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Research Paper

Evaluation of Apoptosis Evidence in Oral Mucosa of Patients Underwent CT Scan

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ABSTRACT

Background and Aim: Computed tomography (CT) scanning is a widely used diagnostic technique in medical imaging, particularly in the head and neck region. Although it provides high-resolution images, concerns remain about ionizing radiation's potential cytotoxic and genotoxic effects.

Materials and Methods: This study aimed to assess the impact of CT scan radiation on the epithelial cells of the oral mucosa, including the buccal, gingival, and lingual regions. Cytological samples were collected before and after CT scan exposure using a cytobrush, and cellular damage was analyzed using the Papanicolaou (Pap) staining method. A pathologist assessed the slides for each cellular parameter, recording abnormalities per 1000 cells.

Results: The results revealed a significant increase in nuclear abnormalities such as micronuclei, pyknosis, nuclear budding, and binucleated cells, especially in the gingival mucosa. Statistical analysis indicated significant differences between pre-exposure and post-exposure samples ($P<0.05$).

Conclusion: This study underscores the cytotoxic and genotoxic risks associated with CT scans and highlights the need for careful consideration of radiation exposure, particularly in the head and neck region.

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Introduction

Computed tomography (CT) scanning is an essential imaging technique for diagnosing various conditions, especially in the head and neck region. It utilizes ionizing radiation to create high-resolution images of internal structures, providing a non-invasive diagnostic tool. However, ionizing radiation raises significant concerns regarding its potential to cause cellular damage, including DNA mutations, chromosomal aberrations, and apoptosis.

The risk of radiation exposure during a CT scan is higher than that of a standard x-ray, and the estimated future risk of developing malignant cancers due to CT scans is approximately 1 in 2000 [1]. This risk increases with the number of CT scans a person undergoes. It may be higher for children, as they are more sensitive to radiation and have more years to develop related conditions potentially [2]. However, the benefits of CT scans often outweigh their small potential risks, mainly when the scan is essential for diagnosis or treatment evaluation.

Apoptosis and its role in cellular health

Apoptosis is a fundamental pattern of cell death in living tissues that is physiologically regulated. It plays a significant role in cell death processes, such as during embryogenesis and normal cell cycles. The induction of apoptosis by ionizing radiation can act as a survival mechanism by eliminating genetically damaged cells [3]. However, with increased levels of genotoxic-induced apoptosis, cellular damage occurs, leading to pathological effects. Radiation-induced damage can result in programmed cell death (apoptosis), genetic instability, and oncogenic mutations [4, 5].

Cellular criteria to assess physiological and pathological apoptosis include micronuclei, pyknosis, karyorrhexis, and karyolysis [6, 7, 8]. Given the increasing use of CT scans in the oral region and considering their potential risks, the present study aimed to evaluate evidence of apoptosis in the oral cavity mucosa of patients undergoing CT scans.

Despite the growing body of research on radiation-induced damage in various tissues, there is a lack of comprehensive studies addressing the cytotoxic and genotoxic effects of CT scans on the oral mucosa. Given that the oral cavity is frequently exposed to radiation during diagnostic imaging, it is crucial to investigate the effects of CT scans on epithelial cells in this region.

This study evaluated CT scan radiation's cytotoxic and genotoxic effects on epithelial cells from the buccal, gingival, and lingual mucosa. Cytological samples were collected before and after CT exposure using a cytobrush, and the samples were stained using the Papanicolaou (Pap) method to identify nuclear abnormalities. A pathologist assessed the slides for each cellular parameter, documenting abnormalities per 1000 cells. The study hypothesized that radiation exposure would lead to significant cytotoxic and genotoxic damage in oral epithelial cells.

Materials and Methods

Patient selection and sample collection

Patients were randomly selected during the summer of 2023 in Isfahan City, Iran, using convenience sampling from those scheduled to undergo CT scans as part of their routine medical care. Only adult patients over the age of 20 were included in the study. Patients with a history of prior radiotherapy, oral cancers, or other conditions that could interfere with the study were excluded. The exclusion criteria were smoking and tobacco use, specific genetic disorders, previous exposure to radiation within the last 30 days, long-term use of antibiotics or chemotherapy drugs, uninterested and non-voluntary patients, trauma patients, and patients with severe dry mouth. In total, 30 patients were enrolled in the study after they provided informed consent.

