

## **Radiomics in lung cancer for oncologists**

Carolina de la Pinta\*, Nuria Barrios-Campo, David Sevillano

Corresponding author: Carolina de la Pinta Alonso Radiation Oncology Department. Ramón y Cajal Hospital, Madrid, Spain.

Handling editor Michal Heger Department of Pharmaceutics, Utrecht University, the Netherlands Department of Pharmaceutics, Jiaxing University Medical College, Zhejiang, China

Review timeline:

Received: 28 Februari, 2020 Editorial decision: 27 March, 2020 Revision received: 12 April, 2020 Editorial decision: 6 May, 2020 Revision received: 23 May, 2020 Editorial decision: 2 June, 2020 Revision received: 7 June, 2020 Editorial decision: 8 June, 2020 Published online: 2 September, 2020

1<sup>st</sup> editorial decision 27-Mar-2020

Ref.: Ms. No. JCTRes-D-20-00009 Radiomics in lung cancer for oncologist Journal of Clinical and Translational Research

Dear Ms De la Pinta,

Reviewers have now commented on your paper. You will see that they are advising that you revise your manuscript. If you are prepared to undertake the work required, I would be pleased to reconsider my decision.

For your guidance, reviewers' comments are appended below.

If you decide to revise the work, please submit a list of changes or a rebuttal against each point which is being raised when you submit the revised manuscript. Also, please ensure that the track changes function is switched on when implementing the revisions. This enables the reviewers to rapidly verify all changes made.

Your revision is due by Apr 26, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.



Yours sincerely

Felipe Couñago Editorial Board Member Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1: This is an important issue whose review would be interesting for oncologist. My main concern is the language (sometimes it is hard to understand the meaning of the sentences) and the order of the article (there are some phrases with no connection with another and it is no clear why they quote some articles).

1. Abstract: I think it would more accurate to explain this article is a review of articles and what was the article selection process.

2. Text

- Page 3 line 18 Review the language "The diagnosis of lung cancer is histological, but sometimes this is not possible because of the high risk it presents to the patient and if the treatment does not change the radiological diagnosis is accepted. The evaluation of clinical images in these patients is not always clear, since no obvious radiological pattern has been established to show the possible malignancy of the lesions".

- Page 3 line 33"In more advanced stages, when metastases are present, chemotherapy and other systemic treatments remain the treatment of choice". This need to be more explain because nowadays it is not completely true.

- Page 3 line 39 "The use of SBRT to treat lung cancer has become increasingly due to its excellent results, demonstrating local control at 3 years of up to 98% with limited relevant acute toxicity"3. This control percentage is based on a determined population and it is not a general concept.

- I think the term radiomics could be explained more in detail, overall the idea that it is based on multiple data number from computer analysis of imaging.

- Page 3 line 51 "Its application is possible in CT, being the most studied, MRI and PET"7. Review language sample "radiomics can be extracted from CT, MR or PET images".

- Page 3 Line 56 "Radiomics allows image evaluation" Better: Radiomics analysis allows evaluation...

- Page 4 line 21. "Mark" does not fit as verb here.

- Page 4 line 55 "For UH CT images, for PET the SUV". There is a typo (UH) and the sentence doesn't make sense.

- Page 5 line 35 "Radiomics provides a more adequate and reproducible measurement of the tumour tan other previously known methods to evaluate response. It is necessary to standardize data and build interconnected platforms. In addition to select the useful information. The main analysis component, the machine learning algorithms and the statistics are used to obtain a set of characteristics before the evaluation of their predictive ability". This paragraph is more a conclusion and it is not the right location in the manuscript.

- Page 6 first paragraph "Some studies have reported that radiomics is

useful for differentiating NSCLC from other benign tumors or pre-malignan lesions, by extracting characteristics of solid nodules". Lacks citation

- Pag 6. Line 15" Other authors had differentiated pre-invasive tumors from invasive adenocarcinomas using texture, high kurtosis and small nodules34". Typo (34) and lacks



citation

- Page 6, line 40:" With respect to PET/CT scans, Li et al35 explored the

SUV use of lymph nodes compared to primary tumor characteristics, and reported that lymph node characteristics added value in predicting relapse". This sentence is from section prediction of risk recurrence

- Page 7 line 16: "In CT findings such as pretreatment spherical shape, texture data, lymph node homogeneity, changes in primary tumor volume and histogram characteristics are potential predictors of patients with NSCLC after CRT". What is CRT? Lacks citation

- Page7 line 22 "the us de shape" What?

- Page 7 line 55 "but with variations in its size with different cut-off points". Meaning what?

- Page 8 line 13 "Texture is related to heterogeneity and is related to aggressiveness. Analysis of heterogeneity can be difficult for a radiologist". Review of language, there is no subject "it".

- I think it would interesting to analyze the role of radiologist in radiomics more consistent with the rest of the paragraphs

Page 8 line 17 "PET is associated with survival with high-order contrast for OS" Meaning?
Page 8 line 52 "Radiogenomics in lung cancer is in development, large studies are needed, and the integration of medical imaging, genomics and clinical data". There is no verb. Review language

- Limitations: first of all, they have to explain the limitations of the review itself and then conclusions about radiomics.

