We would like to thank the Reviewers and the Editorial Office for the comments and suggestions to improve our manuscript.
Before responding point by point to each raised issue, we want to anticipate that, on the basis of reviewers' suggestions, we opted for modifying the manuscript title to "Impact of radiogenomics in esophageal cancer on clinical outcomes: a pilot study.", in order to highlight the preliminary nature of our study due to the small sample size involved.
All comments were carefully read and examined and have been addressed in the revised manuscript as best as possible. A point-by-point reply is attached below (Reviewers' comments in **Bold** and our replies in *Italic*).

Reviewer #1:

Scientific Quality: Grade E (Do not publish)

Language Quality: Grade B (Minor language polishing)

Conclusion: Rejection

Specific Comments to Authors: The authors investigated the impact of the radiogenomics on clinical outcomes in esophageal cancer. They combine transcript expression levels and CT radiomic features to see if they could be a biomarker for esophageal cancer. The data is presented clearly, however the data presented here are not convincing enough to support their conclusions.

1)The major shortcoming of this study is that the patient number is too small for the evaluation. This study may be premature.

We fully agree with the reviewer and we are aware that our patient sample is very small and it constitutes the major limitation of our study. According to your issue, and in order to highlight the preliminary nature of our study, we opted for modifying the title to "Impact of radiogenomics in esophageal cancer on clinical outcomes: a pilot study.". We evaluated that it could be useful to stress the small sample size involved in our study. Moreover, the limitation arising from the small patient number was also highlighted elsewhere in the text. In particular, the words "preliminary" and "pilot" were often expressed, and the limitation section was enriched by adding additional issues arising from the small sample size.

"First, due to the extremely small sample size and the retrospective nature of the study, our results remain to be validated with a larger and prospective patient sample in the future. Second, the small sample size may have affected also prediction model performances. Therefore, a larger and more balanced study group is needed to better conduct a radiomic analysis and build more robust prediction models. In particular, although the IABR strategy we used for model building is a common reliable approach in case of small and imbalanced datasets, a larger sample size would allow to use part of the dataset for the training, and part for testing and validating the performance of the classifier with external datasets."

2)I think the authors need to investigate CT radiomic features alone can predict stage.

We fully agree with the reviewer and thank for the raised issue. In fact, we already evaluated a significant association of radiomic features extracted from CT with the tumor staging but we will further improve this issue by investigating the predictive power of radiomic features in tumor staging and providing additional information on CT radiomic features taken by themselves to improve the quality of the manuscript. In particular, in order to evaluate the predictive power of CT radiomic features taken by themselves for ESCA staging, a fourth step of feature selection based on MI was performed for features associated with stage. For the binary classification task stageI-II versus

stageIII-IV, the reduced feature set (consisting of 5 top ranked features based on MI) was used to build logistic regression models of order from 1 to 5 that would best predict HCC stage by using an imbalanced-adjusted bootstrap resampling (IABR) approach on 1000 bootstrap samples.
The same analyses were performed starting from the first 2, 3, and 4 features surviving after the MI-based feature selection step.
Our results revealed that the top 5 features selected after the MI-based feature selection step were wavelet LLH gldm High Gray Level Emphasis, LLH ngtdm Complexity, HHH glcm Joint Entropy, HLH Entropy and HLL glcm Cluster Prominence. The simplest multivariable model with the best prediction performances were reached by the second order model, which was based on wavelet LLH ngtdm Complexity and HHH glcm Joint Entropy. These results were also confirmed by additional analyses. Below we show a summary of obtained results (which are better described in the main text and the Supplementary Materials).