Epithelial cells were collected from three regions of the oral mucosa: Buccal, gingival, and lingual. These areas were chosen due to their relevance to head and neck CT imaging. The cells were harvested using a cytobrush, a non-invasive method for collecting many epithelial cells. The samples were transferred onto microscope slides, fixed, and stained using the Pap method, which is commonly used for highlighting cellular morphological changes (Figures 1, 2, 3, and 4).

CT scan imaging and exposure parameters

CT scans were performed using the Philips Optimus 16-slice CT scanner. The following exposure parameters were used for all participants:

Voltage (kVp): 120 kVp

Current (mAs): 90 mAs

Field of view (FOV): 20 cm^2

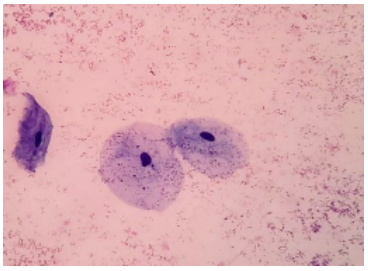

Figure 1. Nuclear bud

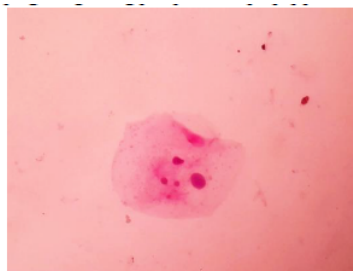

Figure 2. Micronucleus

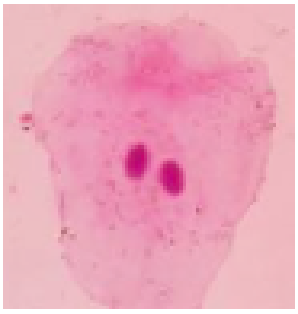

Figure 3. Binucleated cell

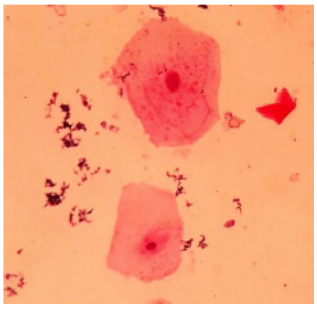

Figure 4. Pyknosis

The radiation dose administered during each CT scan was approximately 170 mGy, a standard dose for head and neck imaging in clinical settings. These parameters were chosen to ensure a consistent and reproducible exposure level across all participants.

Radiation exposure protocol

Each patient underwent a routine CT scan, and cytobrush samples were collected before and after the exposure. This design allowed for comparing cellular abnormalities caused by radiation between pre- and post-exposure samples. The goal was to determine the extent of cytotoxic and genotoxic effects, focusing on nuclear

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abnormalities such as micronuclei, pyknosis, nuclear budding, and binucleated cells.

Slide assessment and cellular parameters

The slides were evaluated by an experienced pathologist blinded to the pre-exposure and post-exposure status of the samples. Cellular abnormalities were assessed per 1000 cells on each slide for all three regions (buccal, gingival, and lingual). The pathologist recorded the following parameters:

Micronuclei: Small, extranuclear bodies formed by chromosome fragmentation or loss during mitosis, indicating genotoxicity,

Pyknosis: The condensation of chromatin in the nucleus, a key early marker of apoptosis (it is essential to note that apoptosis is a continuous process, and pyknosis represents an early indicator within a spectrum of events rather than a discrete stage),

Nuclear budding: The formation of protrusions in the nuclear membrane indicating chromosomal instability,

Binucleated cells: Cells containing two nuclei suggest failed mitosis or cell division abnormalities.

Statistical analysis

Statistical analysis was performed using the McNemar test, the Wilcoxon signed-rank test, and the Kruskal-Wallis test to determine significant differences in the frequency of nuclear abnormalities between pre-exposure and post-exposure samples. The statistical significance level was set at $P<0.05$. All analyses were conducted using SPSS software, version 27 (IBM Corp., Armonk, NY).

Results

The cytological examination of oral mucosal samples before and after CT scan exposure revealed a significant increase in nuclear abnormalities, particularly in the gingival mucosa. The following cellular changes were noted:

Micronuclei: The presence of micronuclei increased significantly in all regions after exposure, with the gingival mucosa showing the highest frequency.

Pyknosis: Pyknosis, a condensation of chromatin in the nucleus, was identified as a primary marker of apoptosis. It was significantly higher in post-exposure samples across all mucosal regions. As apoptosis is a continuum of cellular events, pyknosis should be understood as part of the apoptotic process, reflecting an early stage within a spectrum of events.

Nuclear budding: This abnormality, indicative of chromosomal instability, was observed at a significantly higher frequency in oral mucosa.

Binucleated cells: Cells with two distinct nuclei, indicating abnormal mitosis, were observed more frequently after radiation exposure.

The statistical analysis revealed significant differences in the frequency of these nuclear abnormalities between pre-exposure and post-exposure samples ($P<0.05$), indicating that CT scan radiation-induced cytotoxic and genotoxic effects in oral mucosal cells.

Comparison of pathological findings in buccal mucosa using PAP staining

The McNemar test showed no significant difference in the presence of neutrophils in the buccal mucosa before and after radiation exposure ($P=0.250$). According to the Wilcoxon test results, using PAP staining in the buccal mucosa:

Micronucleated cells significantly increased after radiation exposure ($P=0.002$).

The total number of micronuclei significantly increased ($P=0.041$).

The number of nuclear buds significantly increased ($P=0.003$).

The number of binucleated cells also significantly increased after exposure ($P=0.031$).

The number of pyknotic cells significantly increased ($P<0.001$) (Figure 5).

Comparing pathological findings in gingival mucosa using PAP staining

The McNemar test showed no significant difference in the presence of neutrophils in the gingival mucosa before and after radiation exposure ($P=1.00$). According to the Wilcoxon test results, using PAP staining in the gingival mucosa:

Micronucleated cells significantly increased after radiation exposure ($P<0.001$).