3. Bibliography:

- Could be more precise the first reference?

- Papers that can be relevant:

o Radiomics: Images Are More than Pictures, They Are Data

Robert J. Gillies, Paul E. Kinahan, and Hedvig Hricak

Radiology 2016 278:2, 563-577

o Mao L, Chen H, Liang M, et al. Quantitative radiomic model for predicting malignancy of small solid pulmonary nodules detected by low-dose CT screening. Quant Imaging Med Surg. 2019;9(2):263-272. doi:10.21037/qims.2019.02.02

Reviewer #2: See attach document

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

2<sup>nd</sup> editorial decision 06-May-2020

Ref.: Ms. No. JCTRes-D-20-00009R1 Radiomics in lung cancer for oncologist Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work



was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a pointby-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify your responses.

Your revision is due by Jun 05, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Felipe Couñago Editorial Board Member Journal of Clinical and Translational Research

Reviewers' comments:

Reviewer #1:

Page2; line 23 "Radiomics has revolutionized the world of medical imaging. The aim of this review is to guide medical oncologists in the study of radiomics ." It is indeed a review and you use twice the word study

Page 2; line 39: the diagnosis of lung cancer must be histological, but sometimes it is not possible because the lesion is not accessible or the diagnostic procedure represents high risk for the patient.

Page 2; line 42: the lack of histological diagnosis

Page 3; line 19. Extracted from CT, MR and PET imaging

Page 3: line 24-27 review language

Page 3; line 34. The verb form does not make sense

Page 3; line 50; "is able to adapt to the two previous procedures" What does it mean?

Page 4; line 45: "It is allows the differentiation between benign and malignant tumours" LANGUAGE

Page 4: 3. Extraction and quantification of features. The explanation is very confusing. There are four types of analysis (morphological, statistical, regional and model-basing) but they are not explained nor mentioned. More than 200 features can be evaluated with these different analyses. Then, why some are explained and some not? What is the selection criterion? Page 8; lines 32-34: CT seems to be better than PET for predicting OS. Shape, intensity,

texture and delta radiomics delta as predictive and when combined with clinical factors, predictive ability can be significantly improved. What does it mean?

Page 9; line 16; I think the most important limitation of this review is the number of articles reviewed and the lack of criterion to choose what articles analyze.

Page 9; conclusions: I think the conclusions are very disorganized.

Bibliography numbers in text aren't in order



Reference 13 is not complete Reference 15,16, 17, 18, 21, 28, 29, 20, 49, 50, 51, 52, 55, 58 are not correct in style

This article is very interesting Rizzo, S., Botta, F., Raimondi, S. et al. Radiomics: the facts and the challenges of image analysis. Eur Radiol Exp 2, 36 (2018). https://doi.org/10.1186/s41747-018-0068-z.

Reviewer #2: View upload document

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' response

Comments to Author: A great effort has been made to correct the document, achieving a clearly clearer and more concise text and with better references to the revised articles. I think it is a very interesting article, which can serve as an introduction to Radiomics for oncologists, radiologists and physicians in general

## Thank you so much

Reviewers' comments:

Reviewer #1:

Page2; line 23 "Radiomics has revolutionized the world of medical imaging. The aim of this review is to guide medical oncologists in the study of radiomics." It is indeed a review and you use twice the word study

"Radiomics has revolutionized the world of medical imaging. The aim of this review is to guide oncologists in radiomics and its applications in diagnosis, prediction of response and damage, prediction of survival and prognosis in lung cancer".

Page 2; line 39: the diagnosis of lung cancer must be histological, but sometimes it is not possible because the lesion is not accessible or the diagnostic procedure represents high risk for the patient.

Changed accordingly, thank you.

Page 2; line 42: the lack of histological diagnosis

Changed accordingly, thank you.

Page 3; line 19. Extracted from CT, MR and PET imaging. Changed accordingly, thank you.

Page 3: line 24-27 review language

Review language

Page 3; line 34. The verb form does not make sense

Changed accordingly, thank you.

Page 3; line 50; "is able to adapt to the two previous procedures" What does it mean?



We think is better: "The semiautomatic segmentation is able to combine two previous procedures being the most recommended".

Page 4; line 45: "It is allows the differentiation between benign and malignant tumours" LANGUAGE Review language

Page 4: 3. Extraction and quantification of features. The explanation is very confusing. There are four types of analysis (morphological, statistical, regional and model-basing) but they are not explained nor mentioned. More than 200 features can be evaluated with these different analyses. Then, why some are explained and some not? What is the selection criterion?

We explain and order four types of analysis. We select most important features. Changed accordingly, thank you.

Page 8; lines 32-34: CT seems to be better than PET for predicting OS. Shape, intensity, texture and delta radiomics delta as predictive and when combined with clinical factors, predictive ability can be significantly improved. What does it mean?

Some studied had demonstrated that combination of shape, intensity, texture and delta radiomics with clinical factors, improve the predictive capacity.

Page 9; line 16; I think the most important limitation of this review is the number of articles reviewed and the lack of criterion to choose what articles analyze.

