

INVESTIGATING THE VARIABILITY IN ROOT CANAL FILLING QUALITY EVALUATIONS AMONG ENDODONTIST, RADIOLOGIST AND ARTIFICIAL INTELLIGENCE IN PERIAPICAL AND PANORAMIC RADIOGRAPHS

Sabah M. Sobhy*  and Shereen Fathy Ahmed** 

ABSTRACT

Purpose: The research was conducted to evaluate the differences in the assessment of root canal filling quality among endodontists, radiologists and AI technology (Thakaamed Detect) in periapical and panoramic radiographs.

Methodology: The study included three groups; **Group 1:** Endodontist assessed 500 periapical and 500 panoramic radiographs. **Group 2:** Radiologist assessed the same set of 500 periapical and 500 panoramic radiographs. **Group 3:** AI model (Thakaamed Detect) assessed the same set of 500 periapical and 500 panoramic radiographs after manual evaluations by the endodontist and radiologist. The radiographs were randomly assigned, and the assessors were blinded to each other's evaluations. After manual evaluations, the same radiographs were uploaded to the AI tool (Thakaamed Detect) for assessment. This tool was developed to store and process dental images. Thakaamed Detect generated a report for each radiograph, identifying the quality of the root canal fillings. AI results were compared to manual evaluations to determine differences in assessment of root canal filling quality. Data was statistically analyzed using ANOVA test, followed by Bonferroni's post-hoc test. Kappa statistic was used to assess agreement between Endodontist, Radiologist and AI.

Results: There was statistical significant difference between evaluation of root canal filling quality by Endodontist, Radiologist and AI. Highest quality of root canal filling was evaluated by Endodontist. Radiologist reported statistically significantly lower quality. AI reported the statistically significantly lowest root canal filling quality.

Conclusion: This study has shown significant variability in root canal filling quality assessments among endodontists, radiologists and AI in periapical and panoramic radiographs.

KEYWORDS: Artificial intelligence, panoramic radiographs, periapical radiographs, root canal filling, variability.

* Lecturer of Endodontics, Endodontic Department, Faculty of Dental Medicine for Girls, Al-Azhar University, Cairo, Egypt.

** Lecturer of Oral Radiology, Oral Medicine and Periodontology Department, Faculty of Dentistry, October 6 University

INTRODUCTION

The success of root canal therapy is greatly reliant on quality of root canal filling, which prevents reinfection and supports long term tooth retention⁽¹⁾. Root canal treatment is evaluated using clinical and radiographic examination. Clinical data should determine the presence or absence of signs and symptoms of infection and radiographic examination helps in evaluating the quality of filling in the root canal system⁽²⁾.

The European Society of Endodontology's recommendations for endodontic treatment: as outlined in their consensus report, specify the standards for root canal therapy. According to these guidelines, the canal filling should be homogenous and free of internal or external voids. Furthermore, the root canal filling should terminate at the length of 0.5 to 2.0 mm from the root apex. The lumen of the root canal between the end of the filling and the radiographic apex should not be visible on the postobturation radiographs⁽³⁾.

Quality of root canal treatment may vary among dental students, general dentists and endodontists. The differences are often due to varying levels of experiences, knowledge and dexterity which can be prone to variability⁽²⁾. Integrating artificial intelligence (AI) into this process offers the potential to give more objective and consistent evaluations while successfully removing human error caused by stress, exhaustion, or a lack of expertise⁽⁴⁾. Although AI has numerous advantages, it has some drawbacks such as limited data availability, accessibility, structure and sophistication, lack of rigor and standards in its development, and problems with ethics and responsibility⁽⁵⁾. Despite these challenges, AI is widely used in endodontics and can aid in various clinical applications, including determining working length, detecting root fractures, identifying periapical pathologies, analyzing root morphology, tracing apical foramen and predicting diseases⁽⁶⁾.

Artificial intelligence is the capability of machines to perform tasks that are typically carried out by humans⁽⁷⁾. Machine learning (ML) is a subset of artificial intelligence, allows computers to learn from data and make predictions based on this learning process. ML can analyze massive datasets, enabling the algorithm to learn from the interpreted data and enhance its performance over time⁽⁸⁾. This capability facilitates the development of sophisticated tools that, through exposure to various scenarios, can solve complex problems and enable predictive modeling⁽⁹⁾.