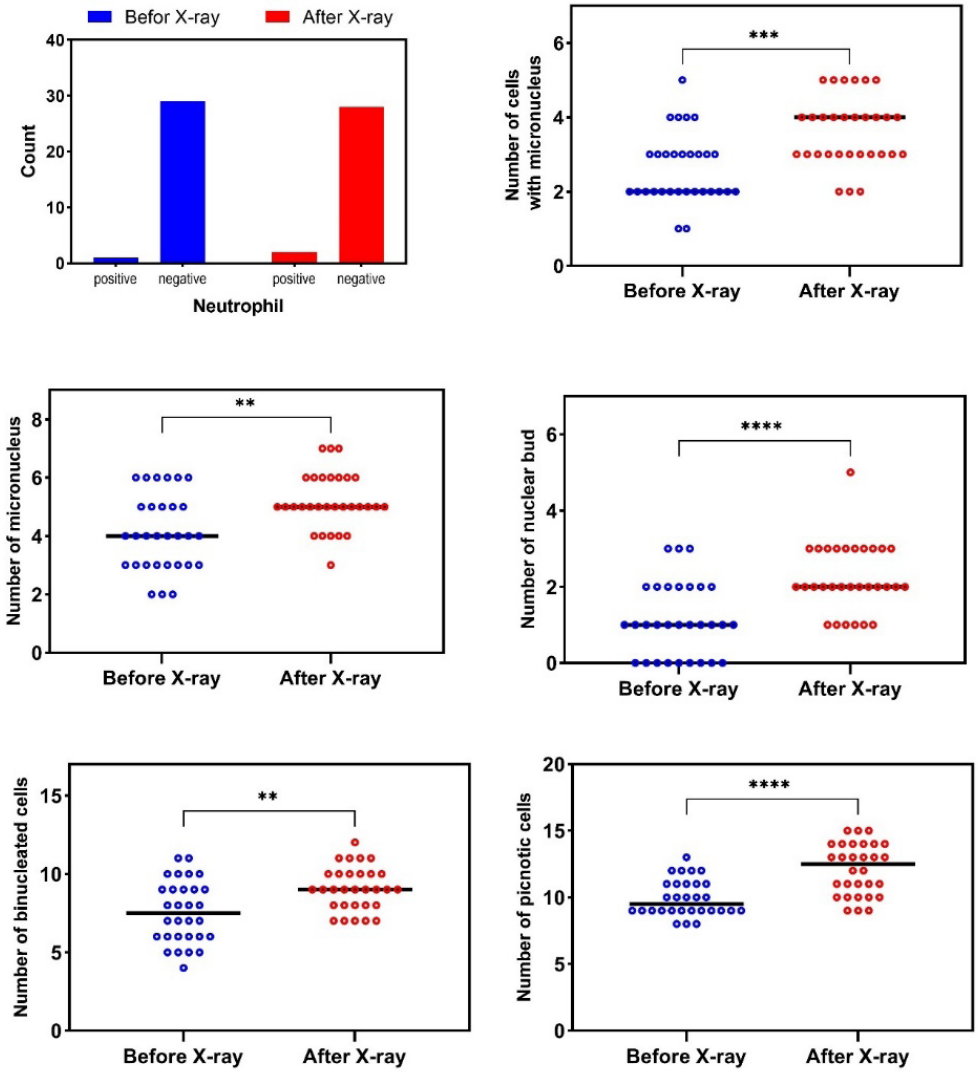

Figure 5. Comparison of cytopathological findings in buccal mucosa before and after CT exposure

The total number of micronuclei significantly increased (P=0.002).

The number of nuclear buds significantly increased (P<0.001).

The number of binucleated cells significantly increased after exposure (P=0.002).

The number of pyknotic cells significantly increased (P<0.001) (Figure 6).

Comparing pathological findings in tongue mucosa using PAP staining

The McNemar test showed no significant difference in the presence of neutrophils in the tongue mucosa before and after radiation exposure (P=0.500). According to the Wilcoxon test results, using PAP staining in the tongue mucosa:

Micronucleated cells significantly increased after radiation exposure (P<0.001).

The total number of micronuclei significantly increased (P<0.001).

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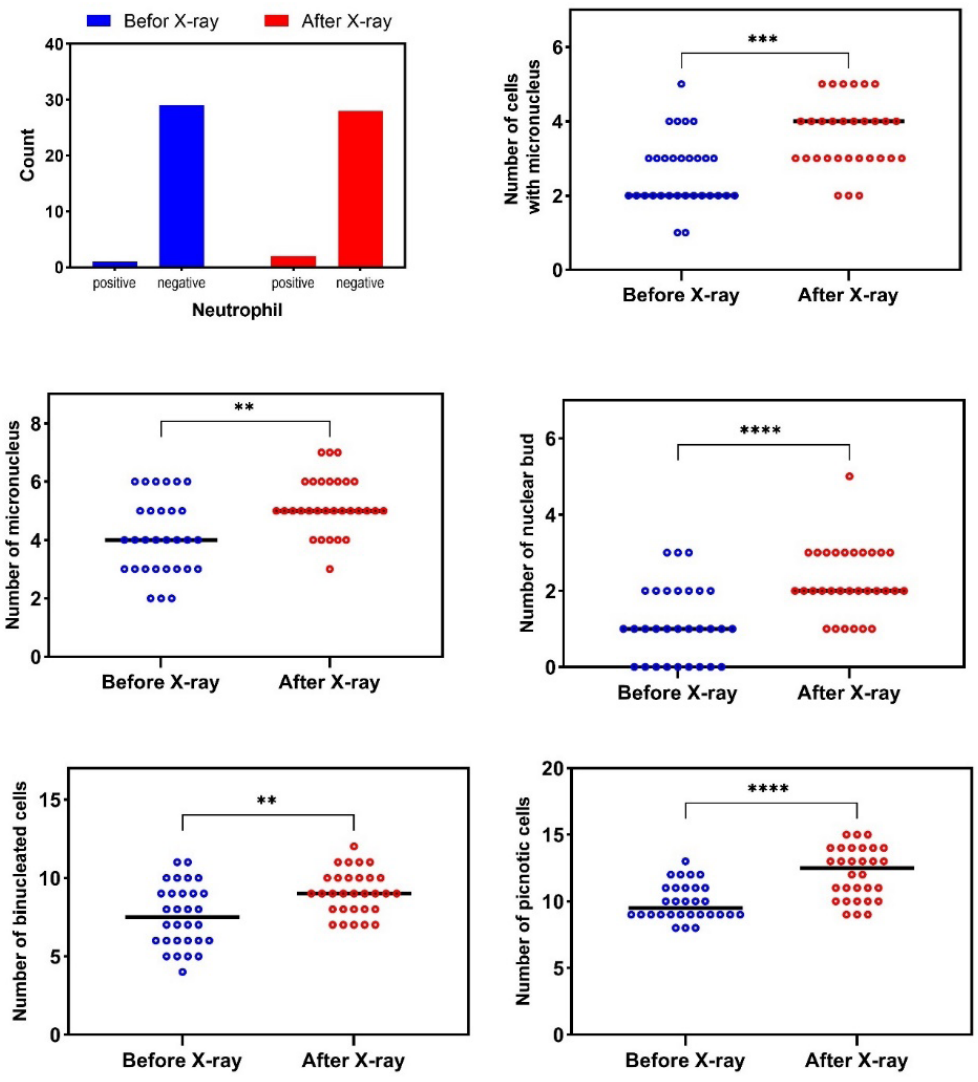

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Figure 6. Comparison of cytopathological changes in gingival mucosa before and after CT scan exposure

The number of nuclear buds significantly increased (P<0.001).

The number of binucleated cells significantly increased after exposure (P<0.001).

The number of pyknotic cells showed a significant increase (P=0.003) (Figure 7).

Discussion

CT scan imaging is one of the advanced conventional medical imaging techniques used in the head and neck region to diagnose and evaluate diseases. This method utilizes x-ray technology to create cross-sectional images of the body, allowing physicians to observe and analyze internal body structures with high precision. CT scans are widely used in diagnosing and managing conditions such as tumors, traumatic injuries, infections, cardiovascular diseases, and musculoskeletal problems [9]. Despite the numerous benefits of CT scans in diagnosis and treatment planning, low x-rays can potentially induce cytotoxic and genotoxic effects. Furthermore, CT scans deliver significantly higher radiation doses compared to newer radiological devices like cone beam C T (CBCT), yet their use in the head and neck region is often unavoidable.

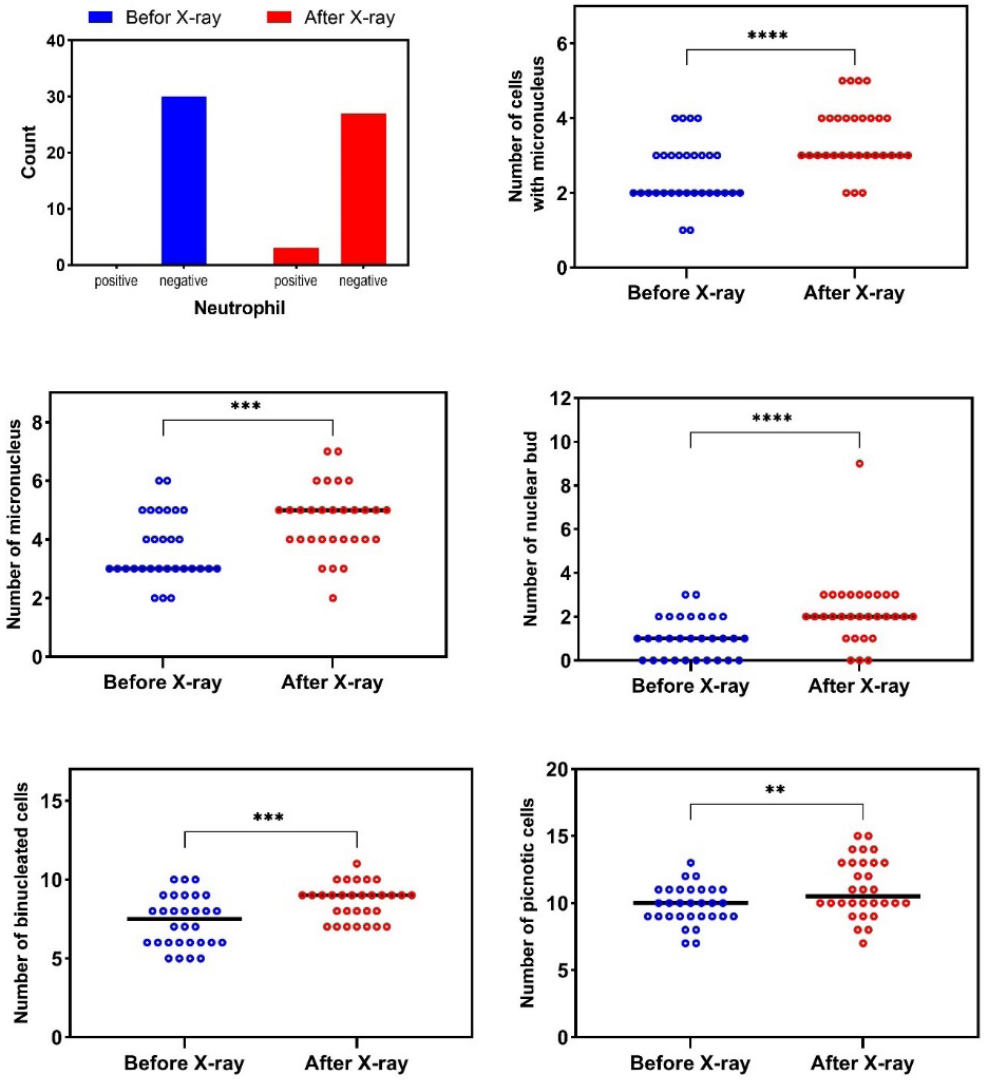

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Figure 7. Comparison of cytopathological findings in tongue mucosa before and after CT scan exposure

X-rays are an ionizing radiation capable of penetrating body tissues and impacting the cells and molecules within. X-rays can ionize water molecules and generate free radicals when they reach body cells. These free radicals can damage DNA and other essential cellular molecules. DNA damage can lead to genetic mutations, cell death (apoptosis) and other cellular alterations, potentially resulting in cancer or other diseases [10].

Given this background, the current study aimed to assess the cytotoxic effects on the oral mucosa in different oral cavity regions before and after a CT scan. The cytological analysis revealed significant cellular changes in the oral mucosa of various regions following exposure to x-rays.

In this study, cytopathological evaluations of the buccal mucosa, gingiva, and tongue showed significant differences in cellular damage before and after radiation exposure. However, no significant differences were observed in the severity of acute inflammation (neutrophils) in the samples, suggesting that the observed cellular damage was not related to inflammation but was directly caused by radiation exposure. If inflammation had been a factor, it might have led to false evidence of dysplasia in the epithelium. Thus, if the dysplastic changes observed were

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related to inflammation, varying levels of inflammation would have been expected in the samples.

Previous studies have examined the cytotoxic effects of CT scan radiation on the oral mucosa [11, 12]. For example, Jahanshahiafshar et al. [11] demonstrated a significant increase in cellular damage in the buccal mucosa of patients after CT scans, consistent with the present study's findings. However, unlike the study by Jahanshahiafshar et al. the current research did not compare results between genders due to certain limitations [11]. Similarly, Altouki et al. [12] found significant differences in cellular damage indicators immediately after radiation exposure, on the tenth day, and one month later. Despite differences in staining techniques (Al-Touki used the fast green method), their findings were similar to the current study, concluding that the cellular damage caused by CT scan radiation was transient [12].

Palla et al. [13] observed that changes remained significant on the 20th day post-radiation, similar to the tenth day. Unlike the current study, their findings showed substantial differences in the number of micronuclei and not in pyknosis or karyolysis, which might be attributed to racial or geographical differences. The current study only evaluated a 10-day period.

Other studies indicate that CT imaging delivers considerable radiation doses to the eyes, forehead, and thyroid. The observed increase in chromosomal abnormalities and micronuclei in lymphocytes suggests that even low-dose radiation effects require protective monitoring measures to enhance patient safety Kanagaraj et al. [14]. Although the non-invasive and precise nature of buccal and gingival mucosa sampling has recently gained attention for evaluating cytotoxicity [15], few studies have focused on apoptosis evidence in the oral cavity following CT scans, with most concentrating on CBCT.