Changed accordingly, thank you.

9: conclusions: Ι think Page the conclusions disorganized. are very "Radiomics is a promising non-invasive tool for the diagnosis and clinical management of lung cancer. Radiomics provides a more adequate and reproducible measurement of the tumour than other previously known methods to evaluate response. Furthermore, the combination of radiomics and genomics has a promising future. However, image acquisition protocols and radiomic analysis systems need to be standardized. More studies are needed to consolidate the data available".

Bibliography numbers in text aren't in order

Reference 13 is not complete. We complete reference Reference 15,16, 17, 18, 21, 28, 29, 20, 49, 50, 51, 52, 55, 58 are not correct in style. Changed accordingly, thank you.

This article is very interesting Rizzo, S., Botta, F., Raimondi, S. et al. Radiomics: the facts and the challenges of image analysis. Eur Radiol Exp 2, 36 (2018). <u>https://doi.org/10.1186/s41747-018-0068-z</u>.

## We include reference

Reviewer #2: View upload document

Page 2, line 23: "and finally construction of predictive and prognostic models with the information identify", identify probably must be changed for identified.

Changed accordingly, thank you.



Page 2, line 35: "can be affect the image value to compare and analyze radiomics studies". Probably better without "be".

Changed accordingly, thank you.

Page 3, line 44: "The evaluation of the tumour heterogeneity is very important in aggressiveness evaluation". Probably its more understandable to change "The evaluation" for "which".

Changed accordingly, thank you.

Page 4, line 13: "has been shown to be a predictor of survival in patients with NSCLC", is it necessary a bibliographic reference?

We include reference

Page 6, line 18: "The authors", probably it's better to write Coroller et al

Changed accordingly, thank you.

Page 6, line 38: "When comparing subjective study characteristics and quantitative changes, results showed that the key to distinguish RILI and early recurrence is in, 9 and 15 months after SBRT, respectively". Is it not better don't change this sentence in relation to the original manuscript?

Changed accordingly, thank you.

Page 8, line 16: "Our review has limitations, including we analyzed retrospective studies, and the heterogeneity of this studies". Consider change "we" for "the and substitute "this" for "these".

Changed accordingly, thank you.

3<sup>rd</sup> editorial decision 02-Jun-2020

Ref.: Ms. No. JCTRes-D-20-00009R2 Radiomics in lung cancer for oncologist Journal of Clinical and Translational Research

Dear author(s),

Reviewers have submitted their critical appraisal of your paper. The reviewers' comments are appended below. Based on their comments and evaluation by the editorial board, your work was FOUND SUITABLE FOR PUBLICATION AFTER MINOR REVISION.

If you decide to revise the work, please itemize the reviewers' comments and provide a pointby-point response to every comment. An exemplary rebuttal letter can be found on at http://www.jctres.com/en/author-guidelines/ under "Manuscript preparation." Also, please use the track changes function in the original document so that the reviewers can easily verify



your responses.

Your revision is due by Jul 02, 2020.

To submit a revision, go to https://www.editorialmanager.com/jctres/ and log in as an Author. You will see a menu item call Submission Needing Revision. You will find your submission record there.

Yours sincerely,

Michal Heger Editor-in-Chief Journal of Clinical and Translational Research

Reviewers' comments:

Dear authors,

Thank you for resubmitting a revised version of your manuscript to JCTR. Inasmuch as the reviewers pointed out that your manuscript required extensive language polishing and I found this to be insufficiently followed up on in your revision, I took the liberty to help a bit with structure and grammar/spelling. However, it is ultimately your responsibility to deliver a manuscript that is properly written. We cannot accept substandard papers in that respect. Please have a native speaker go through the paper and correct the remaining mistakes using the version I appended to this decision email. Thank you.

There is additional documentation related to this decision letter. To access the file(s), please click the link below. You may also login to the system and click the 'View Attachments' link in the Action column.

Authors' response Reviewers' comments:

Thank you for resubmitting a revised version of your manuscript to JCTR. Inasmuch as the reviewers pointed out that your manuscript required extensive language polishing and I found this to be insufficiently followed up on in your revision, I took the liberty to help a bit with structure and grammar/spelling. However, it is ultimately your responsibility to deliver a manuscript that is properly written. We cannot accept substandard papers in that respect. Please have a native speaker go through the paper and correct the remaining mistakes using the version I appended to this decision email. Thank you.

Thank you for the comment. The paper was changed accordingly. Language and grammar have reviewed by a professional English speaker.

4<sup>th</sup> editorial decision 08-Jun-2020



Ref.: Ms. No. JCTRes-D-20-00009R3 Radiomics in lung cancer for oncologists Journal of Clinical and Translational Research

Dear authors,

I am pleased to inform you that your manuscript has been accepted for publication in the Journal of Clinical and Translational Research.

You will receive the proofs of your article shortly, which we kindly ask you to thoroughly review for any errors.

Thank you for submitting your work to JCTR.

Kindest regards,

Michal Heger Editor-in-Chief Journal of Clinical and Translational Research

Comments from the editors and reviewers: