DETECTION OF CARIES ADJACENT TO TOOTH COLORED PROXIMAL RESTORATIONS USING STATIONARY INTRAORAL TOMOSYNTHESIS

Robert L Hilton

A thesis submitted to the faculty at the University of North Carolina at Chapel Hill in partial fulfillment of the requirements for the degree of Master of Science in Oral and Maxillofacial Radiology in the School of Dentistry.

Chapel Hill
2019

Approved by:

Angela Broome

André Mol

Andrea Ferreira Zandona

Apoena de Aguiar Ribeiro

ABSTRACT

Robert L Hilton: DETECTION OF CARIES ADJACENT TO TOOTH COLORED PROXIMAL RESTORATIONS USING STATIONARY INTRAORAL TOMOSYNTHESIS
(Under the direction of André Mol)

Caries adjacent to restorations (CAR) is the most common reason for replacing restorations. This study compared the ability of stationary intraoral tomosynthesis (s-IOT) and conventional bitewings in detecting CAR. Extracted teeth (N=77) with 113 proximal tooth-colored restorations were used. Observers (N=7) utilized a 5-point scale to rate their confidence that CAR was present and stereomicroscopy was used to establish ground truth. S-IOT had a statistically higher (ANOVA $p<0.05$) observer Az than conventional bitewings. S-IOT and conventional bitewings had a sensitivity of 0.48 and 0.44, respectively, which was statistically significant (ANOVA $p<0.05$) and a specificity of 0.57 and 0.61 respectively, which was not statistically significant (ANOVA $p>0.05$). S-IOT showed higher diagnostic accuracy and sensitivity than conventional bitewings and is thus better in detecting caries around proximal composite restorations. While the clinical effect size is small, s-IOT is a promising imaging modality for advancing the detection of CAR.

ACKNOWLEDGEMENTS

Special thanks are due to Christy Inscoe and Connor Puett who generously offered many hours of expertise regarding tomosynthesis image acquisition and processing. Thanks also to Pooja Saha and Dr. Ceib Phillips for their statistical support.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

ANOVA	analysis of variance
Az	area under the ROC curve
CAR	caries adjacent to restorations
CBCT	cone-beam computed tomography
CNT	carbon nanotube
ICDAS	international caries detection and assessment system
IRB	institutional review board
MAR	metal artifact reduction
MDCT	multi-detector computed tomography
micro-CT	micro-computed tomography
PI	principal investigator
ROC	receiver operating characteristic
SD	standard deviation
s-IOT	stationary intraoral tomosynthesis
TPR	true positive rate
TNR	true negative rate
TACT	tuned-aperture computed tomography
UNC	University of North Carolina at Chapel Hill
XCP	extension cone paralleling

INTRODUCTION

Caries adjacent to restorations (CAR) is the most common cause for repair or replacement of dental restorations.[1–4] Each additional operative intervention creates costs for the patient and loss of tooth structure or the tooth itself. Research supports the validity of the increasingly popular philosophy of minimally invasive dentistry.[5–8] This approach emphasizes early detection of carious lesions, tracking progression or regression, and utilizing the least invasive intervention or procedure to achieve the therapeutic goal. Early and accurate detection of CAR helps clinicians choose appropriate interventions for the health of the tooth.

Past literature regarding CAR has used terminology that led to confusion with certain terms being utilized differently by different authors.[9,10] Secondary caries or recurrent caries typically refers to new carious lesions forming next to a restoration at either the "outer wall" or the "inner wall". Outer wall lesions form at the exterior tooth surface in the same manner as primary lesions and are considered analogous. Inner wall lesions form in the gap or micro-gap between the restoration and the prepared tooth surface. Residual caries commonly refers to carious tooth structure that has been left behind, intentionally or not, and is either sealed under the restoration or is present at the restoration margin. In epidemiological surveys, there is no distinction between new and residual caries, and the term CAR is intended to refer to any carious lesion adjacent to a restoration.[10]

Microscopically, three zones of dentin can be identified in the presence of a carious lesion: zone 1, normal unaffected dentin; zone 2: affected dentin, which is demineralized, but not infected and can be remineralized; zone 3: infected dentin, which has bacterial invasion and is incapable of remineralizing. Frequently, because of carious lesions, odontoblasts in dentinal tubules will die, leaving empty tubules called dead tracts. These dead tracts are often dark when visualized on ground sections but they do not represent carious tissue.[11]

Residual caries is often left behind intentionally in accordance with evidence-based recommendations that depend on the proximity of the carious lesion to the pulp chamber and the nature of the carious dentin.[9] Bacterially contaminated and demineralized tissues near the pulp should not be removed in asymptomatic patients with a vital pulp. New terminology has been recommended to help characterize dentin according to the clinical consequences of leaving the dentin behind. While Knoops hardness measurements can help distinguish between normal, affected, and infected dentin, this is not clinically practical and no other clinical techniques correlate histologically. The terms soft, leathery, firm, and hard have been defined to help guide clinicians in caries excavation. Soft dentin will deform when a hard instrument is pressed unto it and can be easily scooped up with little force. Leathery dentin does not deform when pressed, but can still be easily lifted without much force. Firm dentin is resistant to hand excavation and some pressure is needed to lift it. Hard dentine requires a pushing force with a sharp instrument or a bur to lift it. Hard dentin also makes a scratchy sound when a probe is taken across it. It has not been demonstrated decisively how these clinical presentations of dentin relate to the histopathology of carious lesions.[9]

The most effective methods of detecting caries adjacent to restorations include visual, radiographic, and laser fluorescence, which all demonstrate a similar sensitivity (0.50 to 0.59) and specificity (0.78 to 0.83).[2] However, radiographs are more accurate than visual assessment at proximal surfaces, and more accurate than laser fluorescence around amalgam restorations.[2,12–14] In addition, radiographs are able to provide information about the proximity of the carious lesion to the pulp. Unfortunately, the recent technological advances in radiology have not led to a substantial improvement in the detection of primary caries or CAR.

Digital radiography has introduced image enhancement and manipulation with flexibility in storage and display that was not previously possible with film imaging. Despite these advantages, studies have not demonstrated a concomitant improvement in caries detection.[15,16] Cone-beam computed tomography (CBCT) provides improved assessment of interproximal caries depth and detection of surface cavitation, while maintaining no significant increase in overall diagnostic accuracy compared to intraoral radiographs.[12,17] However, with even small composite or metal restorations near the area of interest, beam hardening and streak artifacts severely degrade CBCT image quality and the ability to detect caries. Thus, the detection of caries next to restorations remains a diagnostic challenge.

Tomosynthesis and tuned-aperture computed tomography (TACT) are related imaging systems that have improved primary or secondary caries detection in some studies.[18–20] Both of these techniques obtain multiple image projections at different angles and then mathematically reconstruct them into a stack of images that provide 3D depth information (See figure 1). Conventional tomosynthesis utilizes a known imaging geometry by mechanically coupling a moving x-ray source and a detector, while TACT calculates the imaging geometry after image acquisition using a standardized fiduciary marker next to the object being imaged. The fiducial marker in TACT allows the x-ray source to be moved to custom locations as desired by an operator without needing to know the precise geometry. Whether TACT or tomosynthesis, the individual projections acquired at differing angles are shifted so that an object of interest viewed in each projection is superimposed on itself. The plane including the object of interest is in focus while objects outside that plane are blurred. In theory and in practice this can be done with film, however, with modern computers and digital imaging an entire stack of image planes from the volume of interest can be generated in seconds. The resulting image stacks for both TACT and tomosynthesis allow the clinician to scroll through different 2D planes to focus on a specific 2D plane of interest. The out of plane objects are blurred but are not removed from the image. Many computational approaches are available to reconstruct these images but typically filtered back projection or algebraic iterative reconstruction is used. Iterative reconstructions are often preferred to further remove the out-of-plane objects from the image and increase image sharpness. This approach uses a high-pass filter to suppress blurred out-of-plane objects from the plane containing the object of interest. With each successive iteration, the out-of-plane objects are further suppressed relative to the in-plane objects. In theory, this process, with sufficient iterations, will completely de-blur the entire stack of images. In reality, random noise and quantization artifacts start to predominate when more iterations are applied.[21,22]

A study conducted by Nair et al (1998) demonstrated that TACT images created with a circular x-ray source array and reconstructed with three iterations had superior diagnostic efficacy in detecting secondary caries (artificial caries) compared to film and digital imaging (A_z for TACT iteratively restored images = 0.9171, film = 0.6608, direct digital images = 0.5979).[19] This study makes no mention of metal or beam hardening artifacts, and was completed with both amalgam and composite restorations. The same authors published a related paper that year investigating the effect of the restorative material and lesion location on detection by TACT, film, and digital radiography. It was found for all modalities that caries diagnosis was most efficacious when the lesion was adjacent to an amalgam restoration, followed by a radiopaque composite, and least efficacious next to radiolucent composite restorations. Lesions located at a point angle were easier to detect than lesions located at the mid-gingival floor.[20]

Other studies conducted in the late 1990's and early 2000's demonstrated that TACT enhances root fracture detection, bony periodontal defect characterization, impacted tooth evaluation, and the assessment of implant sites.[23–26] However, neither TACT nor tomosynthesis gained a foothold in the practice of dentistry due to the time intensive process of adjusting the x-ray source position for TACT and speed limitations in detector acquisition and image reconstruction for both modalities. In addition, CBCT started to enter the world of dentistry at this time, providing dentists with 3D information and dominating oral radiology research for the next decade.