Deep learning (DL) is a form of ML that makes use of artificial neural networks (ANNs) which function similarly to the human brain. ANNs are designed to process and learn from large amounts of data⁽¹⁰⁾. Initially, ANNs assign random weights to the connections between neurons, and through the learning process, these weights are adjusted to ensure the network operates properly. In image recognition, each layer of an ANN performs an abstraction process: the first layer distinguishes lines and corners, while subsequent layers identify more complex features such as curvatures. Adding convolution to the network allows it to focus on low-level mechanisms like curves and edges within an image⁽¹¹⁾.

Convolutional neural networks (CNNs) are a type of artificial neural network (ANN) that excel tasks like image classification and object detection. They are specifically designed to analyze the spatial relationships between elements in an image and extract meaningful information. CNNs have been utilized in various fields, including object recognition, categorizing images into different classes, and extracting information⁽¹²⁻¹⁴⁾. These computer algorithms must be "taught" correctly to mimic human brain decision making and produce trustworthy and clinically augmented results^(6,15). In dental medicine, CNNs have been trained to

extract data from images, such as identifying dental caries⁽¹⁶⁾ detecting alveolar crest bone level⁽¹⁷⁾ and periapical pathosis⁽¹⁸⁾.

Radiographs are the principal tool used by dentists to assess tooth anatomy, especially in endodontics, where radiograph analysis is critical for treatment planning and diagnosis⁽¹⁹⁾. Furthermore, Food and Drug Administration (FDA) recently approved numerous AI technologies for dental image processing, representing significant progress in the practical application of AI in dental medicine⁽²⁰⁾. Recently, several researches have explored the diagnostic capabilities of deep learning algorithms in oral and maxillofacial imaging modalities including periapical radiography⁽²¹⁾ and panoramic radiography^(22,23). These studies investigate how AI can enhance accuracy and efficiency in interpreting radiographic images, potentially improving diagnostic outcomes in dental practice.

AI-based X-ray image analysis could benefit from convolutional neural networks with multiple layers since they evaluate adaptive image features and perform image classification thus reducing the need to input predefined image signs for identification process calibration. Despite advancements like CNNs show promise in improving diagnostic processes, further studies are necessary to thoroughly assess their effectiveness, accuracy, and integration into routine clinical practice. Continued research will help validate and refine AI technologies, ensuring they meet the rigorous standards required for reliable diagnostic support in dentistry^(24,25). The present study was conducted to evaluate the differences in the assessment of root canal filling quality among endodontists, radiologists, and AI technology (Thakaamed Detect) in periapical and panoramic radiographs. and the null hypothesis of this study was that there is no difference between AI model and manual assessment.

MATERIALS AND METHODS

Study design:

This research was designed as a retrospective cohort study. All periapical and panoramic radiographs were collected from the dataset obtained from patients who came to radiology clinic of the faculty of dental medicine of Al-Azhar and October6 universities between January 2021 and December 2022. All procedures followed the Helsinki Declaration of Human Rights guidelines. Ethical approval was obtained following guidelines from the Research Ethics Committee (REC) (RECO6U/8-2024) of Faculty of Dentistry, October 6 University.

The inclusion criteria:

- a. An average patient age of 50-20 years old
- b. Periapical and panoramic radiographs of permanent teeth.
- c. Radiographs with optimum resolution.
- d. Showing at least one tooth with root canal filling.

The exclusion criteria:

- a. Radiographic error such as a cone-cut.
- b. Deciduous teeth radiographs.
- c. Poor quality radiograph where root canal filling of the teeth was not visible.

Sample selection:

The current study selected anonymized 500 periapical and 500 panoramic radiographs of 1000 patients that meet the inclusion criteria. These radiographs were retrospectively selected from 4,000 collected periapical and panoramic radiographs. Periapical radiographs were taken using dental x ray machine (Planmecca ProMax) set at 70 kvp ,8 mA and 0.08-0.04s, panoramic radiographs were taken using panoramic imaging system (OrthoPhos 3D, Sirona,Germany.) set at KVp:70, mA:12 and exposure time 11 seconds.

