Peer Review File

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Reviewer A

The study addresses an interesting and relevant question. However, the number of patients (n=18) is very small and can only be seen as a „proof of concept". Thus, the main statements from the study should be formulated more cautiously.

Reply: We agree with the reviewer. We adjusted our discussion as follows: "The results of this study show that a model of surface regularity and two GLCM features (energy, and information measure II of correlation) in contrast-enhanced CT imaging may accurately and noninvasively predict high-grade MEC."

Our concluding statement emphasizes that our study serves as a proof of concept. "This study serves as a proof of concept for using radiomic features as predictors of pathological grade in MEC."

Introduction:

A short paragraph should be included here on which histopathological features may influence radiomic features. Are there already results from studies on salivary gland carcinomas and CT analyses?

Reply: We agree with the reviewer. In our literature search there was only one radiomic study that studied salivary gland tumors. That study (https://doi.org/10.1186/s13550-020-00631-3) focused on CT-PET analyses. We added the following: "Radiomics were able to successfully discriminate between multiple histopathologic features in HNSCC tumors including grade, perineural invasion, lymphovascular invasion and extracapsular spread (14,15). To our knowledge, there has been no previous work on CT-based radiomic analyses for salivary gland tumors."

Methods:

Why could only 18 patients be included from so many tumors, which is a very low rate overall?

Were the patients measured with one CT device or were different CT devices used?

Reply: This is described in our flowsheet. 23 patients were not able to be included due to a lack of CT imaging in our image storage system. This is likely due to the time range (1995 – 2017) and many of the images were not transition to an electronic image storage system and could not be included in the study. Also some patients were referred from outside hospitals and were imaged at the outside hospital. These

external images were also not available for analyses. Patients were measured with different CT devices.

Results
Did the authors find differences regarding the parameters studied in terms of primary tumor vs. recurrence, localization in the Gld. parotis vs. outside the Gld. parotis? Does the age of the patients influence the radiomic features? Was the T stage not included?
A summary table of the clinical data of the included patients could lead to more clarity and transparency.
Reply: A table including this information has been added. There was no significant difference in the parameters with recurrence, extraparotid tumors nor age. T stage was not included. None of the cases had parotitis.

Discussion
The small number of included patients leaves little room for interpretation of the results. From my point of view, no relevant differences between high-grade and low-grade MEC can be extracted from the study (certainly this interpretation is based on the small number of cases).
Why did the authors not address whether different tumor entities of salivary gland carcinomas can be distinguished by radiomics. It is reasonable to assume that different tumor entities might show greater differences.
Reply: We agree with the reviewer that no statistically significant differences in radiomic features could be extracted from the study. However, the combined radiomic model had an AUC of 0.80. We added a reference related to comparing pleomorphic adenoma and Warthin tumor using CT texture analysis.
What practical benefit could this additional evaluation in CT performed preoperatively provide? If a high-grade carcinoma is detected, should a different therapeutic approach be chosen?
We agree with the reviewer and added the following to the introduction: “A noninvasive quantitative analysis of these radiomic features could be clinically useful, particularly in cases where biopsies are difficult to obtain or when there is tumor heterogeneity that may not be fully captured by biopsy.”

Reviewer B
The manuscript by Zhang et al. reports on the potential of textural analysis of CT datasets to differentiate low- and high-grade salivary gland tumors.
Major comments:
1. *Introduction: The authors introduce the disease (MEC) in the first paragraph*

which is appropriate. However, the diagnostic challenge (if histopathologic assessment is challenging) or the need for radiomics in the diagnostic differentiation of low and high-grade MEC is not clearly stated. (See additional comments re: Discussion).

Reply: We agree with the reviewer and added the following to the introduction: "A noninvasive quantitative analysis of these radiomic features could be clinically useful, particularly in cases where biopsies are difficult to obtain or when there is tumor heterogeneity that may not be fully captured by biopsy."

2. *Introduction: The initial introduction to radiomics is adequate. Although the literature of radiomics for distinguish salivary gland tumors is minimal, at least some of the published work on the use of radiomics to identify histology/grade of head and neck tumors should be recognized (e.g. PMID: 32538891). Importantly, a few publications have reported on the potential of MR radiomics for distinguishing salivary gland tumors (e.g. PMID: 33153140; PMID: 32538891). The authors should introduce some of this work and state the gap in knowledge.*

Reply: We agree with the reviewer and described previous studies in our introduction. There currently exists a gap in CT-based radiomics

"While radiomic features were able to successfully discriminate between histologic grade in HNSCC tumors in addition to other histopathological features such as perineural invasion, lymphovascular invasion and extracapsular spread, this present study is the first to do so in salivary gland tumors (14,15). In the realm of salivary gland tumors, Cheng et al. recently developed a prognostic model incorporating PET/CT radiomics for patients with salivary gland tumors (18). Radiomic features have also been utilized to discriminate between benign and malignant parotid gland tumors on MR imaging (16,17). To our knowledge, this present study is the first to study CT-based radiomic features in salivary gland tumors."

3. *Methods: Establishing standardized procedures/data curation methods (e.g. standardized image acquisition, segmentation routines, pre-processing checks, normalization, noise correction procedures) is critical for implementing any radiomic approaches to generate robust high quality radiomic biomarkers. Although the authors have completed the STARD checklist, the description of the imaging datasets. Virtually, no description of the radiomics pipeline that was employed for this study is presented. Please refer to PMID: 32154773 PMID: 32209816.*

Reply: A B30s smoothing algorithm was implemented without iterative reconstruction techniques. Our segmentation routine was done manually on soft tissue window images by one operator and reviewed by a board-certified neuroradiologist. There were no pre-processing or other correction procedures.

4. *Results: Given that small dataset, it is not surprising that none of the extracted features were not significantly different. It is unclear why only a small number of features were extracted. The small sample size combined with the small number of extracted features is likely contributing to this limited finding. The authors should also recognize these limitations. Additionally, did adding clinical parameters/or size to the model improve its performance?*

Reply: We agree with the reviewer. We chose to limit the number of features given our small sample size as to avoid overfitting. While the model may appear more statistically significant if we chose more features, it would likely not be statistically appropriate given our small sample size. Adding clinical parameters did not improve performance.

5. *Discussion: As stated above, a considerable body of evidence exists on employing CT radiomics to examine disease aggressiveness, therapeutic response, nodal metastasis and normal tissue complication probability. The findings from some of these studies should be succinctly discussed.*

Reply: We agree with the reviewer and added a brief summary of CT-based radiomics in head and neck cancers to the discussion. "The field of radiomics offers the ability to provide additional non-invasive information in the context of head and neck cancer imaging. CT-based radiomic features have been used to evaluate histopathological features such as HPV status. correlation with driver gene mutations and extranodal metastasis (20–23). Other studies demonstrated the ability of radiomics to provide additional insight regarding tumor response and clinical prognosis (7,24,25). In this study we link a group of novel CT features to the pathological grade in MEC. The results of this study show that a model of surface regularity and two GLCM features (energy, and information measure II of correlation) in contrast-enhanced CT imaging may accurately and noninvasively predict high-grade MEC."

The authors should also provide a brief description of how the authors envision integration of CT radiomics (i.e. if successful) to add to or fit into the diagnostic paradigm for MEC.

Reply: We agree with the reviewer and have added the following to the discussion: "Ultimately, we hope CT-based radiomics may help predict grade in difficulty to biopsy cases. Further work may also lead to the use of the radiomic features identified in this study to better predict response to treatment or overall prognosis."