While CBCT was growing within dentistry, tomosynthesis found broad applications within medicine. Compared to conventional medical radiography, tomosynthesis is more effective when detecting breast cancer, lung nodules, and fractures.[27] It has found applications in imaging paranasal sinus and gastrointestinal disease. It also presents advantages over MDCT, including lower patient dose, higher in-plane resolution, and more options for positioning the patient.[27–31]

Recent advances in carbon nanotube (CNT) x-ray emission, digital sensor speed, and computer processing have addressed most of the hurdles limiting the application of tomosynthesis in dentistry and it has been demonstrated that an intraoral image can be acquired and reconstructed in less than 10 seconds.[22] A prototype s-IOT unit was made available for research at the UNC School of Dentistry radiology clinic. This unit utilizes seven CNT x-rays sources arranged in a horizontal linear array and compact enough to fit in a standard size dental tube head. These stationary CNT sources eliminate cumbersome image acquisition techniques as well as motion blur that plagued other tomosynthesis systems using a moving x-ray source. It is expected that a commercially viable s-IOT system will be brought to market soon; however, there are only a few published studies demonstrating the diagnostic efficacy of a CNT s-IOT system.

Whereas s-IOT overcomes some of the limitations of early tomosynthesis techniques, some issues related to image reconstruction remain challenging. Of particular concern are the dark "shadow" artifacts that appear next to radiopaque objects in the direction of the linear x-ray source array. These artifacts are most pronounced next to metal restorations, but are still readily apparent next to composite restorations and even enamel (see figure 2).[22] The intensity of these artifacts is proportional to the radiodensity of the object and the number of iterations used in the tomosynthetic reconstruction. There are no artifacts seen after one iteration. A light grey artifact can be seen around composite restorations at 5 iterations, and the artifact becomes a dark black after 15 iterations. These artifacts have the potential to obscure the area of interest and hide caries next to restorations or periodontal defects next to implants.[22] The false positive rate may also increase in CAR caries detection, due to the potential for confusing artifact for caries. Early TACT and tomosynthesis researchers suggested the optimal number of iterations to be between 3 and 5 to maximize image sharpness without introducing too much noise and computational time. However, the most recent work published about s-IOT has used as many as 20 iterations, helping improve the visibility of primary caries and fractures while keeping the noise at a reasonable level.[18]

PILOT STUDY

A pilot study was conducted evaluating s-IOT images of composite restorations using 1, 3, 5, 10, 15, 30, and 50 iterations (see figure 3) and comparing them against conventional bitewings. Two observers chose the number of iterations that produced the best subjective image quality while producing the least confusion about what was artifact and what was a radiolucency attributable to a caries lesion. It was unanimously agreed that 1 and 3 iterations had too much blur, making caries lesions less visible than on the conventional bitewings. 5, 10, and 15 iterations made the caries easier to see, however, the artifact produced by restorations was too close in appearance to caries, making false positives likely. The artifact produced by 30 and 50 iterations was deemed too dark to be confused with caries to a trained observer and therefore not likely to produce many false positive responses. 50 iterations was dismissed as it produced far too much noise degrading image quality relative to 30 iterations. Therefore, 30 iterations were selected based on the subjective ease of caries visualization without the potential of confusing artifact with caries. The proper number of iterations to maximize the diagnostic efficacy for detecting CAR is unknown and requires further research.

SPECIFIC AIMS

The objectives of this *ex vivo* study are to compare stationary intraoral tomosynthesis (s-IOT) against conventional 2D digital radiography (conventional bitewings) in its accuracy and reliability (sensitivity, specificity, area under the ROC curve, and intraobserver and interobserver reliability) for detecting caries around composite restorations.

MATERIALS AND METHODS

Institutional review board (IRB) approval was sought to collect de-identified extracted human teeth from existing tooth repositories and to perform observer sessions at the UNC School of Dentistry (Study # 18-0306). The submission was reviewed by the Office of Human Research Ethics, which determined that the submission does not constitute human subjects research as defined under federal regulations [45 CFR 46.102 (d or f) and 21 CFR 56.102(c)(e)(l)] and does not require IRB approval. Posterior molar and premolar teeth with tooth-colored proximal restorations were selected and sorted into groups using visual examination according to the International Caries Detection and Assessment Criteria (ICDAS) and sorted into groups as follows: (1) ICDAS 0, no visually detectable caries lesion; (2) ICDAS 1&2, an enamel lesion only; (3) ICDAS 3&4, an enamel cavitation or a dark shadow; (4) ICDAS(5), a cavitation extending to the dentin.[32,33] Teeth with proximal caries lesions at any proximal surface were included. Teeth with a caries lesion at the occlusal surface were excluded. Also, surfaces with a cavitation larger than 2mm were excluded from the study. To simulate the situation where the clinician left residual caries, either intentionally or not, teeth with large carious lesions were collected and then prepared by leaving various amounts of carious dentin within a class II preparation prior to restoration with Filtek Supreme Ultra composite (3M ESPE, St. Paul, MN, USA). Caries was left either at the margin or at the deepest part of the preparation. For controls, 37 teeth were prepared using a class II preparation and restored using composite resin (Filtek Supreme Ultra) so no carious or discolored enamel or dentin was left behind. All teeth were stored in a 0.1% thymol solution. 77 teeth were included in the study with a total of 113 proximal restorations to be imaged and evaluated.

The sample teeth were mounted individually with three other randomly selected posterior teeth that had no restorations. The teeth were mounted in Play-Doh within a radiolucent plastic Lego block (see figure 4). The Play-Doh simulated the attenuation of alveolar hard and soft tissues. To simulate the soft tissues of the cheek, a 1cm thick slab of wax was placed between the x-ray source and the mounted teeth at a distance of 1 cm from the Lego block. Each quadrant was then imaged using the tomosynthesis unit and a conventional x-ray tube and CMOS detector. The geometry was standardized such that the relationship between the tube head, sample, and detector could be reproduced between the tomosynthesis unit and the conventional intraoral unit. The x-ray sources were directed so the central x-rays traveled parallel to the floor creating an orthogonal relationship to the long axis of the mounted teeth. This was done to simulate a typical bitewing geometry even though teeth were imaged without an opposing arch in a similar fashion to a periapical projection. If the image showed overlapping contacts extending more than halfway through the enamel of the adjacent tooth at the interproximal surface of interest, the image was retaken until less than half of the enamel was overlapped.

The conventional bitewings were acquired using a Schick 33 CMOS digital sensor. They were taken at the UNC School of Dentistry radiology clinic using the school's standard intraoral source (Instrumentarium Dental, Tuusula, Finland) at 70kVp, 7mA, 0.08s, at 40cm SID with 30cm rectangular collimation. A stationary tomosynthesis system at the UNC School of Dentistry was used to image all the samples. The system had a 7 CNT source array (model 2008-08-L75-002; XinRay Systems Inc., Research Triangle Park, NC), and an intraoral digital CMOS sensor (SuniRay2; Suni Medical Imaging Inc., San Jose, CA).[22] The CNT source array used 70 kVp and 100mAs. The intraoral sensor was a size 2 sensor with a field-of-view of 35.2 X 25.2 mm and a pixel size of 33 X 33 µm.