Sample distribution

All periapical and panoramic radiographs were coded with sequential numbers, then randomly assigned to three assessor groups. Each assessor (endodontist, radiologist, AI) was provided with the same set of 1000 radiographs, which included 500 periapical and 500 panoramic radiographs.

Study groups

The study included three groups based on assessor type:

Group 1: Endodontist

Endodontist assessed 500 periapical and 500 panoramic radiographs.

Group 2: Radiologist

Radiologist assessed the same set of 500 periapical and 500 panoramic radiographs.

Group 3: AI model (*Thakaamed Detect*)

AI model assessed the same set of 500 periapical and 500 panoramic radiographs after the manual evaluations by the endodontist and radiologist.

Randomization and blinding

Randomization of the samples was performed using random number generator. <https://www.random.org/>. The endodontist and radiologist were blinded to each other's assessments and the AI assessments and the AI model was blinded to the manual evaluations and did not receive any input or

feedback from the manual evaluations.

Manual evaluation

Two examiners, including an endodontist and oral and maxillofacial radiology expert with over ten years of experience conducted an independent manual radiographic evaluation. In case of disagreement, they discussed the image to achieve a consensus. The assessment of quality of root canal filling on the radiograph adhered to guidelines from European Society of Endodontology (ESE) ⁽²⁶⁾ and using the criteria established by **Balto et al. (2010)**⁽²⁷⁾ which include evaluating the distance between the end of the filling and the radiographic apex, assessing the density of the filling and considering the taper of the root filling ⁽²⁷⁾.

AI evaluation

The deep neural network software, originally trained through transfer learning, has been adapted for use with periapical and panoramic X-ray images following extensive training. This software is capable of applying the World Dental Federation (FDI) notation for tooth numbering and identifying normal anatomical structures such as the mandible, mental foramen, mandibular canal, maxillary sinus, and dental pulp. Additionally, it can detect various dental diseases and treatments on radiographs, including dental caries, root canal treatments, periapical lesions, root remnants, periodontal bone loss, crowns, bridges, impacted teeth, implants, and fillings (Fig.1).

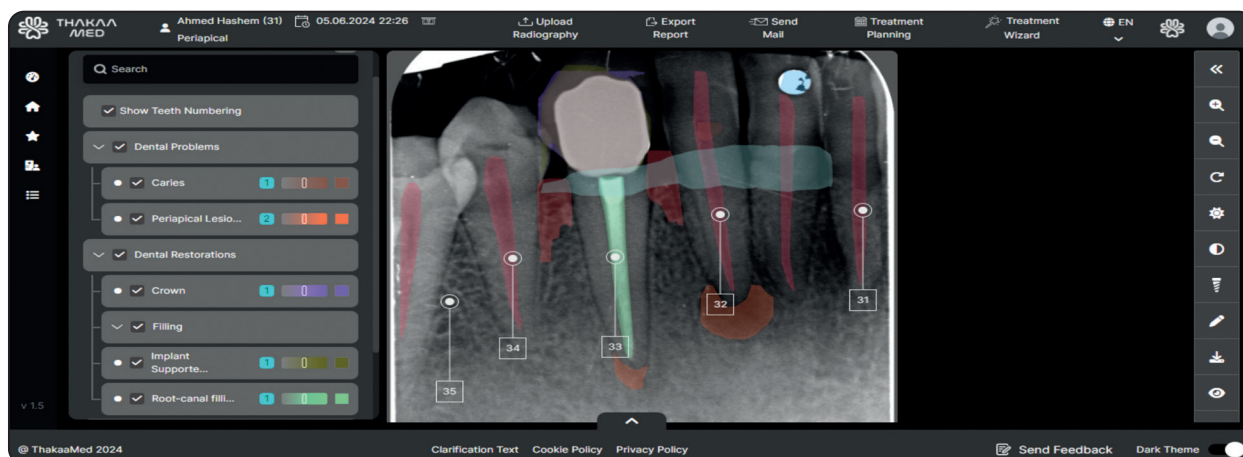


Fig. 1 A

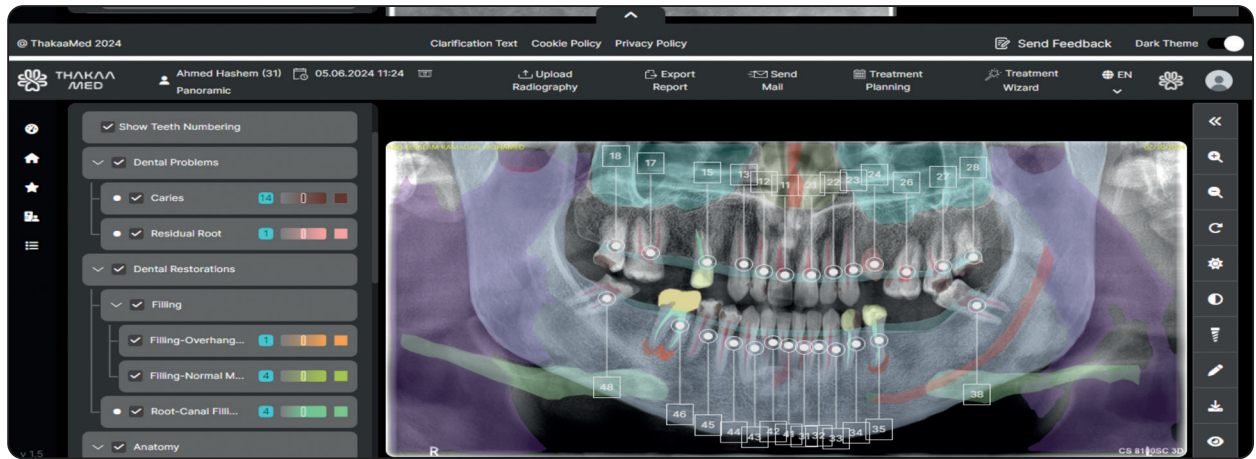


Fig. 1 B

Fig. (1) Teeth numbering and detection of caries, root canal filling, periodontal bone loss, periapical lesions and crowns by AI model (Thakaamed Detect) on radiograph. A) Periapical radiograph. B) Panoramic radiograph.

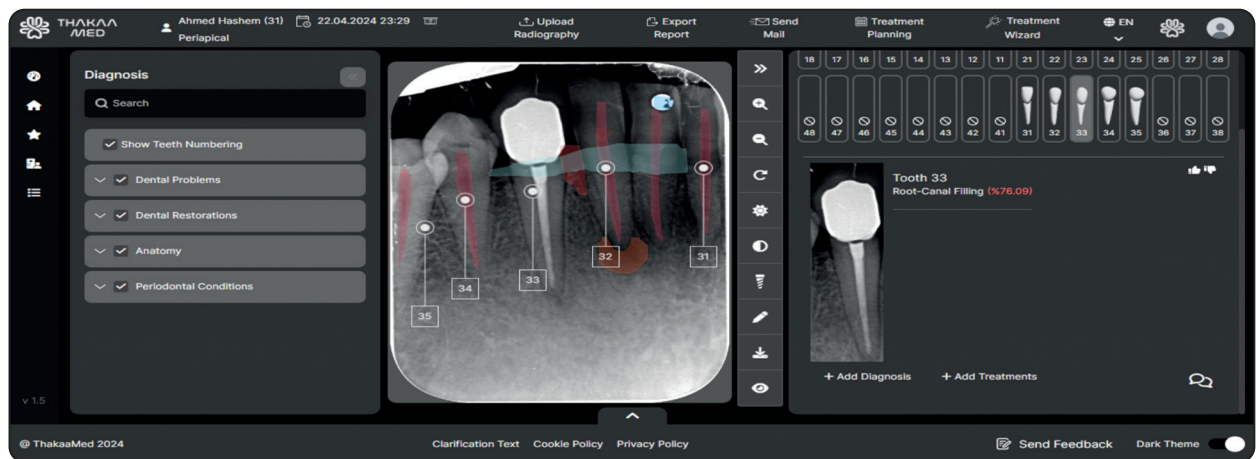


Fig. 2 A

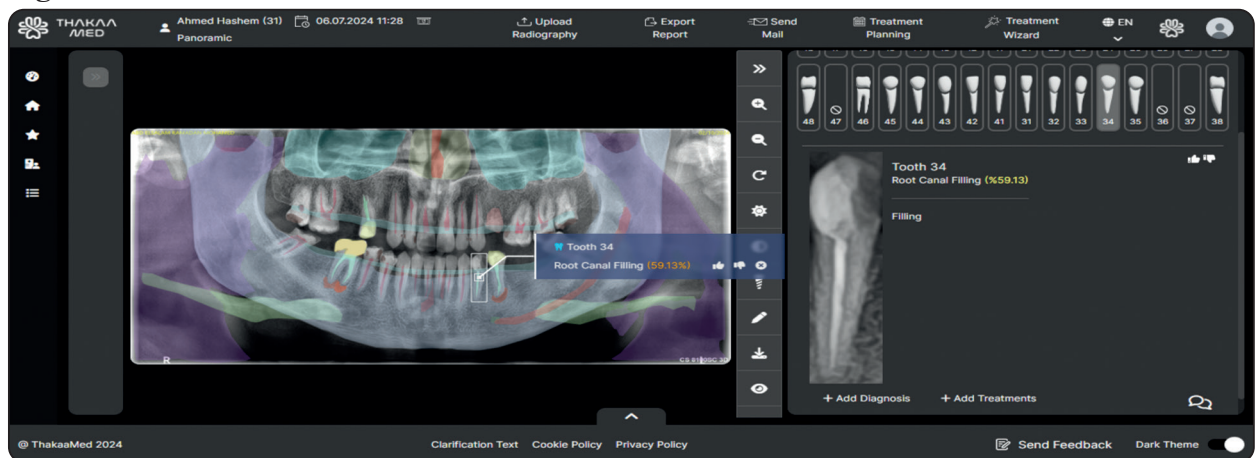


Fig. 2 B

Fig. (2) AI model (Thakaamed Detect) assessment of root canal filling quality on radiographs. A) Periapical radiograph. B) Panoramic radiograph.

Periapical and panoramic radiographs in JPEG format were uploaded to Thakaamed Detect (Thakaamed Detect, KSA), a tool was designed to store and process dental images. For each radiograph, Thakaamed Detect generated a report evaluating root canal filling quality (Fig.2). AI results were then compared to the manual evaluations to determine the differences in the assessment of root canal filling quality.

Statistical analysis

In the study, numerical data were assessed for normality through examination of their distribution and using tests (Kolmogorov-Smirnov and Shapiro-Wilk tests). All data followed normal (parametric) distribution. Results were presented as mean and standard deviation (SD) values. Bonferroni's post-hoc test was used for pair-wise comparisons when ANOVA test is significant. Kappa statistic was used to assess agreement between Endodontist, Radiologist and AI. Kappa values ranging from 0.8 to 1 indicate very good to perfect agreement. The significance level was set at $P \leq 0.05$. All statistical analysis was performed with IBM SPSS Statistics for Windows, Version 23.0. Armonk, NY: IBM Corp.

RESULTS

Quality of root canal filling: (Table 1)

The study found a statistical significant difference between evaluation of root canal filling quality by Endodontist, Radiologist and AI (P -value < 0.001). The highest quality of root canal filling was evaluated by Endodontist. The Radiologist reported statistically significantly lower quality. AI reported the statistically significantly lowest quality of root canal filling.

Agreement between Endodontist, Radiologist and AI: (Table 2)

Whether with panoramic or periapical radiographs, there was perfect agreement ($Kappa = 1$) between Endodontist and Radiologist.

With panoramic radiograph, there was very good agreement ($Kappa = 0.867$) between Endodontist and AI as well as Radiologist and AI.

With periapical radiograph, there was very good agreement ($Kappa = 0.848$) between Endodontist and AI as well as Radiologist and AI.

TABLE (1) Descriptive statistics and results of repeated measures ANOVA test for comparisons between quality of root canal filling (%) evaluated by Endodontist, Radiologist and AI

Endodontist		Radiologist		AI		P-value
Mean	SD	Mean	SD	Mean	SD	
72.8 ^A	16.8	66.5 ^B	17.8	61.6 ^C	17	<0.001*

*: Significant at $P \leq 0.05$, Different superscripts indicate statistically significant differences

TABLE (2) Results of Kappa statistic for agreement between Endodontist, Radiologist and AI:

Evaluator		Kappa statistic
Endodontist and Radiologist		1
Panoramic	Endodontist and AI	0.867
	Radiologist and AI	0.867
Endodontist and Radiologist		1
Periapical	Endodontist and AI	0.848
	Radiologist and AI	0.848

DISCUSSION

The present study analyzed an AI model named (Thakaamed Detect) in assessing root canal filling quality in digital periapical and panoramic radiographs. This is the first study to test the use of AI in evaluating root canal filling quality. AI

is increasingly utilized in radiology to identify problems in images that might otherwise go unnoticed⁽²⁸⁾. Many clinicians and scientists are still unaware of the full potential of AI and its impact on personal and professional lives⁽²⁹⁾.

Root canal treatment quality can vary between dental students, dentists, and endodontists due to different levels of knowledge and experience⁽²⁾. Integrating artificial intelligence (AI) into this process can provide more objective and consistent judgments, effectively reduce man-made errors caused by stress or a lack of expertise⁽⁴⁾. The endodontist and oral and maxillofacial radiology expert who participated in the comparison were qualified specialists, and their results served as the reference standard.

The current standards for assessing root canal filling quality are based on periapical radiographs, which dentists and specialists routinely do and requires lower radiation dosage. However, dentists may interpret radiographs inconsistently, and radiation issues make them unsuitable for screening all of the dentition⁽³⁰⁾. Panoramic radiographs are commonly utilized in dentistry despite their lower resolution, they have the ability to capture a larger area of the oral cavity with fewer radiation doses than full mouth periapical and CBCT imaging. This imaging modality enables a thorough examination of the entire dentition, including the alveolar bone, temporomandibular joints, and surrounding structures, making them an important screening tool^(31,32). we performed a retrospective study to evaluate the variability in assessment of root canal filling quality among endodontists, radiologists, and AI technology in digital periapical and panoramic radiographs.

The number of images used in this study (500 periapical and 500 panoramic) was comparable to those used in previous studies. For instance, **Li CW et al**⁽³³⁾ used 476 periapical radiographs to detect apical lesion using AI and **Gunec et al**⁽³⁴⁾ used

500 panoramic radiographs to evaluate diagnostic accuracy of AI on identifying caries and periapical infection.

In the current study, the highest root canal filling quality was evaluated by the endodontist.

Radiologist reported statistically significantly lower quality while AI reported the statistically significantly lowest root canal filling quality. This can be explained by the endodontist's specialized training and experience which may increase their confidence in root canal filling quality. The radiologist, with a focus on radiographic features and potential concerns that endodontists may not notice, demonstrating their expertise in detecting small radiographic errors and artifacts. AI algorithms, being objective and can identify subtle issues that manual examination may miss.

Endodontist and radiologist offer deep understanding of clinical needs, disease processes, and subtleties of imaging interpretation, they can incorporate new clinical information or research findings into their practice immediately, whereas AI algorithms may lag in incorporating the latest evidence or may require additional training⁽³⁵⁾ Endodontist and radiologists bring years of training and experience that enable them to identify radiographic errors, anatomical variations, and pathological lesions that AI might miss due to its reliance on predefined pattern⁽³⁶⁾.

CONCLUSION

This study has shown significant variability in root canal filling quality assessments among endodontists, radiologists, and AI technology in periapical and panoramic radiographs.

Future research with a larger dataset should focus on refining AI tools and understanding discrepancies to improve clinical outcomes.

Conflicts of interest: no conflicts of interest.

Financial support: None.

REFERENCES

1. Estrela C, Holland R, Estrela CR, Alencar AH, Sousa-Neto MD, Pecora JD. Characterization of Successful Root Canal Treatment. *Braz Dent J* . 2014;25(1):3–11.
2. Pietrzycka K, Radwanski M, Hardan L, Bourgi R, Mancino D, Haikel Y, et al. The Assessment of Quality of the Root Canal Filling and the Number of Visits Needed for Completing Primary Root Canal Treatment by Operators with Different Experience. *Bioengineering*. 2022;9(9):468.
3. Löst C. Quality guidelines for endodontic treatment: Consensus report of the European Society of Endodontology. Vol. 39, *Int EndodJ*. 2006. p. 921–30.
4. Nguyen TT, cLarrivé N, Lee A, Bilaniuk O, Durand R. Use of Artificial Intelligence in Dentistry: Current Clinical Trends and Research Advances. 2021;87(17):1488–2159.
5. Campo L, Aliaga IJ, De Paz JF, Garcia AE, Bajo J, Villarubia G, et al. Retreatment Predictions in Odontology by means of CBR Systems. *Comput Intell Neurosci*. 2016;2016:7485250.
6. Karobari MI, Adil AH, Basheer SN, Murugesan S, Savadamoorthi KS, Mustafa M, et al. Evaluation of the Diagnostic and Prognostic Accuracy of Artificial Intelligence in Endodontic Dentistry: A Comprehensive Review of Literature. Vol. 2023, *Comput Math Methods Med* . Hindawi Limited; 2023.
7. Schwendicke F, Samek W, Krois J. Artificial Intelligence in Dentistry: Chances and Challenges. *J Dent Res*. 2020 Jul 1;99(7):769–74.
8. Sarker IH. AI-Based Modeling: Techniques, Applications and Research Issues Towards Automation, Intelligent and Smart Systems. *SN Comput Sci*. 2022 Mar;3(2).
9. Pierre K, Haneberg AG, Kwak S, Peters KR, Hochegger B, Sananmuang T, et al. Applications of Artificial Intelligence in the Radiology Roundtrip: Process Streamlining, Workflow Optimization, and Beyond. *Semin Roentgenol*. 2023 Apr 1;58(2):158–69.
10. Janiesch C, Zszech P, Heinrich K. Machine learning and deep learning. *Electronic Markets*. 2021 Sep 1;31(3):685–95.
11. Corbella S, Srinivas S, Cabitza F. Applications of deep learning in dentistry. *Oral Surg Oral Med Oral Pathol Oral Radiol*. 2021;132:225–38.
12. Ker J, Wang L, Rao J, Lim T. Deep Learning Applications in Medical Image Analysis. *IEEE Access*. 2017 Dec 28;6:9375–9.
13. Yamashita R, Nishio M, Do RKG, Togashi K. Convolutional neural networks: an overview and application in radiology. Vol. 9, *Insights into Imaging*. Springer Verlag; 2018. p. 611–29.
14. Ngoc VTN, Viet DH, Anh LK, Minh DQ, Nghia LL, Loan HK, et al. Periapical lesion diagnosis support system based on x-ray images using machine learning technique. *World Journal of Dentistry*. 2021;12(3):189–93.
15. Schwendicke F, Samek W, Krois J. Artificial Intelligence in Dentistry: Chances and Challenges. *J Dent Res*. 2020 Jul 1;99(7):769–74.
16. Musri N, Christie B, Ichwan SJA, Cahyanto A. Deep learning convolutional neural network algorithms for the early detection and diagnosis of dental caries on periapical radiographs: A systematic review. *Imaging Sci Dent*. 2021;51:1–6.
17. Lee JH, Kim DH, Jeong SN, Choi SH. Diagnosis and prediction of periodontally compromised teeth using a deep learning-based convolutional neural network algorithm. *J Periodontal Implant Sci*. 2018 Apr 1;48(2):114–23.
18. Orhan K, Bayrakdar IS, Ezhov M, Kravtsov A, Özyürek T. Evaluation of artificial intelligence for detecting periapical pathosis on cone-beam computed tomography scans. *Int Endod J*. 2020 May 1;53(5):680–9.
19. Bhat S, Birajdar GK, Patil MD. A comprehensive survey of deep learning algorithms and applications in dental radiograph analysis. Vol. 4, *Healthcare Analytics*. Elsevier Inc.; 2023. p. 100282.
20. Center for Devices and Radiological Health. Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices. U.S. Food and Drug Administration.
21. Altukroni A, Alsaeedi A, Gonzalez-Losada C, Lee JH, Alabudh M, Mirah M, et al. Detection of the pathological exposure of pulp using an artificial intelligence tool: a multicentric study over periapical radiographs. *BMC Oral Health*. 2023 Dec 1;23(1):553.
22. De Angelis F, Pranno N, Franchina A, Di Carlo S, Brauner E, Ferri A, et al. Artificial Intelligence: A New Diagnostic Software in Dentistry: A Preliminary Performance Diagnostic Study. *Int J Environ Res Public Health*. 2022 Feb 1;19(3):1728.
23. Zhu J, Chen Z, Zhao J, Yu Y, Li X, Shi K, et al. Artificial intelligence in the diagnosis of dental diseases on panoramic radiographs: a preliminary study. *BMC Oral Health*. 2023 Dec 1;23(1):358.