	Features involved	**AUC ± SE**	**Sens ± SE**	**Spec ± SE**	**Acc ± SE**
Model of Order 2 for analyses involving the top 2 ranked features based on MI	Wavelet LLH ngtdm Complexity; wavelet LLH gldm HighGrayLevelEmphasis	0.75 ± 0.009	0.478 ± 0.017	0.849 ± 0.011	0.751 ± 0.007
Model of Order 2 for analyses involving the top 3 ranked features based on MI	wavelet LLH ngtdm Complexity; wavelet HHH glcm JointEntropy	0.862 ± 0.008	0.632 ± 0.021	0.833 ± 0.008	0.786 ± 0.006
Model of Order 2 for analyses involving the top 4 ranked features based on MI	wavelet LLH ngtdm Complexity; wavelet HHH glcm JointEntropy	0.872 ± 0.007	0.632 ± 0.022	0.835 ± 0.008	0.789 ± 0.006
Model of Order 2 for analyses involving the top 5 ranked features based on MI	wavelet LLH ngtdm Complexity; wavelet HHH glcm JointEntropy	0.869 ± 0.008	0.643 ± 0.021	0.834 ± 0.008	0.79 ± 0.006

Interestingly, correlation analysis with the 5 up-regulated miRNA revealed a significant positive correlation between miRNA-93 HHH glcm Joint Entropy ($\rho = 0.58$, $p < 0.05$), which contributed to building the best predictive models for stage assessment. This was also stressed in both Results and Discussions.
The paragraph "Predictive models building and analysis for stage assessment" was added in both Methods and Results sections in order to describe performed analysis and the associated results.

3)Tobacco and alcohol synergistically increase risk, please add smoking history to authors investigation.

We fully agree with the reviewer and thank for the suggestion. In order to solve the reviewer issue, we proceeded to add info on smoking variables (namely smoking history, age at starting smoking, pack year smoked) to the characteristics of included patients summarized in Table 1. Info on stopped smoking year were not reported due to the unavailability of this info for all patients. Unfortunately, smoking variables were very small due to the unavailability of most of them for several included patients. For example, smoking history outcome was not available for 4/15 patients, age at starting smoking for 6/15 patients and pack-year smoked for 6/15. This prevented us to perform analyses involving outcomes associated with smoking. In order to highlight the importance of smoking as ESCA risk factor, as well as the increasing risk arising from its association with alcohol, the following paragraph was added at the end of Discussion Section:

"It would have been interesting to perform similar analyses considering smoking variables as clinical outcomes. In fact, in addition to alcohol, tobacco is an established risk factor for ESCA and has been proven to act synergically with alcohol to increase the risk of ESCA. However, we could not perform analyses involving outcomes associated with smoking due to the incompleteness of these data for the included patients cohort."

The following references were also provided:

- *Prabhu A, Obi KO, Rubenstein JH. The Synergistic Effects of Alcohol and Tobacco Consumption on the Risk of Esophageal Squamous Cell Carcinoma: A Meta-Analysis. American Journal of Gastroenterology 2014;* ***109****: 822–827. [PMID: 24751582 DOI: 10.1038/ajg.2014.71]*
- *Dong J, Thrift AP. Alcohol, smoking and risk of oesophago-gastric cancer. Best Pract Res Clin Gastroenterol 2017;* ***31****: 509–517. [PMID: 29195670 DOI: 10.1016/j.bpg.2017.09.002]*

4)It would be helpful if the authors gave more information about the relationship between eight m6A RNA regulators and 5 miRNAs, because previous reports have shown that m6A modification involved in miRNA expression.

We thank the reviewer for the raised issue. According to the reviewer suggestion we added the following statements to the Introduction Section and the Discussion Section, also according to the Reviewer 2 issue 4):

Introduction: "Recently, several studies have also suggested that N6-methyladenosine (m6A) methylation can play a crucial role in cancer progression by regulating biological functions which affect noncoding RNA expression. In particular, a recent study highlighted the role of m6A methylation regulators, aberrantly expressed in ESCA to predict clinical outcomes."