Once all the teeth had been imaged, they were sectioned in the mesial-distal plane, using a diamond saw. The first section was made in the area of any visually detectable carious lesion, or in the absence of a lesion, at the middle of the restoration. The teeth were then serially sectioned in 1mm increments until either a carious lesion or discolored dentin was found. If no caries was found under stereomicroscopy, the tooth was sectioned until the entire restoration was removed, demonstrating that there was no caries adjacent to the restoration. The sections were viewed under a stereomicroscope at 56x magnification to establish the presence or absence of caries. Two independent observers assessed the ground sections for the presence of either caries at the margin or infected/affected dentin that did not communicate with the margin. Particular attention was given to distinguish dead tracts, which form a comet-tail shape and run parallel to the course of the dentin tubules, from infected/affected dentin. Although micro-hardness testing of the dentin was not used, an explorer was utilized to assess restoration margins to distinguish caries from a defective margin. If there was any disagreement between the histologic assessments of the two observers, a third expert observer with training in oral microbiology was used as a tiebreaker.

A total of 7 observers were recruited from the UNC School of Dentistry and were either faculty members or residents in a graduate training program. All 7 observers had at least 4 years of experience as dentists evaluating intraoral radiographs for caries. Observers attended calibration sessions to discuss the purpose of the study and to learn interpretation principles for detecting caries with both imaging systems. Observers were taught the proper use of a 5-point scale for scoring their confidence level regarding the presence or absence of caries adjacent to the restoration in question. Observers were allowed to view sample images of teeth with CAR and discuss the images with the PI. The observers then rated the likelihood of caries presence on the 5-point scale where 1 = caries definitely not present, 2 = caries probably not present, 3 = unsure, 4 = caries probably present, and 5 = caries definitely present.

All observation sessions were conducted in the UNC School of Dentistry's radiology consultation room where the PI was present at each session to clarify questions and troubleshoot any issues. There were two workstations with three monitors each for viewing the images. Each monitor underwent quality control checks prior to the observation sessions using test group 18 test patterns from the American Association of Physicists in Medicine. Images from both modalities were viewed using the trial version of the RadiAnt Dicom Viewer under subdued lighting conditions. Observers were permitted to use contrast, brightness, and zoom functions while all other image processing parameters were held constant between observers. To establish intraobserver reliability, all 7 observers repeated the observation session no less than 2 weeks later and evaluated 25% of the original sample chosen at random.

Scores from the observers for each imaging modality were entered into a spreadsheet (Microsoft Excel 2013, Redmond, WA) along with the ground truth value. Receiver operating characteristic (ROC) curves and the corresponding areas under the curve (Az) were generated through an internet based ROC analysis tool made available through the Johns Hopkins University School of Medicine (www.jrocfit.org). Sensitivity and specificity were calculated by collapsing observer confidence ratings of 4 and 5 to a positive response and ratings of 1 to 3 as a negative response. Az, sensitivity, and specificity were calculated for each imaging modality-observer combination.

Two-way analysis of variance (ANOVA) tests were performed on the responses (Az, sensitivity, and specificity) respectively, using modality and observer as main covariates. A p-value < 0.05 was considered a statistically significant test result. Interobserver agreement was assessed by calculating the intraclass correlation coefficient for each modality. The observation scores from the second session were used to determine the intraobserver agreement. Weighted kappa statistics were calculated and a chi-squared test was used with statistical significance set at $p<0.05$. Intraclass correlation and kappa values between 0.01 – 0.20 had slight agreement, 0.21 – 0.40 had Fair agreement, 0.41 – 0.60 had moderate agreement, 0.61 – 0.80 had substantial agreement, and 0.81 – 0.99 had almost perfect agreement.

RESULTS

An examples of a carious lesion imaged using 2D digital intraoral radiography, s-IOT, and stereomicroscopy can be seen in figure 5. After sectioning and stereomicroscopic analysis, 57 of the 113 restorations had either caries adjacent to the restoration (table 1). 47 of these restorations had CAR at the margin, whether they were outer wall or inner wall lesions. Seven of the teeth showed only affected or infected dentin under the restoration that did not communicate with the surface margin. Three of the teeth had both caries adjacent to the restoration at the margin and a separate area of carious dentin under the restoration. All 37 control restorations were negative for caries adjacent to the restoration under stereomicroscopy. Overall there were 56 restored surfaces without caries adjacent to the restoration and 57 with caries adjacent to the restoration.

A summary of statistical findings for CAR detection is provided in Table 4. ROC analysis was conducted for each observer-modality combination and Az scores for each combination are provided in Table 2, while sensitivity and specificity scores are provided in table 3. Diagnostic accuracy as measured by Az scores was higher for s-IOT (0.720) than for conventional bitewings (0.684) and was found to be statistically significant (p=0.021) using a two-way ANOVA test. S-IOT demonstrated a higher mean sensitivity (0.48) than conventional bitewings (0.44), which was also statistically significant (p=0.019). There was no statistically significant difference (p=0.077) in mean specificity for s-IOT (0.57) and conventional bitewings (0.61).

Interobserver agreement as measured by intraclass correlation coefficients was fair for s-IOT (0.374) and moderate for conventional bitewings (0.459). The intraobserver agreement as measured by mean weighted kappa coefficients for was moderate for s-IOT (0.584) and substantial for conventional (0.658) bitewings with no statistically significant difference between modalities. Only observer 7 had a statistically significant difference (p=0.016) in intraobserver agreement between conventional (0.708) and s-IOT (0.305) bitewings.

DISCUSSION

This study used ROC analysis and derived Az values to discern differences in caries detection around restorations between conventional digital radiography and s-IOT. The advantage of ROC analysis is that it permits assessment of diagnostic accuracy despite varying decision thresholds between observers and the resulting differences in observer sensitivity and specificity values.[34] With 6 out of 7 observers having a higher Az for tomosynthesis, statistical analysis showed that there was a significant difference between the modalities' mean Az values, indicating better performance in detection of caries around composite restorations for s-IOT compared to conventional bitewings.

Sensitivity and specificity were also analyzed in this study because a false positive and a false negative result often do not carry the same weight in clinical dentistry. Some clinicians feel that maintaining specificity is valued over increasing the sensitivity because the slow advance of caries makes it likely that a carious lesion will eventually be detected before becoming too large.[35] Also, a false positive leads to needless loss of tooth structure at additional expense to the patient.[36] However, early non-surgical treatments are becoming more popular in dentistry with many researchers emphasizing the importance of minimally invasive dentistry. This trend may place more emphasis on increasing sensitivity if the practitioner utilizes early interventions that are less expensive and preserve tooth structure. In the case of interproximal CAR the same logic applies, however, there is the additional consideration that the restoration may obscure early radiographic detection of a carious lesion and may also permit an easy pathway for caries-causing bacteria to spread deeper before a lesion is detected.[37] To our knowledge, there are no patient or society level studies regarding the tradeoff between radiographic sensitivity and specificity of CAR that was left behind intentionally.

The absolute mean sensitivity for tomosynthesis was 4 percent higher than bitewings (a 9 percent relative increase) with an approximately equal loss in specificity. However, only the difference in sensitivity was statistically significant. The apparent equality in specificity was a slightly surprising result in light of the artifacts that composite restorations produce in tomosynthesis images. Depending on the radiodensity of the composite and the buccal-lingual thickness of the restoration, the intensity of the artifact varies from black to light grey. It was thought to be inevitable that some of the artifacts would have a shade of gray indistinguishable from caries, leading to false positive responses from observers. That there was no difference in specificity is likely due to the observers being well-trained in recognizing the signs of this artifact.

The precise reason for the increase in sensitivity for tomosynthesis is not as clear. In radiography, a carious lesion is detectable due to its lower mineral content relative to adjacent healthy tooth structure, thereby permitting less attenuation of x-rays. This differential attenuation within the tooth represents subject contrast and is common between both imaging modalities. However, s-IOT images teeth at different angles. Some angles have x-ray beams that pass through less superimposed healthy tooth structure and more carious demineralized tooth structure. This results in greater differential attenuation between healthy and carious tooth structure and gives the lesion more contrast in some of the projections. However, the exposure for each individual projection is approximately a seventh of what is used in conventional digital radiography and the images produced by a single projection likely lacks the contrast that a conventional digital projection taken at the same angle would have. The hypothesized reason for the increase in image contrast seen in s-IOT is the ability to reduce superimposition by mathematically blurring out-of-plane objects and focusing on in-plane objects. Therefore, the differential attenuation between the carious lesion and the in-plane healthy tooth structure does not get washed out by superimposed planes in which there is no differential attenuation. Caries detection has long been understood to be a contrast limited diagnostic task and this increase in contrast is very likely to produce an increase in sensitivity.[38,39]

It has been proposed that some carious lesions that would go undetected in both conventional and tomosynthetic imaging are correctly identified in tomosynthesis for the incorrect reason: artifact next to the restoration is mistaken for a carious lesion, while the real lesion is not visible at all. If the observer always interprets artifact as caries this would lead to perfect sensitivity for the wrong reasons, and at the unacceptable cost of having no specificity. The extent to which observers have a false rationale for correctly identifying a lesion could be answered with studies that track eye movements or allow the observer to record the rationale behind their caries detection decisions. On the other hand, it has also been argued that s-IOT will lead to higher specificity from observers with a more conservative approach who may interpret a radiolucency as artifact, when it is actually a void; again, making the correct choice for the wrong reason. It is the opinion of the author that this scenario would occur less often because voids have a very different appearance than artifacts produced by tomosynthesis, whereas artifacts quite frequently mimic caries (see figure 2). Teaching correct principles in tomosynthesis interpretation would minimize the effect of making the correct diagnosis for the wrong reason; however, it is unlikely that even the best observers would be immune to these errors. The small increase in sensitivity for tomosynthesis seen in this study may be the result of the observers' tendency to call an artifact a carious lesion, whether or not a lesion is present. However, this argument is not supported by the fact that we do not observe a statistically significant decrease in the specificity from s-IOT. While it was assumed that observers are identifying artifacts as carious lesions, this assumption is not supported by statistical analysis. The extent to which an observer will err on the side of either aggressive or conservative caries diagnoses will vary for each observer and is accounted for in ROC analysis. Since s-IOT had a statistically higher mean Az and mean sensitivity, without a loss in specificity, it may be presumed that s-IOT is the more effective diagnostic tool.

Interobserver agreement was moderate for conventional bitewings, while it was only fair for tomosynthesis. Intraobserver agreement was substantial for conventional bitewings, while it was only moderate for tomosynthesis. This suggests that observers were less consistent with each other and with themselves when observing tomosynthesis images. This is likely due to the limited experience observers had with tomosynthesis prior to the study. All observers had at least 4 years of experience evaluating conventional radiographs. In contrast, the brief calibration and training session prior to observations was the only experience observers had using s-IOT to evaluate caries adjacent to restorations. There was also a wide disparity between observers' intraobserver agreement for s-IOT ranging from 0.305 to 0.746.

This suggests that some observers felt more confident and were more consistent with s-IOT than were other observers. Additional training and better calibration of the observers in the interpretation of s-IOT images could have led to different results, and perhaps better diagnostic performance for s-IOT.

The mean sensitivity (0.44) and specificity (0.61) for conventional bitewings found in this study is lower than most studies reported in a 2016 meta-analysis, which showed a mean sensitivity of 0.53 and a mean specificity of 0.83 across 13 studies. The lower sensitivity and specificity values in this study suggests that the carious lesions were diagnostically more challenging than the lesions in the studies that were included in the meta-analysis. In this study, it was attempted to use an even distribution of lesions across the ICDAS categories. Reporting sensitivity and specificity values according to ICDAS categories has not been done consistently in the literature. However, reporting this information will allow better comparisons between studies in the future. It is not feasible at this time to report that data for this study, but this information will be included in any future publications of this study.

Stereomicroscopy was used for establishing ground truth in this study and has a long history in published caries literature as a reliable reference standard.[40] There is no consensus gold standard for assessing CAR as microradiography, stereomicroscopy, clinical visualization, and tactile assessment all have advantages and disadvantages.[2] Micro-CT would have been an ideal reference standard for this study as x-ray attenuation related to levels of mineralization in carious lesions is common to 2D digital radiography, tomosynthesis, and micro-CT. However, access to micro-CT for imaging 77 teeth was cost prohibitive in this investigation. Removal of the composite restorations for visual and tactile assessment could result in accidental removal of a carious lesion prior to assessment.   Sectioning and using stereomicroscopy for the assessment of CAR is not always straightforward and discrepancies between microradiography and stereomicroscopy have been reported.[41] Discolorations of enamel and dentin do not always correlate to a specific zone of the caries process due to different staining that may result from various diets and microbial flora. Discolored dentin may represent either infected dentin, affected dentin, sclerotic dentin, or dead tracts. Distinguishing between infected dentin and affected dentin is not always possible using stereomicroscopy. For this reason, it was decided to include infected and affected dentin as positive for caries, even though affected dentin is often left behind by clinicians intentionally when trying to preserve tooth structure.

Weaknesses in this study include a heterogeneous observer group that consisted of residents and faculty from different specialties. Ideally, the observers should all be experts in the diagnosis of caries for both modalities so that variations in education and experience level do not confound the results. Most of the observers had no experience with tomosynthesis prior to this study. The example images shown in the calibration sessions did not have ground truth for the teeth shown. This may have favored conventional bitewings because all of the observers had at least four years of experience using 2D intraoral radiography. Another weakness was the *ex vivo* design of the study. When imaging real patients, the scatter radiation from the soft tissues may be slightly different from the soft-tissue equivalent material used in this study. It is not clear how this might benefit one modality over the other in terms of contrast or diagnostic performance. In addition, it may be more difficult to manipulate one of the imaging systems to open contacts and obtain diagnostic quality radiographs when dealing with a real patient. Imaging real patients using s-IOT has a learning curve, is somewhat cumbersome, and takes some additional time. These difficulties may be overcome in subsequent versions of s-IOT systems making the coupling of the tube head and the XCP device more intuitive and less prone to error. Despite these difficulties, it has been suggested that TACT and tomosynthesis are better at obtaining open contacts than 2D intraoral radiography. This is based on the idea that at least one projection will be at an angle where the contacts are open. In this study, the imaging geometry was standardized between both modalities ensuring that contacts would be open.

Another considerable limitation to this study was the choice to use tooth colored restorations and to exclude metallic restorations. Despite the fact that a previous study on TACT showed that caries was more easily detectable next to amalgam restorations[20], that study made no mention of metal or beam hardening artifacts. It is not clear why those investigators did not run into metal artifacts but it is likely due to the low number of iterations (3) they used in the study and possibly a higher number of projections (9) with a non-linear source array. These artifacts would likely play a larger role in detecting caries next to metallic restorations had they been included in this study.

A circular or conical source array has been shown to provide better depth discrimination than linear sources arrays. Studies still need to be conducted to determine whether this increased depth discrimination would aid in CAR diagnosis. It has also been proposed that a circular or conical source array may decrease the amount of artifact produced around a restoration by "spreading it around". This does not seem supported by the fact that the artifact produced is a limited-angle artifact and the limited angle will still remain in a circular geometry. However, no published papers were found which investigated the effect of circular and linear source arrays on the extent of artifact production.

With a horizontal linear source array, objects that are oriented in a horizontal direction are less amenable to the depth discrimination capabilities of tomosynthesis. If the source array is linear in a vertical direction, vertical objects such as implants and tooth roots would be less amenable to depth discrimination. In this study, if a carious lesion at a gingival point angle was obscured by the restoration in one projection, then it would be obscured in all of the projections due to the horizontal linear source array. If a vertical source array had been used, it is more likely that one or more of the projections would have shown the carious lesion at the gingival floor. However, a vertical linear source array would also have produced artifacts that would likely be superimposed on that same carious lesion at the gingival floor. It is not clear whether a vertical linear source array would have performed better or worse than a horizontal source array.

Many papers have been published concerning the reduction of metal artifacts in both medical and dental applications of tomography in general but also specifically for tomosynthesis. These papers have demonstrated significant reduction in artifacts size and intensity and have restored fine hard-tissue detail next to metal objects. However, the MAR techniques available in s-IOT are quite time consuming, require some customization depending on exposure settings and patient factors, and are not easily applied for all images.[22] The choice was made to not use a MAR in this investigation because no clinically feasible MAR technique was available for s-IOT at the time this study was conducted. However, this is an active area of research that shows promise in the medical and dental literature.[22,42–44] Many of the techniques focus on segmenting the metal restorations out of the projection images and replacing them with grey values similar to neighbor structures prior to reconstruction. After reconstruction, the metallic object is re-inserted back into the reconstructed stack of images. This is an active area of research and studies ought to be conducted to compare new MAR reconstruction methods.

Further investigation is also needed to determine the optimal number of iterations in the reconstruction for detecting CAR. In this study, a subjective decision was made by the investigators based on optimizing subjective image contrast while making artifact as easy to distinguish from caries as possible. It is entirely reasonable that the ideal number of iterations for CAR detection is much lower than the 30 iterations used in this study and closer to the 3 iterations used in the TACT study by Nair et al (1998). While the images appear sharper and there is less blurring, noise and artifacts increase with the number of iteratons.[21] The ideal number of iterations suitable for one diagnostic task may not be the ideal number for a different diagnostic task.

CONCLUSIONS

S-IOT is a promising imaging modality for advancing the detection of CAR as seen in this *ex vivo* study. S-IOT showed a statistically significant increase in sensitivity compared to conventional bitewings without a corresponding change in specificity. There was also a statistically significant increase in the diagnostic accuracy of s-IOT in the detection of caries adjacent to proximal composite restorations. More research should be completed to investigate how to optimize s-IOT, including effects of metal artifact reduction, iterative reconstruction techniques, source array geometries, and restorative material type. The reference standard in this study could not distinguish between infected and affected dentin, nor did it distinguish between soft, leathery, firm, and hard dentin. Therefore, no conclusions could be drawn regarding the radiographic appearance of carious lesions on s-IOT images and the clinical extent of the carious lesions. In a field that is moving toward conservative non-invasive therapies, an increase in the sensitivity of caries detection from s-IOT imaging may improve the care the dental profession can give its patients.

TABLES AND FIGURES

Table 1. Ground truth as assessed by stereomicroscopy

Caries	*Surfaces*	*Caries Location*	*Surfaces*
Sound	56	-	56
Lesion	57	Margin Only	47
		Pulpal Only	7
		Margin and Pulpal*	3
Total	113		113

*Carious lesion at the margin and carious dentin toward the pulp separated by healthy dentin.

Table 2. Caries detection Az by modality and observer

	Observer									
Modality	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*Mean*	*SD*	*p-value*[1]
Conventional	0.653	0.649	0.704	0.685	0.675	0.705	0.720	0.684	0.027	0.021
Tomo	0.692	0.739	0.732	0.712	0.721	0.691	0.756	0.720	0.024	
Mean	0.673	0.694	0.718	0.699	0.698	0.698	0.738			
SD	0.028	0.064	0.020	0.019	0.033	0.010	0.025			

Abbreviations: SD standard deviation, Az area under the curve.

[1]ANOVA testing comparing modality Az values with statistical significance set at $p<0.05$

Table 3. Sensitivity and specificity by modality and observer

Observer		*Modality* Conventional	*Modality* Tomosynthesis	***Mean***	*SD*
1	TPR	0.278	0.403	0.340	0.088
	TNR	0.812	0.609	0.710	0.143
2	TPR	0.319	0.306	0.313	0.010
	TNR	0.797	0.710	0.754	0.061
3	TPR	0.444	0.514	0.479	0.049
	TNR	0.580	0.565	0.572	0.010
4	TPR	0.514	0.542	0.528	0.020
	TNR	0.565	0.594	0.580	0.020
5	TPR	0.431	0.472	0.451	0.029
	TNR	0.551	0.551	0.551	0.000
6	TPR	0.500	0.542	0.521	0.029
	TNR	0.522	0.449	0.486	0.051
7	TPR	0.458	0.528	0.493	0.049
	TNR	0.652	0.565	0.609	0.061
Mean	TPR	0.444	0.484	*p=0.019*[1]	-
	TNR	0.611	0.572	*p=0.077*[1]	-
SD	TPR	0.089	0.089	-	-
	TNR	0.111	0.072	-	-

Abbreviations: TPR, true positive rate (sensitivity); TNR, true negative rate (specificity)
[1]ANOVA test of modality TPR and TNR values with statistical significance set at p<0.05

Table 4. Summary statistical findings from two-way ANOVA comparing Az, sensitivity, specificity scores

Measure	*Effect*	*p-value*
Fitted Az	Observer	0.25
	Modality	0.021*
Sensitivity	Observer	0.002*
	Modality	0.019*
Specificity	Observer	0.025*
	Modality	0.077

*denotes statistically significant effect

Table 5. Interobserver agreement using intraclass correlation coefficient

Modality	*Intraclass Correlation**	*Agreement*
Conventional BW	0.459	Moderate
Tomo BW	0.374	Fair

*Shrout-Fleiss reliability

Table 6. Intraobserver agreement between session 1 and 2 using weighted kappa coefficients

Observer	*Conv kappa*	*Tomo kappa*	*p-value*[1]
1	0.514	0.746	0.084
2	0.701	0.563	0.385
3	0.698	0.666	0.822
4	0.694	0.626	0.603
5	0.645	0.702	0.676
6	0.646	0.479	0.308
7	0.708	0.305	0.016*
Mean	0.658	0.584	0.480

[1]Chi-squared test for difference in kappa between modalities
*Statistically significant difference

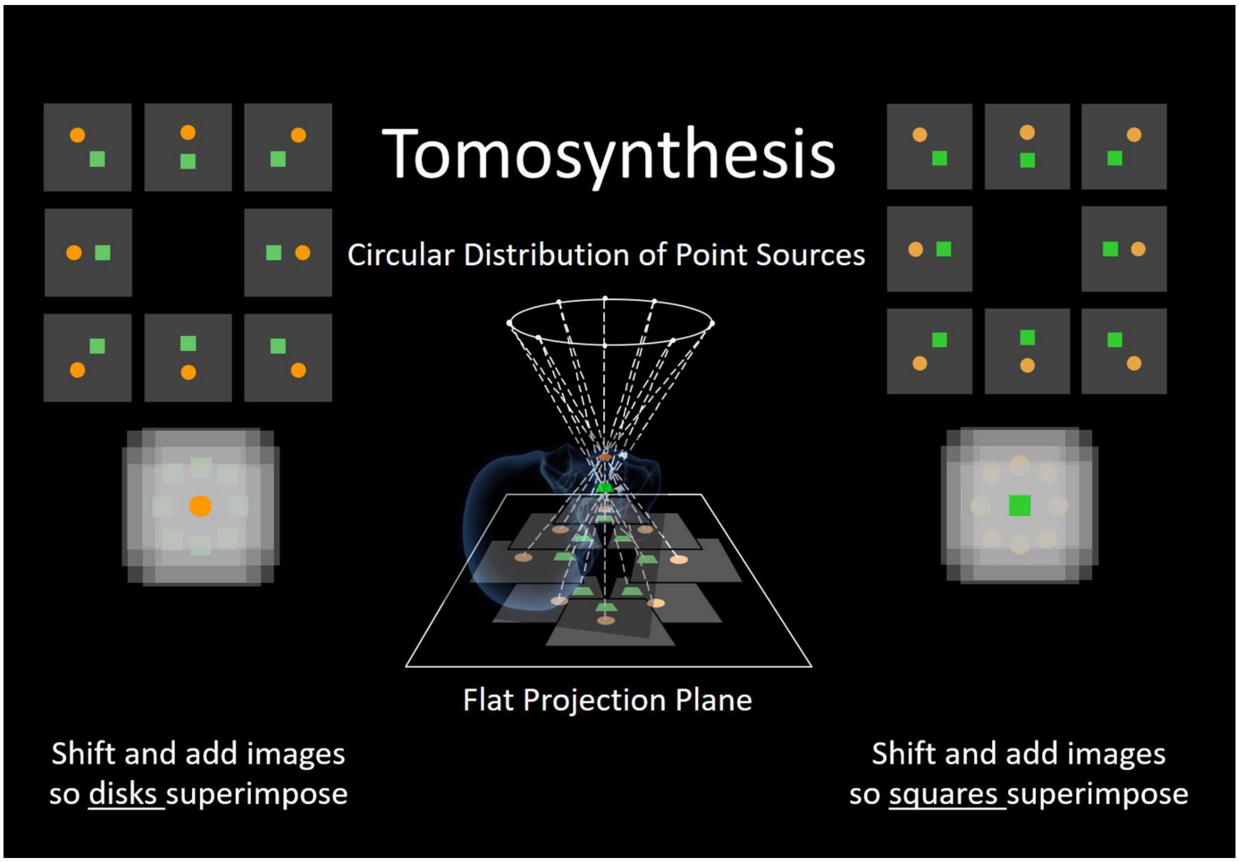

Figure 1. Tomosynthesis geometrical concept. A disc and a square at located within two different coronal planes. Individual projections taken at different angles from a circular x-ray source array arranged at the top left and top right. Projections are shifted and overlapped so that the disc(left) and square on the right are overlapped and objects from different planes are blurred.

