LETTER TO THE EDITOR

Ultra-high frequency ultrasound as a clinical adjunct for imaging the oral cavity: added value of quantitative analysis

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We read with interest the recently published article by Izzetti et al. 2020 in *DMFR*. The article reports on the potential of ultra-high frequency ultrasound (UHFUS) for imaging the oral cavity.¹ As recognized by the authors, Ultrasound (typically using low frequencies) has been previously utilized as a valuable tool in oral and maxillofacial radiology for soft tissue imaging including oral cancers, salivary glands, nodal and non-nodal neck masses.²⁻⁴ While the work presented in the paper published in *DMFR* describes their experience in imaging the oral mucosa in healthy volunteers, additional work published by the authors provides encouraging evidence on the potential clinical utility of UHFUS for imaging of oral premalignant lesions (OPML) and invasive oral cancer.⁵ However, two aspects of their work, namely, quantitative analysis and reproducibility, warrant further consideration and discussion.

Quantitative analysis: While we commend the authors for imaging multiple sites and subsites in the oral cavity using UHFUS, much of the description is qualitative. The authors provide gray value distribution (mean $\pm$ standard deviation) for each of the sites/subsites based on B-mode ultrasound measurements from all 20 volunteers. Given that grayscale values reflect tissue microstructure, quantitative analysis of gray value distribution can be used for oral tissue characterization. As shown in [Figure 1](#), we plotted the gray values reported in their work and observed a significant difference between the palate and the lip/tongue tissues ($p < 0.05$, one-way ANOVA) in their healthy volunteer cohort. This is likely reflective of the differences in tissue layering between these sites (bone

in the case of palate/gingiva and muscle in the case of tongue/lip). We therefore submit that quantitative analysis of B-mode images may provide added value to the use of UHFUS for imaging the oral cavity. Due to the relatively recent introduction of this technology for clinical imaging, technical limitations of UHFUS systems may prevent routine reporting of quantitative metrics. Nevertheless, given the early vascular changes associated with carcinogenesis, the use of quantitative Doppler indices of vascularity may further enhance the diagnostic utility of UHFUS especially in the context of longitudinal imaging of OPMLs.

Repeatability and Reproducibility: In their work, the authors state that imaging was performed by two observers who were calibrated prior to the study. The calibration process ensured good agreement between ultrasound measurements performed by the two examiners. However, it does not provide a measure of the precision of the measurement (*i.e.* repeatability) over time.⁶ Evaluating the repeatability of the measurements (*e.g.* calculation of coefficient of variance of measurements for a given intraoral site in healthy volunteers when performed by the same examiner on two separate days) would provide further confidence in the consistency of UHFUS performance. Comparative performance evaluation with a traditional low frequency ultrasound system would also be insightful in better understanding the benefits and trade-offs with UHFUS.

Nevertheless, the work by Izzetti et al represents an important step in the evaluation of UHFUS as a potential chairside tool for the clinical evaluation of oral lesions. Further investigation into the quantitative analysis and reproducibility will help us realize the true potential of UHFUS for clinical applications in oral radiology.

Correspondence to: Dr Mukund Seshadri, E-mail: mukund.seshadri@roswell-park.org

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Figure 1 Bar graph shows average gray value distributions of the various sub-sites in the oral cavity in 20 healthy subjects as reported by Izzetti et al. 2020. Errors bars represent the standard deviation (* $p < 0.05$ – one-way analysis of variance)

¹Celia R. DeJohn and ^{1,2}Mukund Seshadri

¹Center for Oral Oncology, Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States; ²Department

of Dentistry and Maxillofacial Prosthetics, Roswell Park Comprehensive Cancer Center, Buffalo, New York, United States

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What perspectives for ultra-high frequency ultrasound of the oral cavity?

We were pleased to read the letter from DeJohn and Seshadri¹ that discusses our article “Discovering a new anatomy: exploration of oral mucosa with ultra-high frequency ultrasound.”²

We consider their comments to be insightful to the readers due to the suggestion to perform adjunctive analyses to the evaluation of ultra-high frequency ultrasonography (UHFUS) parameters.

Quantitative analysis. The importance of quantitative analysis in terms of grey value distribution was previously presented in our work on the diagnosis of oral diseases by means of intraoral UHFUS, where grey scale analysis was described for the discrimination between different lesions of the oral cavity.^{3,4} Actually, we could expect to find a difference in terms of grey value distribution among oral mucosal sites due to the presence of a different tissue layering. As a matter of fact, the presence of the bone beneath the gingival and palatal mucosa may create a different ultrasound beam reflection if compared to the labial, buccal and tongue mucosa, where

tissue stratification consists of mucosa, submucosa and muscular layer. Moreover, the application of pulsed wave (PW) Doppler appears extremely valuable in the study of the blood flow in the area of interest, due to the advantage of the arteries evaluated which are superficially located and present a relatively slow blood flow, making aliasing phenomena more difficult to occur. The ability to get information also on vascularity enhances the diagnostic utility of UHFUS especially in the follow-up of malignant lesions.

Reliability and reproducibility. We recognize that learning curve and training are pivotal for the performance of UHFUS examination, both in terms of image acquisition and analysis. Interestingly, the coefficient of variance calculation retrieved a precision of the replicates of 88.74%, thus suggesting that the training process and calibration performed prior to the study were effective in guaranteeing a standardization of the image analysis process. Considering comparative performance evaluation with conventional US frequencies, we

Figure 1 Panel representing the labial mucosa as imaged intraorally by means of different US frequencies. The scans of the labial mucosa were performed with a state-of-the-art conventional US equipment (Resona 7, Mindray), employing 11 and 20 MHz probes, and with an UHFUS equipment (Vevo MD, Fujifilm VisualSonics), equipped with 48 and 70 MHz probes. (A) B-mode of 11 MHz US of the lower lip mucosa. The greater depth of penetration of the US beam hinders the clear visualization of tissue layering in the shallower strata; (B) B-mode of 20 MHz US of the lower lip mucosa. Mucosal stratification can be evaluated, although there is a lack of fine anatomical detail; (C) B-mode of 48 MHz US of the lower lip mucosa. It is possible to discriminate between mucosal layer (thin hyperechoic superficial stratum) and submucosal layer (thicker hyperechoic stratum located beneath the mucosa); (D) B-mode of 70 MHz US of the lower lip mucosa. All the anatomical structures present in this region can be distinctly imaged. Mucosal and submucosal layers appear as two well-demarcated strata, and the structures localized in the submucosa, *i.e.* salivary glands and blood vessels, are clearly shown.

provide in [Figure 1a](#) comparison between conventional US, very high-frequency US and UHFUS.

We are grateful for the comments received, which allowed to better address some of the aspects related to UHFUS application in oral medicine. Although this novel technique undoubtedly presents several advantages if compared to conventional US, further assessment is mandatory to fully evaluate the possibilities of UHFUS in the study of oral lesions.

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¹Rossana Izzetti, ¹Marco Nisi, ²Giacomo Aringhieri,
²Davide Caramella, ¹Filippo Graziani and
¹Mario Gabriele

¹Unit of Dentistry and Oral Surgery, Department of Surgical, Medical and Molecular Pathology and Critical Care Medicine, University of Pisa, Pisa, Italy; ²Diagnostic and Interventional Radiology, Department of Translational Research and of New Technologies in Medicine and Surgery, University of Pisa, Pisa, Italy