Discussion: "In addition, miRNAs, more generally noncoding RNAs, have the ability to regulate m6A modifications, thereby affecting gene expression in cancer progression. Previous studies highlighted a strong relation between RNA methylation and breast cancer. In particular, Zhang et al. reported significant difference in expression levels and prognostic value of five m6RNA regulators (YTHDF3, ZC3H13, LRPPRC, METTL16 and RBM15B) in breast cancer. Furthermore, in a recent study, Zaho H. et al. showed that m6A regulators genomic aberration is associated with prognosis of ESCA patients."

Appropriate references were provided to support these statements:

- *Ma S, Chen C, Ji X, Liu J, Zhou Q, Wang G, Yuan W, Kan Q, Sun Z. The interplay between m6A RNA methylation and noncoding RNA in cancer. J Hematol Oncol 2019;* ***12****: 121. [DOI: 10.1186/s13045-019-0805-7]*
- *Lan Q, Liu PY, Haase J, Bell JL, Hüttelmaier S, Liu T. The Critical Role of RNA m ^{6} A Methylation in Cancer. Cancer Res 2019;* ***79****: 1285–1292. [DOI: 10.1158/0008-5472.CAN-18-2965]*
- *Xu L, Pan J, Pan H. Construction and Validation of an m6A RNA Methylation Regulators-Based Prognostic Signature for Esophageal Cancer. CMAR 2020;* ***Volume 12****: 5385–5394. [DOI: 10.2147/CMAR.S254870]*
- *Zhang B, Gu Y, Jiang G. Expression and Prognostic Characteristics of m6 A RNA Methylation Regulators in Breast Cancer. Front Genet 2020;* ***11****: 604597. [DOI: 10.3389/fgene.2020.604597]*
- *Zhao H, Xu Y, Xie Y, Zhang L, Gao M, Li S, Wang F. m6A Regulators Is Differently Expressed and Correlated With Immune Response of Esophageal Cancer. Front Cell Dev Biol 2021;* ***9****: 650023. [DOI: 10.3389/fcell.2021.650023]*

Reviewer #2:

Scientific Quality: Grade C (Good)

Language Quality: Grade B (Minor language polishing)

Conclusion: Minor revision

Specific Comments to Authors: I would like to congratulate the authors for a good attempt at writing an insightful article , which explores radiogenomics in esophageal cancer. I would like to suggest few comments as follows:

1) needs grammatical and spelling corrections

We thank the reviewer for the raised issue. We proceeded to revise the manuscript and account for grammatical and spelling corrections as best as possible.

2)introduction line 11,, needs modification/clarification, which suggests imaging techniques helps to evaluate pathology.

We agree with the reviewer and thank for the suggestion. We proceeded to clarify the sentence and modify it as reported below:

"This imaging technique allows to evaluate the loco-regional extension of ESCA by showing the extent of involvement of the esophageal wall by tumor, as well as the tumor invasion of the peri-esophageal fat. Moreover, it is also useful to detect the presence of distant metastases."

Study by Milsom et al. was also cited to support the statement:

- *Milsom JW, Senagore A, Walshaw RK, Mostosky UV, Wang P, Johnson W, Chaudry IH. Preoperative radiation therapy produces an early and persistent reduction in colorectal anastomotic blood flow. J Surg Res 1992;* ***53****: 464–469. [PMID: 1434596 DOI: 10.1016/0022-4804(92)90091-d]*

3) kindly elaborate about the possible clinical implications of your results/ findings.

We thank the reviewer for the suggestion. In order to highlight the possible clinical implications of our work, we added the following statement in the Conclusions Section:

"Our results strengthen the role of miRNA overespression and the possible characterization of biomarkers from liquid biopsy for ESCA assessment and staging, introducing new insigths for omics integration toward a personalised medicine approach."

4) in discussion ----- discuss in detail, about other studies(if available) which have individually studied either radiomics or genomics in esophageal cancer.