Figure 2. A slice from a reconstructed s-IOT image stack showing a proximal composite restoration and a dark artifact that mimics the radiographic appearance of CAR. This tooth was found to have sound enamel and dentin after being serially sectioned.

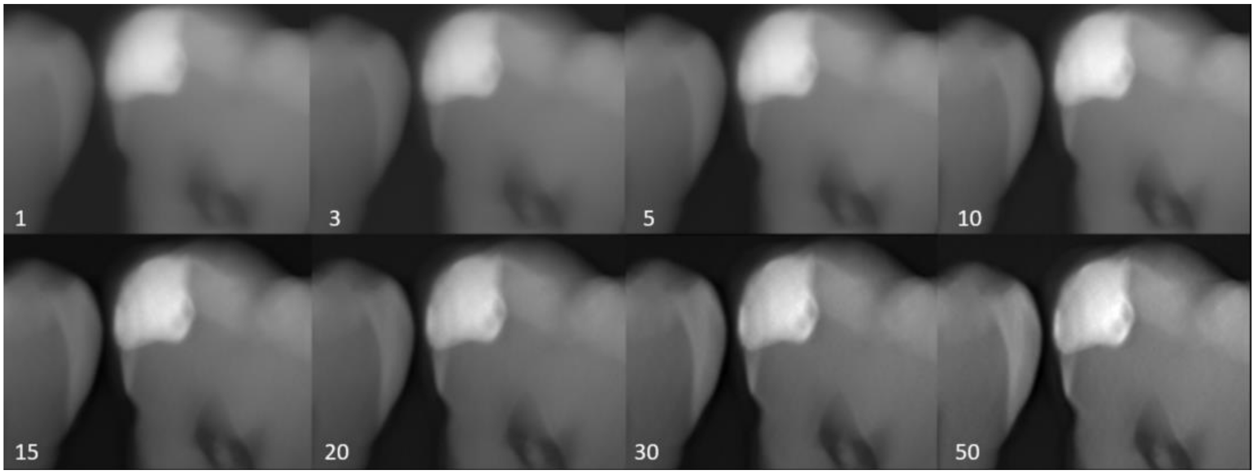

Figure 3. Pilot study image comparing various numbers of iterative reconstructions. A very subtle incipient lesion located at the gingival margin. The same image projections have be reconstructed using an iterative reconstruction technique using either 1,3,5,10,15,20,30,50 iterations. More iterations creates more image sharpness, noise and darker artifacts next to the restoration.

Figure 4. The s-IOT unit at the UNC School of Dentistry. Four teeth are mounted in a plastic Lego block using Play-Doh.

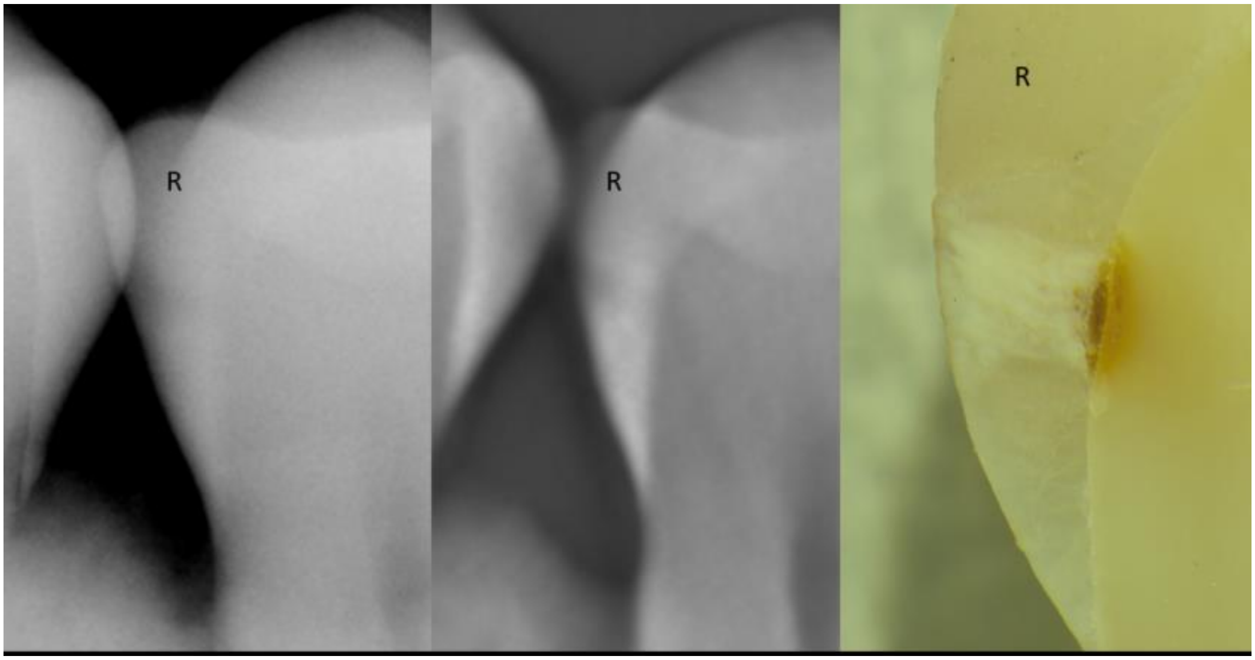

Figure 5. Carious lesion extending to the DEJ. Left, conventional intraoral bitewing. Center, a center slice from stationary intraoral tomosynthesis bitewing. Right, ground section under stereomicroscopic 56x. R denotes the composite restoration, which is difficult to visualize on all three images.

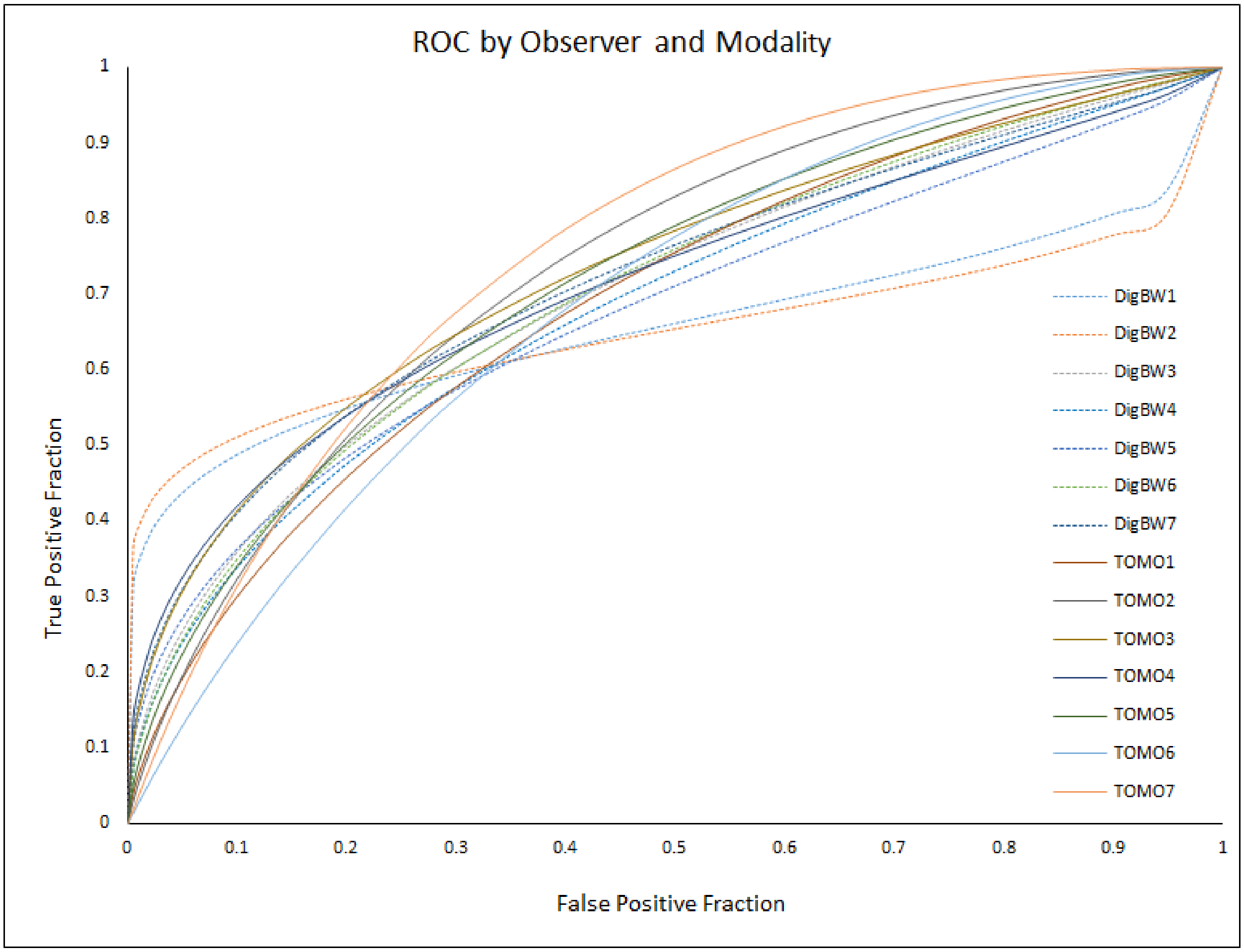

Figure 6. ROC curves by observer and modality

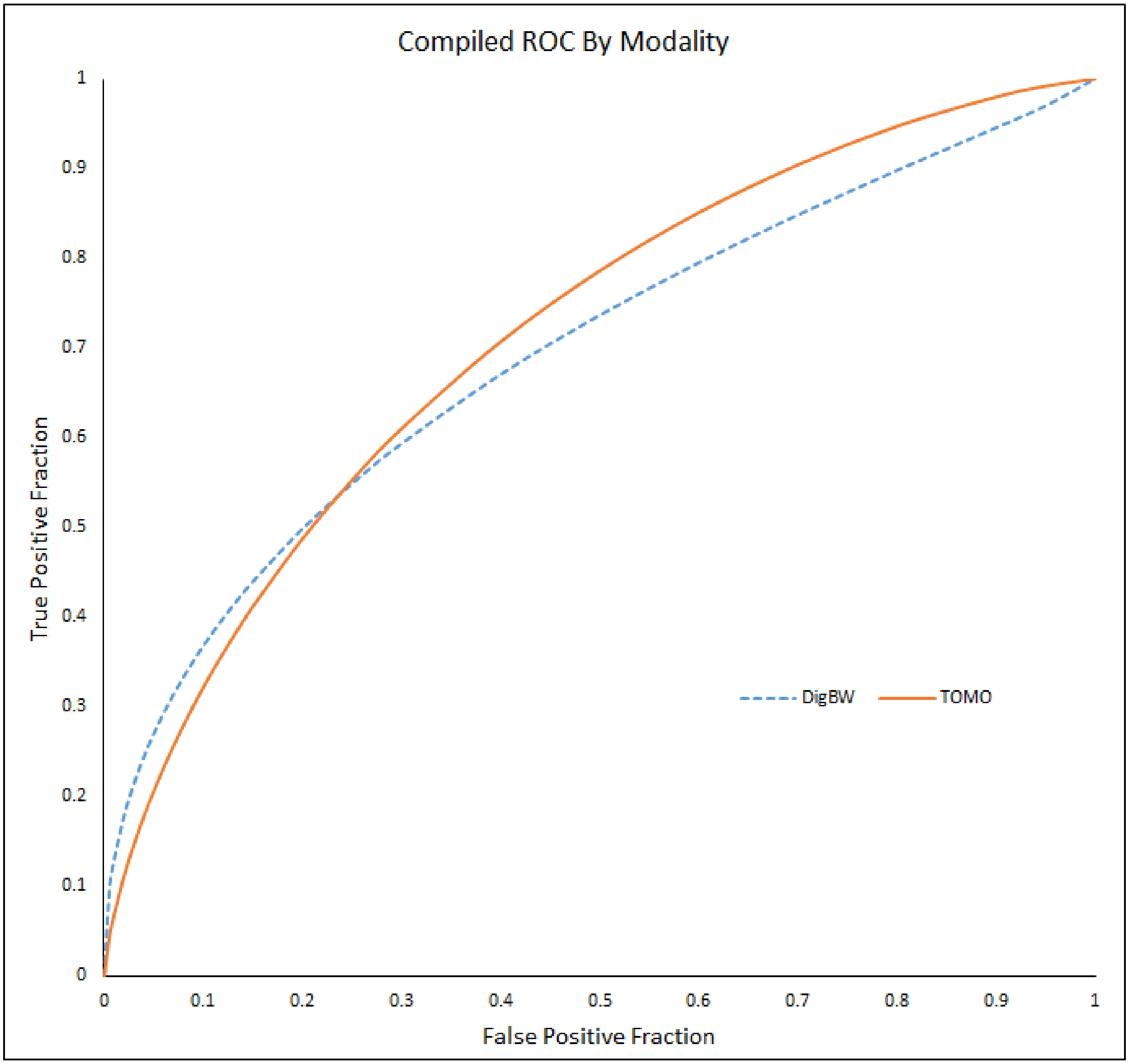

Figure 7. Compile observers ROC curves by modality

REFERENCES

1. Burke FJ, Cheung SW, Mjör IA, Wilson NH. Reasons for the placement and replacement of restorations in vocational training practices. *Prim Dent Care*. 1999;6(1):17-20. http://www.ncbi.nlm.nih.gov/pubmed/10752459. Accessed March 8, 2019.

2. Brouwer F, Askar H, Paris S, Schwendicke F. Detecting Secondary Caries Lesions. *J Dent Res*. 2016;95(2):143-151. doi:10.1177/0022034515611041

3. Forss H, Widström E. Reasons for restorative therapy and the longevity of restorations in adults. *Acta Odontol Scand*. 2004;62(2):82-86. http://www.ncbi.nlm.nih.gov/pubmed/15198387. Accessed March 8, 2019.

4. Gordan V V, Riley JL, Geraldeli S, et al. Repair or replacement of defective restorations by dentists in The Dental Practice-Based Research Network. *J Am Dent Assoc*. 2012;143(6):593-601. http://www.ncbi.nlm.nih.gov/pubmed/22653939. Accessed March 8, 2019.

5. Lallam C, Decup F. Minimal intervention dentistry II: part 2. Management of caries and periodontal risks in general dental practice. *Br Dent J*. 2014;216(4):179-185. doi:10.1038/sj.bdj.2014.143

6. Holmgren C, Gaucher C, Decerle N, Doméjean S. Minimal intervention dentistry II: part 3. Management of non-cavitated (initial) occlusal caries lesions – non-invasive approaches through remineralisation and therapeutic sealants. *Br Dent J*. 2014;216(5):237-243. doi:10.1038/sj.bdj.2014.147

7. Holmgren CJ, Roux D, Doméjean S. Minimal intervention dentistry: part 5. Atraumatic restorative treatment (ART) – a minimum intervention and minimally invasive approach for the management of dental caries. *Br Dent J*. 2013;214(1):11-18. doi:10.1038/sj.bdj.2012.1175

8. Colon P, Lussi A. Minimal intervention dentistry: part 5. Ultra-conservative approach to the treatment of erosive and abrasive lesions. *Br Dent J*. 2014;216(8):463-468. doi:10.1038/sj.bdj.2014.328

9. Innes NPT, Frencken JE, Bjørndal L, et al. Managing Carious Lesions: Consensus Recommendations on Terminology. *Adv Dent Res*. 2016;28(2):49-57. doi:10.1177/0022034516639276

10. Shivakumar K, Prasad S, Chandu G. International Caries Detection and Assessment System: A new paradigm in detection of dental caries. *J Conserv Dent*. 2009;12(1):10-16. doi:10.4103/0972-0707.53335

11. Heymann H, Swift EJ, Ritter A V., et al. *Sturdevant's Art and Science of Operative Dentistry*. 6th ed. Elsevier/Mosby; 2013.

