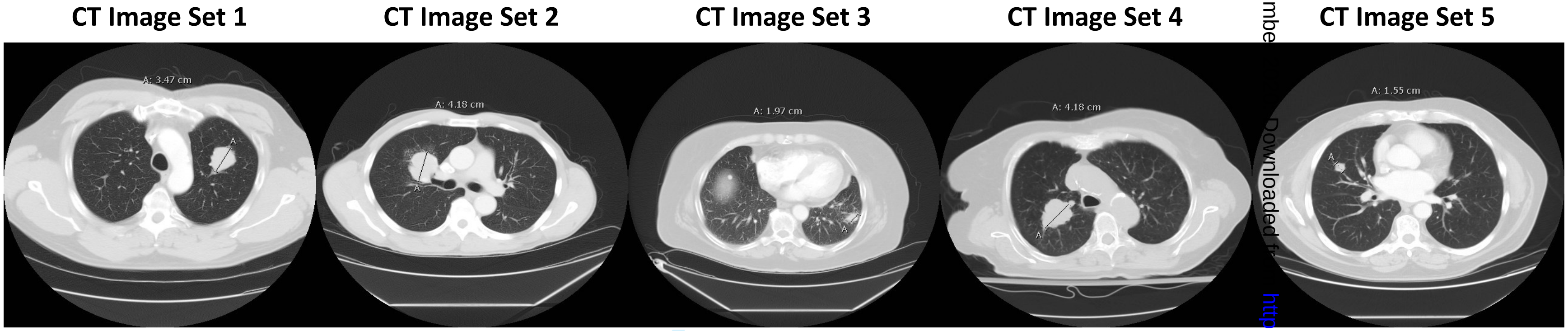
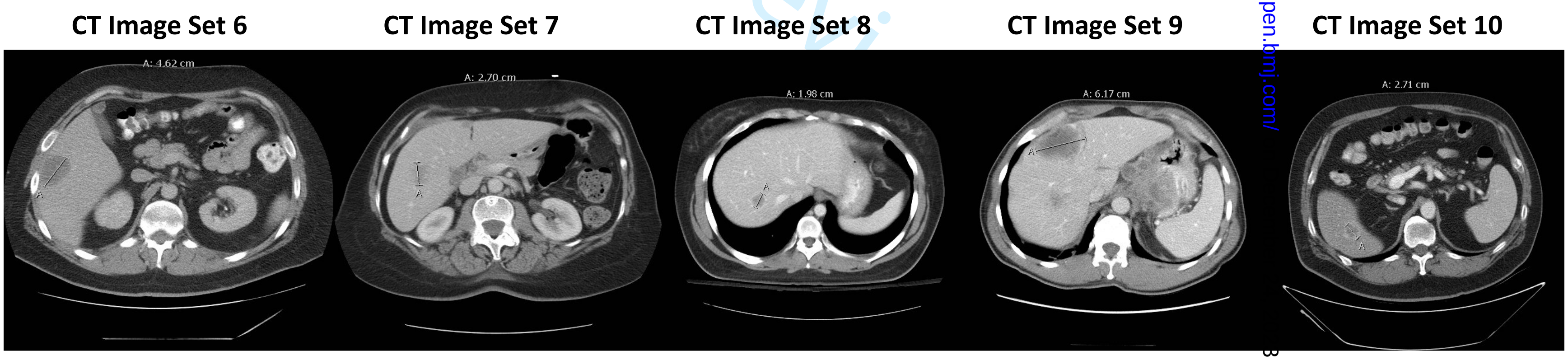


Figure 5. Standard Bland-Altman plotting for the selected pairs. The upper and lower Limit of Agreement (LOA) were calculated using 2 standard deviations. The dotted and solid lines represent LOA and mean difference, respectively. Different colors represent different radiologist pairs. While there were a total 78 possible pairs, the plotting included 6 selected pairs for visualization purposes. The total number of outliers was unchanging across the different cases, regardless of the number of pairs in the plotting,

Supplementary 1.

Examples of measurement for all CT image sets used in this study.





Supplementary 2.

To generate new data M'_{ik} for the *i*-th radiologist measurement of the *k*-th case representing each case, we used the following formula with a function of a scaling factor *d* on a percent scale:

$$M'_{ik} = \overline{M_k} + (1 + d/100)(M_{ik} - \overline{M_k}).$$

Here, M_{ik} is the observed reading of the *i*-th radiologist *i* for the *k*-th case, and $\overline{M_k}$ is the median of measurements for the k-th case over all 13 radiologists. Specifically, we adjusted the inter-observer variability by assigning different values of the factor *d* to the deviation $M_{ik} - \overline{M_k}$ for each radiologist. We assigned *d* = 40, 0, and -40 so that the generated new M'_{ik} measurement data represent those with increased, observed, and decreased inter-observer variability, respectively; the deviation of each radiologist-level measurement from the case-specific mean was increased, unchanged, or decreased by *d*%.