We thank the reviewer for the raised issue. According to your suggestion, we proceeded to discuss about other studies which individually investigated on radiomics and genomics in ESCA. Concerning genomic studies, the following lines were added in the Discussion Section:

"In addition, miRNAs, more generally noncoding RNAs, have the ability to regulate m6A modifications, thereby affecting gene expression in cancer progression. Previous studies highlighted a strong relation between RNA methylation and breast cancer. In particular, Zhang et al. reported significant difference in expression levels and prognostic value of five m6RNA regulators (YTHDF3, ZC3H13, LRPPRC, METTL16 and RBM15B) in breast cancer. Furthermore, in a recent study, Zaho H. et al. showed that m6A regulators genomic aberration is associated with prognosis of ESCA patients."

Moreover, we also inserted the following sentence to the Introduction Section (also according to the Reviewer 1 suggestions):

"Recently, several studies have also suggested that N6-methyladenosine (m6A) methylation can play a crucial role in cancer progression by regulating biological functions which affect noncoding RNA expression. In particular, a recent study highlighted the role of m6A methylation regulators, aberrantly expressed in ESCA to predict clinical outcomes."

Appropriate references were provided to support these statements:

- *Ma S, Chen C, Ji X, Liu J, Zhou Q, Wang G, Yuan W, Kan Q, Sun Z. The interplay between m6A RNA methylation and noncoding RNA in cancer. J Hematol Oncol 2019; **12**: 121. [DOI: 10.1186/s13045-019-0805-7]*
- *Lan Q, Liu PY, Haase J, Bell JL, Hüttelmaier S, Liu T. The Critical Role of RNA m ^{6} A Methylation in Cancer. Cancer Res 2019; **79**: 1285–1292. [DOI: 10.1158/0008-5472.CAN-18-2965]*
- *Xu L, Pan J, Pan H. Construction and Validation of an m6A RNA Methylation Regulators-Based Prognostic Signature for Esophageal Cancer. CMAR 2020; **Volume 12**: 5385–5394. [DOI: 10.2147/CMAR.S254870]*
- *Zhang B, Gu Y, Jiang G. Expression and Prognostic Characteristics of m6 A RNA Methylation Regulators in Breast Cancer. Front Genet 2020; **11**: 604597. [DOI: 10.3389/fgene.2020.604597]*
- *Zhao H, Xu Y, Xie Y, Zhang L, Gao M, Li S, Wang F. m6A Regulators Is Differently Expressed and Correlated With Immune Response of Esophageal Cancer. Front Cell Dev Biol 2021; **9**: 650023. [DOI: 10.3389/fcell.2021.650023]*

Concerning studies aiming at evaluating the role of CT radiomic features for ESCA management, the following statements were added in the Discussion Section:

"It is recognized that the use of CT radiomics is rapidly increasing in the field of ESCA management, playing an important role in preoperative nodal staging, diagnosis, prognosis, and for predicting treatment response to chemoradiotherapy. Wu et al. showed that CT radiomic features were able to discriminate between stage I-II and III-IV ESCA. In study by Yang et al., predictive models based on CT radiomic features were able to predict complete pathologic response after neoadjuvant chemoradiotherapy of ESCA patients. CT texture features were also found to be independent predictor of survival, while CT wavelet features were associated with the 3-year overall survival after chemoradiotherapy in a study involving 165 patients performed by Larue et al."

Appropriate references of previous radiomics studies on ESCA were provided:

- *Jin X, Zheng X, Chen D, Jin J, Zhu G, Deng X, Han C, Gong C, Zhou Y, Liu C, Xie C. Prediction of response after chemoradiation for esophageal cancer using a combination of dosimetry and CT radiomics. Eur Radiol 2019; **29**: 6080–6088. [PMID: 31028447 DOI: 10.1007/s00330-019-06193-w]*
- *Ganeshan B, Skogen K, Pressney I, Coutroubis D, Miles K. Tumour heterogeneity in oesophageal cancer assessed by CT texture analysis: Preliminary evidence of an association with tumour metabolism, stage, and survival. Clinical Radiology 2012; **67**: 157–164. [DOI: 10.1016/j.crad.2011.08.012]*
- *Yang Z, He B, Zhuang X, Gao X, Wang D, Li M, Lin Z, Luo R. CT-based radiomic signatures for prediction of pathologic complete response in esophageal squamous cell carcinoma after neoadjuvant chemoradiotherapy. Journal of Radiation Research 2019; **60**: 538–545. [DOI: 10.1093/jrr/rrz027]*

- *Hu Y, Xie C, Yang H, Ho JWK, Wen J, Han L, Chiu KWH, Fu J, Vardhanabhuti V. Assessment of Intratumoral and Peritumoral Computed Tomography Radiomics for Predicting Pathological Complete Response to Neoadjuvant Chemoradiation in Patients With Esophageal Squamous Cell Carcinoma. JAMA Netw Open 2020;* ***3****: e2015927. [DOI: 10.1001/jamanetworkopen.2020.15927]*
- *Piazzese C, Foley K, Whybra P, Hurt C, Crosby T, Spezi E. Discovery of stable and prognostic CT-based radiomic features independent of contrast administration and dimensionality in oesophageal cancer. PLoS One 2019;* ***14****: e0225550. [PMID: 31756181 DOI: 10.1371/journal.pone.0225550]*
- *Larue RTHM, Klaassen R, Jochems A, Leijenaar RTH, Hulshof MCCM, van Berge Henegouwen MI, Schreurs WMJ, Sosef MN, van Elmpt W, van Laarhoven HWM, Lambin P. Pre-treatment CT radiomics to predict 3-year overall survival following chemoradiotherapy of esophageal cancer. Acta Oncol 2018;* ***57****: 1475–1481. [PMID: 30067421 DOI: 10.1080/0284186X.2018.1486039]*
- *Hou Z, Yang Y, Li S, Yan J, Ren W, Liu J, Wang K, Liu B, Wan S. Radiomic analysis using contrast-enhanced CT: predict treatment response to pulsed low dose rate radiotherapy in gastric carcinoma with abdominal cavity metastasis. Quant Imaging Med Surg 2018;* ***8****: 410–420. [PMID: 29928606 DOI: 10.21037/qims.2018.05.01]*

Reviewer #3:

Scientific Quality: Grade A (Excellent)

Language Quality: Grade A (Priority publishing)

Conclusion: Accept (High priority)

Specific Comments to Authors: This is a well-written paper. Though the sample size is small, the results are interesting.

We thank the reviewer for having evaluated positively our work.

EDITORIAL OFFICE'S COMMENTS

(1) Science editor: 1 Scientific quality: The manuscript describes a retrospective study of the radiogenomics in esophageal cancer. The topic is within the scope of the WJG. (1) Classification: Grade A, Grade C and Grade E; (2) Summary of the Peer-Review Report: The authors found a good attempt at writing an insightful article, which explores radiogenomics in esophageal cancer. It is well-written and interesting. However, the grammatical and spelling mistakes need correction. The questions raised by the reviewers should be answered; and (3) Format: There are 3 tables and 5 figures. (4) References: A total of 41 references are cited, including 15 references published in the last 3 years; (5) Self-cited references: There are no self-cited references; and (6) References recommend: The authors have the right to refuse to cite improper references recommended by peer reviewer(s), especially the references published by the peer reviewer(s) themselves. If the authors found the peer reviewer(s) request the authors to cite improper references published by themselves, please send the peer reviewer's ID number to the editorialoffice@wjgnet.com. The Editorial Office will close and remove the peer reviewer from the F6Publishing system immediately. 2 Language evaluation: Classification: Grade A, Grade B and Grade B. A language editing certificate issued by AJE was provided. 3 Academic norms and rules: The authors provided the Biostatistics Review Certificate, and the Institutional Review Board Approval Form. Written informed consent was waived. No academic misconduct was found in the Bing search. 4 Supplementary comments: This is an

unsolicited manuscript. The study was supported by 1 grant. The topic has not previously been published in the WJG.