While CBCT devices deliver lower doses than CT scans, their ionizing nature still poses a cytotoxic potential. For instance, Ayres et al. [16] found no evidence of genotoxicity despite increased micronuclei frequency following CBCT exposure. However, cytotoxic effects were observed in the CBCT (I-CAT) system. Similarly, Carlin et al. [17] noted no significant differences in the frequency of micronuclei before and after CBCT exposure but confirmed its cytotoxic potential. Yang et al et al. [18] reported no mutagenic effects on buccal mucosa cells from radiation but highlighted distinct micronuclei changes in CBCT recipients compared to radiography groups [18]. Other studies, such as Da Fonte et al. [19], reported significant differences in micronuclei frequency in full and partial jaw exposures with CBCT. However, Yang et al. [18] observed only cytotoxic changes and not micronuclei alterations, differing from the current study's findings. Yang's study concluded that CBCT caused tissue cytotoxicity without chromosomal damage in buccal, lingual, or gingival cells.

Micronuclei assays are widely used to assess genetic and cellular toxicity across various species. Notably, in the gingiva, the number of micronuclei per cell and the total number per 1000 cells significantly differed before and after radiation, indicating a potentially higher risk in this region than in other oral areas. Micronuclei are the first biological evidence of high-risk cellular changes caused by DNA damage. Therefore, given the results of this study and the routine use of CT and magnetic resonance imaging (MRI) for periodic examinations, applying the ALARA (as low as reasonably achievable) principle and considering CBCT as a follow-up alternative due to its lower dose is recommended.

Based on prior research, some studies have examined radiation field sizes (FOV), device voltage, and dose levels both in vitro and in vivo [20-22]. However, many studies lack precise records of radiation parameters. This study conducted the CT scan using 120 kVp, 90 mAs, and a 20 cm² FOV, with an absorbed dose of approximately 170 mGy. Some researchers have studied radiotherapy effects and x-ray exposures conducted 5-6 times per week over 5-7 weeks [23, 24]. Differences in CT scan parameters, such as device voltage, milliampere, exposure duration, irradiation field size, device types, individual characteristics, and apoptosis evidence assessment methods, could influence reported results.

Other studies have evaluated occupational exposures to low-dose x-rays [25, 26]. Additionally, alcohol and tobacco use and prolonged mouthwash use have been linked to increased genotoxicity [26-28]. Previous research has shown genotoxicity [29] and apoptosis following radiographic exposures [30]. Ultimately, given the significant increase in CT scan applications in the head and neck region, particularly in rhinoplasty and sinonasal surgeries, revisiting CT scans in maxillofacial areas is essential. Protective measures such as lead aprons and thyroid collars are strongly recommended.

One of the limitations of the current study is the lack of molecular methods to assess the extent of cell damage accurately. Additionally, the sample size was limited due to the requirement for patient consent for future referrals and their willingness to participate in the research. Furthermore, limitations were noted regarding

the inherent characteristics of the CT scan machine and its fixed parameters.

Conclusion

This study demonstrates that CT scan radiation induces significant genotoxic and cytotoxic effects in the epithelial cells of the oral mucosa, particularly in the gingival region. The presence of micronuclei, pyknosis, nuclear budding, and binucleated cells is clear evidence of radiation's genotoxic and cytotoxic impact on oral epithelial cells. Given the increasing use of CT scans in head and neck imaging, it is crucial to implement strategies to minimize radiation exposure, such as following the ALARA principle and considering alternative imaging methods like CBCT when appropriate.

Study recommendations

Long-term studies: Future studies should consider long-term follow-up to assess the potential delayed effects of radiation on oral mucosal cells.

Use of additional staining techniques: Incorporating techniques like immunohistochemistry and fluorescence in situ hybridization could provide deeper insights into the DNA damage and repair mechanisms triggered by radiation.

Minimizing radiation exposure: Clinicians should adhere to the ALARA principle when performing CT scans and consider lower-radiation alternatives when feasible.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Khorasgan Branch, Islamic Azad University, Isfahan, Iran (Code: IR.IAU.KHUISF.REC.1402.295). All participants were informed about the study objectives and procedures, and written informed consent was obtained from each participant prior to sample collection

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Authors' contributions

All authors contributed equally to the conception and design of the study, data collection and analysis, interpretation of the results, and drafting of the manuscript. Each author approved the final version of the manuscript for submission.

Conflict of interest

The authors declared no conflict of interest.

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