Case with Increased Inter-observer Variability													
Set	Radiologist												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1	5.14	4.20	3.52	3.71	4.46	4.06	4.65	4.19	4.62	4.23	4.46	5.45	4.79
2	2.87	2.47	2.79	2.91	2.23	2.14	2.52	3.07	2.80	3.15	2.35	2.68	2.55
3	2.23	1.84	1.98	1.91	1.88	1.64	1.67	2.38	2.38	2.12	1.70	1.98	1.74
4	6.86	5.36	6.14	6.51	6.51	4.97	4.90	5.63	6.06	6.73	6.66	6.58	5.75
5	3.14	2.27	2.12	2.57	2.86	2.46	2.32	3.30	2.86	3.07	2.57	3.37	2.68
6	3.46	3.44	4.13	3.62	3.40	3.34	4.10	3.61	3.06	3.36	3.99	3.18	3.61
7	4.40	3.95	4.63	4.01	3.79	3.86	4.63	4.18	3.91	4.21	4.64	3.81	4.28
8	2.03	2.48	2.06	1.88	2.03	1.56	1.89	1.92	1.56	2.00	2.07	2.00	2.07
9	4.15	4.29	4.96	5.19	4.15	4.01	4.22	4.36	3.61	5.47	4.57	4.26	4.59
10	1.70	1.47	1.12	1.46	1.35	1.60	1.60	1.50	1.56	1.68	1.50	1.58	1.68

Case with Observed Inter-observer Variability													
Set	Radiologist												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1	4.95	4.28	3.79	3.93	4.46	4.18	4.60	4.27	4.58	4.30	4.46	5.17	4.70
2	2.82	2.53	2.76	2.85	2.36	2.30	2.57	2.96	2.77	3.02	2.45	2.68	2.59
3	2.14	1.86	1.96	1.91	1.89	1.72	1.74	2.25	2.25	2.06	1.76	1.96	1.79
4	6.65	5.58	6.14	6.40	6.40	5.30	5.25	5.77	6.08	6.56	6.51	6.45	5.86
5	3.01	2.39	2.28	2.60	2.81	2.52	2.42	3.12	2.81	2.96	2.60	3.17	2.68
6	3.46	3.45	3.94	3.58	3.42	3.38	3.92	3.57	3.18	3.39	3.84	3.26	3.57
7	4.34	4.02	4.50	4.06	3.90	3.95	4.50	4.18	3.99	4.20	4.51	3.92	4.25
8	2.02	2.34	2.04	1.91	2.02	1.68	1.92	1.94	1.68	2.00	2.05	2.00	2.05
9	4.19	4.29	4.77	4.93	4.19	4.09	4.24	4.34	3.80	5.13	4.49	4.27	4.50
10	1.66	1.50	1.25	1.49	1.41	1.59	1.59	1.52	1.56	1.65	1.52	1.58	1.65

Case with Decreased Inter-observer Variability													
Set	Radiologist												
	1	2	3	4	5	6	7	8	9	10	11	12	13
1	4.75	4.35	4.05	4.14	4.46	4.29	4.54	4.34	4.53	4.36	4.46	4.88	4.60
2	2.76	2.59	2.72	2.78	2.48	2.45	2.61	2.84	2.73	2.88	2.54	2.68	2.62
3	2.04	1.88	1.94	1.91	1.89	1.79	1.80	2.11	2.11	2.00	1.82	1.94	1.83
4	6.45	5.81	6.14	6.30	6.30	5.64	5.61	5.92	6.11	6.40	6.37	6.33	5.98
5	2.88	2.51	2.44	2.63	2.76	2.58	2.52	2.94	2.76	2.85	2.63	2.97	2.68
6	3.46	3.45	3.74	3.53	3.43	3.41	3.73	3.52	3.29	3.41	3.68	3.34	3.52
7	4.27	4.08	4.37	4.11	4.01	4.04	4.37	4.18	4.06	4.19	4.38	4.02	4.22
8	2.02	2.21	2.03	1.95	2.02	1.81	1.96	1.97	1.81	2.00	2.03	2.00	2.03
9	4.23	4.29	4.58	4.68	4.23	4.17	4.26	4.32	4.00	4.80	4.41	4.28	4.42
10	1.62	1.52	1.37	1.51	1.47	1.57	1.57	1.53	1.56	1.61	1.53	1.57	1.61

Supplementary 3.

Average percent systematic difference using pairwise approach

The pairwise average percent systematic difference δ_{ij} was calculated for Bland-Altman analysis. The measure is based on the average difference in measurement between any pair of the i-th and j-th radiologists for the k-th cases as follows.

$$\delta_{ij} = \frac{2}{K} \sum_{k=1}^{K} \frac{M_{ik} - M_{jk}}{M_{ik} + M_{jk}}$$

Here, K is the number of cases (in our study $K = 10$), and M_{ik} is a measurement value of the i-th radiologist for the k-th case.

Bland-Altman outlier scores with standard and fixed-limit

The standard Bland-Altman outlier scores Υ_{2SD} is reliant on the percentage of pairwise measurement difference less than 2 standard deviations. Similarly, the Bland-Altman scores $\Upsilon_{20\%}$ with 20% fixed limit is reliant on the percentage of pairwise measurement difference less than 20% and calculated as follows:

$$\Upsilon_{\mathrm{2SD}} = \frac{(N-2)!}{N!} \sum_{i=1}^{N} \sum_{j=1}^{N} 1\left(\frac{|M_{ik} - M_{jk}|}{M_{ik} + M_{jk}} < 2SD \right)$$

$$\Upsilon_{20\%} = \frac{(N-2)!}{N!} \sum_{i=1}^{N} \sum_{j=1}^{N} 1\left(\frac{|M_{ik} - M_{jk}|}{M_{ik} + M_{jk}} < 0.2 \right)$$

Here, 1(A) is an indicator function whose value is 1 if A is true and 0 otherwise. N represents the number of radiologists. The fixed-limit Bland-Altman outlier scores were based on the percentage of pairs where a pair of radiologists reviewed the same CT image set and resulted in measurements that differ by less than 20%.