24. Hiraiwa T, Ariji Y, Fukuda M, Kise Y, Nakata K, Katsumata A, et al. A deep-learning artificial intelligence system for assessment of root morphology of the mandibular first molar on panoramic radiography. *Dentomaxillofacial Radiology*. 2019;48(3):20180218.
25. Issa J, Jaber M, Rifai I, Mozdziaik P, Kempisty B, Dyszkiewicz-Konwińska M. Diagnostic Test Accuracy of Artificial Intelligence in Detecting Periapical Periodontitis on Two-Dimensional Radiographs: A Retrospective Study and Literature Review. *Medicina (Lithuania)*. 2023 Apr 1;59(4):768.
26. Löst C. Quality guidelines for endodontic treatment: Consensus report of the European Society of Endodontology. Vol. 39, *Int Endod J*. 2006. p. 921–30.
27. Balto H, Al Khalifah S, Al Mugairin S, Al Deeb M, Al-Madi E. Technical quality of root fillings performed by undergraduate students in Saudi Arabia. *Int Endod J*. 2010 Apr;43(4):292–300.
28. Kim JE, Nam NE, Shim JS, Jung YH, Cho BH, Hwang JJ. Transfer learning via deep neural networks for implant fixture system classification using periapical radiographs. *J Clin Med*. 2020 Apr 1;9(4):1117.
29. Sur J, Bose S, Khan F, Dewangan D, Sawriya E, Roul A. Knowledge, attitudes, and perceptions regarding the future of artificial intelligence in oral radiology in India: A survey. *Imaging Sci Dent*. 2020 Sep 1;50(3):193–8.
30. Li CW, Lin SY, Chou HS, Chen TY, Chen YA, Liu SY, et al. Detection of dental apical lesions using cnns on periapical radiograph. *Sensors*. 2021 Nov 1;21(21):7049.
31. Du X, Chen Y, Zhao J, Xi Y. A Convolutional Neural Network Based Auto-Positioning Method for Dental Arch in Rotational Panoramic Radiography. In *Proceedings of the 2018 40th Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, Honolulu, HI, USA, 18–21 July 2018; IEEE: Piscataway, NJ, USA, 2018. :2615–8.
32. Ba-Hattab R, Barhom N, Osman SAA, Naceur I, Odeh A, Asad A, et al. Detection of Periapical Lesions on Panoramic Radiographs Using Deep Learning. *Applied Sciences (Switzerland)*. 2023 Feb 1;13(3):1516.
33. Li CW, Lin SY, Chou HS, Chen TY, Chen YA, Liu SY. Detection of dental apical lesions using cnns on periapical radiograph . *Sensors*. 2021;21(21):7049.
34. Güneç HG, Ürkmez EŞ, Danacı A, Dilmaç E, Onay HH, Aydın KC. Comparison of artificial intelligence vs. junior dentists' diagnostic performance based on caries and periapical infection detection on panoramic images. *Quant Imaging Med Surg*. 2023 Nov 1;13(11):7494–503.
35. Makeeva V. An Essential Roadmap for AI in Radiology. [(accessed on 20 May 2023)];*Am. Coll. Radiol*. 2022 .
36. Mun SK, Wong KH, Lo SCB, Li Y, Bayarsaikhan S. Artificial Intelligence for the Future Radiology Diagnostic Service. Vol. 7, *Front. Mol. Biosci*. Frontiers Media S.A.; 2021. p. 614258.