5 Issues raised:

(1) The title is too long, and it should be no more than 18 words;

We thank the Science Editor for the raised issue. According to this issue, and also issue 1) by Reviewer 1, and in order to highlight the preliminary nature of our study, we opted for shortening and modifying the title to "Impact of radiogenomics in esophageal cancer on clinical outcomes: a pilot study.".

(2) The authors did not provide the approved grant application form(s). Please upload the approved grant application form(s) or funding agency copy of any approval document(s);

This work has no supportive foundations. A mistake had been made.

(3) The authors did not provide original pictures. Please provide the original figure documents. Please prepare and arrange the figures using PowerPoint to ensure that all graphs or arrows or text portions can be reprocessed by the editor;

The original pictures were provided and they were arranged using ppt in the file named as "64873-Image_File.pptx".

(4) PMID and DOI numbers are missing in the reference list. Please provide the PubMed numbers and DOI citation numbers to the reference list and list all authors of the references. Please revise throughout;

We thank the Science Editor for the raised issue. All references were carefully rechecked and missing PMID and DOI were inserted.

(5) The "Article Highlights" section is missing. Please add the "Article Highlights" section at the end of the main text;

We thank the Science Editor for the raised issue. The "Article Highlights" section was added at the end of the main text.

(6) The scientific quality can't meet the requirement of WJG. 6 Recommendation: Transferring to the WJCC.

(2) Company editor-in-chief: I have reviewed the Peer-Review Report, full text of the manuscript, and the relevant ethics documents, all of which have met the basic publishing requirements of the World Journal of Gastroenterology, and the manuscript is conditionally accepted. I have sent the manuscript to the author(s) for its revision according to the Peer-Review Report, Editorial Office's comments and the Criteria for Manuscript Revision by Authors.

ANSWERING REVIEWERS FOR RE-REVIEW

We would like to thank the reviewer and the Editor for the comments and suggestions to improve our manuscript. All comments have been addressed in the revised manuscript (64873_Auto_Edited_R file). Since also Table file and Supplementary files were modified, a zip folder was provided with the new version of these files (64873-Supplementary-Material-R and 64873-Table-File-revision-R). A point-by-point reply is attached below (Reviewers' comments in **Bold** and our replies in *Italic*).

SPECIFIC COMMENTS TO AUTHORS

The question I would like to ask is whether the stage determined using routine clinical CT findings or the stage determined using radiogenomics was accurate. Please described whether the clinical CT findings or radiogenomics predicted the stage more accurately. If possible, please examine the accuracy of the two tests for T category, N category and M category.

We thank the reviewer for the comment. Thanks to the raised issue we realized that stage assessment from CT radiomic findings or radiogenomics should be compared and better described. According to obtained results, CT radiomic features were found to be predictors of stage with an AUC =87%, sensitivity = 64%, specificity = 83% and accuracy = 79%. In particular, CT radiomic features on which the best predictive model for ESCA staging was based were wavelet LLH ngtdm Complexity and HHH glcm Joint Entropy. Of note, HHH glcm Joint Entropy was also positively correlated with miRNA-93 contributed to building the best predictive models for stage assessment. In light of this, it could be highlighted that the combination of CT radiomic features and genomic features might provide added value in the field of ESCA management than radiomics features taken alone do.