12. Wenzel A. Bitewing and digital bitewing radiography for detection of caries lesions. *J Dent Res*. 2004;83(1):72-75. doi:10.1177/154405910408301S14

13. Gordan V V., Riley JL, Geraldeli S, et al. Repair or replacement of defective restorations by dentists in the dental practice-based research network. *J Am Dent Assoc*. 2012;143(6):593-601. doi:10.14219/jada.archive.2012.0238

14. Mann J, Pettigrew JC, Revach A, Arwas JR, Kochavi D. Assessment of the DMF-S index with the

use of bitewing radiographs. *Oral Surgery, Oral Med Oral Pathol*. 1989;68(5):661-665. doi:10.1016/0030-4220(89)90257-0

15. Syriopoulos K, Sanderink GC, Velders XL, van der Stelt PF. Radiographic detection of approximal caries: a comparison of dental films and digital imaging systems. *Dentomaxillofac Radiol*. 2000;29(5):312-318. doi:10.1038/sj/dmfr/4600553

16. Wenzel A. Digital imaging for dental caries. *Dent Clin North Am*. 2000;44(2):319-38, vi. http://www.ncbi.nlm.nih.gov/pubmed/10740771. Accessed April 6, 2019.

17. Valizadeh S, Tavakkoli MA, Karimi Vasigh H, Azizi Z, Zarrabian T. Evaluation of Cone Beam Computed Tomography (CBCT) System: Comparison with Intraoral Periapical Radiography in Proximal Caries Detection. *J Dent Res Dent Clin Dent Prospects*. 2012;6(1):1-5. doi:10.5681/joddd.2012.001

18. Shan J, Tucker AW, Gaalaas LR, et al. Stationary intraoral digital tomosynthesis using a carbon nanotube X-ray source array. *Dentomaxillofacial Radiol*. 2015;44(9):1-9. doi:10.1259/dmfr.20150098

19. Nair MK, Tyndall DA, Ludlow JB, May K. Tuned Aperture Computed Tomography and Detection of Recurrent Caries. *Caries Res*. 1998;32(1):23-30. doi:10.1159/000016426

20. Nair MK, Tyndall DA, Ludlow JB, May K, Ye F. The effects of restorative material and location on the detection of simulated recurrent caries. A comparison of dental film, direct digital radiography and tuned aperture computed tomography. *Dentomaxillofacial Radiol*. 1998;27(2):80-84. doi:10.1038/sj.dmfr.4600323

21. van der Stelt PF, Ruttimann UE, Webber RLL. Restoration and enhancement of tomosynthetic images and its applications in dentistry. *Proc Annu Symp Comput Appl Med Care*. 1985;(May):673. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2578107/.

22. Puett C, Inscoe C, Hilton R, et al. Stationary digital intraoral tomosynthesis: Demonstrating the clinical potential of the first-generation system. In: *Progress in Biomedical Optics and Imaging - Proceedings of SPIE*. Vol 10573. ; 2018. doi:10.1117/12.2293722

23. Nair MK, Bezik J. Tuned-Aperture Computed Tomography for Detection of Induced Mid-Buccal/Lingual Alveolar Bone Defects. *J Periodontol*. 2006;77(11):1833-1838. doi:10.1902/jop.2006.050452

24. Limrachtamorn S, Edge MJ, Gettleman L, Scheetz JP, Farman AG. Array geometry for assessment of mandibular implant position using tuned aperture computed tomography (TACT™). *Dentomaxillofacial Radiol*. 2004;33(1):25-31. doi:10.1259/dmfr/18567887

25. Harase Y, Araki K, Okano T. Diagnostic ability of extraoral tuned aperture computed tomography (TACT) for impacted third molars. *Oral Surgery, Oral Med Oral Pathol Oral Radiol Endodontology*. 2005;100(1):84-91. doi:10.1016/j.tripleo.2004.12.001

26. Nair MK, Nair UDP, Gröndahl HG, Webber RL, Wallace JA. Detection of artificially induced vertical radicular fractures using tuned aperture computed tomography. *Eur J Oral Sci*. 2001;109(6):375-379. http://www.ncbi.nlm.nih.gov/pubmed/11767273. Accessed March 8, 2019.

27. Machida H, Yuhara T, Tamura M, et al. Whole-Body Clinical Applications of Digital Tomosynthesis. *RadioGraphics*. 2016;36(3):735-750. doi:10.1148/rg.2016150184

28. Yoo JY, Chung MJ, Choi B, et al. Digital Tomosynthesis for PNS Evaluation: Comparisons of Patient Exposure and Image Quality with Plain Radiography. *Korean J Radiol*. 2012;13(2):136. doi:10.3348/kjr.2012.13.2.136

29. Wells ITP, Raju VM, Rowberry BK, Johns S, Freeman SJ, Wells IP. Digital tomosynthesis--a new lease of life for the intravenous urogram? *Br J Radiol*. 2011;84(1001):464-468. doi:10.1259/bjr/95862259

30. Ha AS, Lee AY, Hippe DS, Chou S-HS, Chew FS. Digital Tomosynthesis to Evaluate Fracture Healing: Prospective Comparison With Radiography and CT. *AJR Am J Roentgenol*. 2015;205(1):136-141. doi:10.2214/AJR.14.13833

31. Quaia E, Baratella E, Cernic S, et al. Analysis of the impact of digital tomosynthesis on the radiological investigation of patients with suspected pulmonary lesions on chest radiography. *Eur Radiol*. 2012;22(9):1912-1922. doi:10.1007/s00330-012-2440-3

32. International Caries Detection and Assessment System Coordinating Committee. *Rationale and Evidence for the International Caries Detection and Assessment System (ICDAS II)*.; 2005. https://www.iccms-web.com/uploads/asset/592848be55d87564970232.pdf. Accessed April 6, 2019.

33. Dikmen B. Icdas II criteria (international caries detection and assessment system). *J Istanbul Univ Fac Dent*. 2015;49(3):63-72. doi:10.17096/jiufd.38691

34. Metz CE. ROC analysis in medical imaging: a tutorial review of the literature. *Radiol Phys Technol*. 2008;1(1):2-12. doi:10.1007/s12194-007-0002-1

35. Dove SB. Radiographic diagnosis of dental caries. *J Dent Educ*. 2001;65(10):985-990. http://www.ncbi.nlm.nih.gov/pubmed/11700001. Accessed March 8, 2019.

36. Dove SB. Radiographic diagnosis of dental caries. *J Dent Educ*. 2001;65(10):985-990. http://www.ncbi.nlm.nih.gov/pubmed/11700001.

37. González-Cabezas C, Fontana M, Gomes-Moosbauer D, Stookey GK. Early detection of secondary caries using quantitative, light-induced fluorescence. *Oper Dent*. 2003;28(4):415-422. http://www.ncbi.nlm.nih.gov/pubmed/12877427. Accessed March 8, 2019.

38. Huda W, Rill LN, Benn DK, Pettigrew JC. Comparison of a photostimulable phosphor system with film for dental radiology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1997;83(6):725-731. http://www.ncbi.nlm.nih.gov/pubmed/9195631. Accessed March 8, 2019.

39. Kashima I. Computed radiography with photostimulable phosphor in oral and maxillofacial radiology. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1995;80(5):577-598. http://www.ncbi.nlm.nih.gov/pubmed/8556466. Accessed March 8, 2019.

40. Hintze H, Wenzel A LM. Stereomicroscopy, film radiography, microradiography and naked-eye inspection of tooth sections as validation for occlusal caries diagnosis. *Caries Res*. 1995;29(5):359-363.

41. Meira KRS, Forte FDS, Silva PF, de Sousa FB, de Holanda Ferreira DA, Chaves AMB. Dentin reactions to caries are misinterpreted by histological "gold standards." *F1000Research*. 2014;3:13. doi:10.12688/f1000research.3-13.v1

42. Lu Y, Chan H-P, Wei J, Hadjiiski LM, Samala RK. Improving image quality for digital breast tomosynthesis: an automated detection and diffusion-based method for metal artifact reduction. *Phys Med Biol*. 2017;62(19):7765-7783. doi:10.1088/1361-6560/aa8803

43. Guo S, Tang H, Zhou Y, Huang Y, Shao H, Yang D. Accuracy of Digital Tomosynthesis With Metal Artifact Reduction for Detecting Osteointegration in Cementless Hip Arthroplasty. *J Arthroplasty*. 2018;33(5):1579-1587. doi:10.1016/j.arth.2017.12.037

44. Zhang Z, Yan M, Tao K, Xuan X, Sabol JM, Lai H. Metal artifact reduction in tomosynthesis imaging. In: Hoeschen C, Kontos D, Flohr TG, eds. *Proceeding of SPIE: Medical Imaging 2015-Physics of Medical Imaging*. Vol 9412. Bellingham, Wash: International Society for Optics and Photonics; 2015:94125A. doi:10.1117/12.2080923