In addition, according to the reviewer comment, we further investigate TNM staging. Specifically, we evaluated if selected CT radiomic features used for predicting the final stage could be also useful to assess TNM staging. Of the 15 patients, 3 patients had T1 tumor, 2 T2, 8 T3 and 2 T4 by final histopathologic examination. Concerning lymph nodes involvement, 4 patients had N0, 6 N1, 3 N2 and 2 N3 by final histopathologic examination. Finally, 12 out of 15 patients present no distant metastases. This information was reported in Table 1. Given the extremely small number of patients constituting each T group, we considered it appropriate to perform analyses dividing patients into two groups according to T1-T2 or T3−T4 tumor status, making T stage outcome binary. Similarly, we evaluated if CT radiomic features could assess N status by dividing patients into two groups according to the absence (N0) or presence (N1-N2-N3) lymph node status. We could not perform analyses assuming M status as clinical outcome due to the extremely unbalanced sample (12 M0 vs 3 M1).

According to all the above-mentioned comments, the manuscript was modified as follows, with appropriate references added:

<u>Materials and Methods section – Radiomic analysis/Predictive models building and analysis for stage assessment subparagraph:</u>

"Moreover, given that the overall stage is determined after the cancer is assigned categories

describing the tumor (T), node (N), and metastasis (M) categories, we tested the capability of these features for predicting T and N status. Analyses assuming M status as clinical outcome were not performed due to the extremely unbalanced sample. Patients were divided into two groups according to T1-T2 or T3−T4 tumor status, making T stage outcome binary. Similarly, we evaluated if CT radiomic features could assess N status by dividing patients into two groups according to the absence (N0) or presence (N1-N2-N3) lymph node status[43]"
The following reference was added: Berry MF. Esophageal cancer: staging system and guidelines for staging and treatment. J Thorac Dis 2014; 6 Suppl 3: S289-297. [PMID: 24876933 DOI: 10.3978/j.issn.2072-1439.2014.03.11]

<u>Results section – Radiomic analysis/Predictive models building and analysis for stage assessment subparagraph:</u>
The top 5 features were also found to be able to predict T and N staging, with best AUCs (0.79 and 0.80, respectively) reached by second order models (See Supplementary Tables S10 and S14).

<u>Results section – Radiogenomic analysis/stage subparagraph:</u>
Notably, HHH glcm Joint Entropy contributed to building the best predictive models for stage assessment, as well as T and N assessment.

<u>Discussions Sections</u>
"Similar performances were achieved when using the same features for predicting T and N, and this could be because T and N assignments contribute to determine the overall ESCA stage[43]. These results are in line with those found by Liu et al., even if they did not include textural features from wavelet CT images[53]."
The following study was cited: Liu S, Zheng H, Pan X, Chen L, Shi M, Guan Y, Ge Y, He J, Zhou Z. Texture analysis of CT imaging for assessment of esophageal squamous cancer aggressiveness. J Thorac Dis 2017; 9: 4724–4732. [DOI: 10.21037/jtd.2017.06.46]

"It is worth to note that the wavelet feature HHH glcm Joint Entropy was positively correlated with miRNA-93 and contributed to building the best predictive models for the overall stage assessment, and for the assessment of the T and N categories. From the literature, miR-93 is reported to be associated in various tumors and it is recently found to regulate mechanisms of drug resistance in triple negative breast cancer. Moreover, Ansari et al. evaluated miR-93 as potential deregulated biomarker for early detection of esophageal cancer. Based on these considerations, combining genomic features with radiomic ones might be of further added value for ESCA staging, thereby influencing the personalized medicine workflow in the field of ESCA."
The following references were added:

- *Qattan A, Al-Tweigeri T, Alkhayal W, Suleman K, Tulbah A, Amer S. Clinical Identification of Dysregulated Circulating microRNAs and Their Implication in Drug Response in Triple Negative Breast Cancer (TNBC) by Target Gene Network and Meta-Analysis. Genes 2021; 12: 549. [DOI: 10.3390/genes12040549]*
- *Ansari MH, Irani S, Edalat H, Amin R, Mohammadi Roushandeh A. Deregulation of miR-93 and miR-143 in human esophageal cancer. Tumor Biol 2016; 37: 3097–3103. [DOI: 10.1007/s13277-015-3987-9]*