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REVIEW ARTICLE

How radio and chemotherapy can affect the development of the teeth

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Abstract:

Introduction: The evolution of chemo and radiotherapy, added to the increased frequency in its use, have led to an increase in the survival rate of pediatric patients with head and neck cancer. Thus, the effects of this therapy are increasingly common, and may affect even the teeth in formation. **Objective:** Conduct a literature review on the main dental anomalies of development in patients undergoing chemo and radiotherapy. Material and methods: The databases "Pubmed", "Google Scholar" and "Science Direct" were consulted using the keywords "dental alterations", "children", "dentistry", "cancer", "chemotherapy" and " radiotherapy". Twenty-seven articles published in English were selected. **Results:** Based on the articles included in the study, the effects of chemoradiotherapy on developing teeth can be both quantitative and qualitative. Those patients who underwent treatment during childhood, in this literature review, were between 0.8 and 15 years old. The main dental anomalies found include microdontia, hypodontia and root anomalies. In addition, it was also observed that the late effects of the therapy vary according to the radiation dose and the chemotherapy dose. **Conclusions:** Although there are few studies on dental alterations caused by chemotherapy and radiotherapy, it is necessary to implement protocols aimed at oral care during and after treatment to reduce the incidence and severity of such complications.

Keywords: "dental alterations", "children", "dentistry", "cancer", "chemotherapy" and "radiotherapy".

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INTRODUCTION

With the evolution of antineoplastic treatment, including radio and chemotherapy, there was an increase in the survival rate of pediatric patients with head and neck cancer, mainly due to the intensification of this treatment. However, as a consequence, the late effects of this therapy have become increasingly frequent. These disorders may affect several locations of the craniofacial region, among them, the oral cavity, including teeth, in which these changes are irreversible. During dental development, the teeth are susceptible to several changes. Several dental anomalies resulting from radio and chemotherapy treatment have been reported in the literature, including taurodontia, hypodontia, enamel hypoplasia and radicular hypoplasia. In this sense, it is known that the more intense the antineoplastic treatment, the greater the presence of anomalies present in the oral cavity of these patients[1,2,3].

The objective of this study was to carry out a literature review about the main dental anomalies in pediatric patients undergoing radio and chemotherapy, highlighting the importance of the dentist in monitoring and supporting these individuals.

MATERIAL AND METHODS

To carry out this work, bibliographic searches were carried out in Pubmed, Google Scholar and Science Direct databases, using the keywords "dental alterations", "children", "dentistry", "cancer", "chemotherapy" and "radiotherapy". The survey of bibliographic productions took place from February to April 2021. The selected articles should be in English and available in full for reading. During the search, all duplicate production and studies that did not relevantly address the objective of this work were excluded. Of all the articles found, 24 works published between the years 1999 and 2020 were selected. In addition, 3 more articles were chosen outside this period, due to their scientific relevance.

RESULTS

INCA (National Institution of Cancer), in 2009, reported the presence of more than 9000 cancer cases per year in pediatric patients. Although the incidence of head and neck neoplasias in children is not extensive as in other anatomical locations, their treatment and prognosis are specific. The treatment is capable of providing a cure for most patients, but it can result in the development of side effects in about two-thirds of them. Children are still in the development stage, so they are more prone to have problems related to organs and systems. The chances of pediatric patients that were exposed for a long period to the radiotherapeutic treatment of head and neck to develop moderate to serious damages in soft tissues and bones, go from 77% to 100%. The severity of the damage is related to age, dose, and place that the therapy was developed[2,4,5,6].

While the immediate effects on soft tissues are more studied and reported in the literature, the effects on dental tissues are less documented and observed in the clinic. Those abnormalities are developed by doses of radiation from the treatment, and it was already reported that chemotherapy induces qualitative and quantitative modifications in dental tissues. According to the literature, it has already been notified that antineoplastic agents can inhibit both odontogenesis and dentary growth.[7]

It is known that dental development is more susceptive to radiation therapy during the morph differentiation and calcification stage, which can result in hypodontia. In a more advanced stage of dental development, radiation therapy can result in microdontia, enamel hypoplasia, and incomplete calcification[3,8,9].

Sequels occasioned by chemotherapy and radiation in dentition are irreversible, being the main dental anomalies related to the post-treatment: microdontia, hypodontia, root defects, taurodontism, root dilacerations, and supernumerary teeth.

In this literature review, children diagnosed with head and neck cancer were between 0.8 and 15 years, however, it is worth mentioning that most changes, such as number and shape, occur during childhood, at the time of teeth development.

Long duration treatments and the ones made with increased doses can occasion more dental anomalies, and consequently, more severe cases. The prevalence of dental anomalies is variable, probably because there are many kinds of protocols inside chemotherapy. The main drugs that cause impacts in odontogenesis are vincristine, cisplatin, doxorubicin, and cyclophosphamide. Systemic or localized disturbs in ameloblasts and odontoblasts during their formation and eruption can result in abnormalities in the tissues born from these cells. Most of the medications used lead to disturbs for their cytostatic and cytotoxic effects. As an example of it, vincristine presents a negative effect in pre-odontoblasts and odontoblasts, leading to problems in the formation of dentine[11,12,13,14,15].

Ionizing radiation is capable of causing changes in dental morphology, directly and indirectly. The reasons for the structural damages are controversial, but it is believed that the rupture of the pulp collagen and the odontoblasts process degeneration may be a possible explanation for it since they can lead to dental weakness. It is believed that the support tissues are hitten in the same way as other tissues in the oral cavity. When the periodontium is irradiated, it can result in a reduction of vascularization, hypocellularity, and more production of collagen, causing fibrosis. While the cement can become acellular and with low Sharpey's fibers regeneration capacity, leading to periodontal disease, and even osteoradionecrosis in those cases.[16]

The radiosensitivity in development teeth has already been observed in animals, where mature ameloblasts are permanently damaged by 10Gy. Damage occurs also in the bone region, periodontal ligament, and pulp. The severity of the teeth anomalies varies with the age that the child received the diagnosis, dental development stage, and radiation dose. The most common anomalies presented in radiotherapy are the destruction of the dental germ, disturbs in root formation, and incomplete calcification. Chemo and radiotherapy together can lead to problems in dental formation, like microdontia, enlarger pulp chamber, and root disturbs.[15]

Radiotherapy can also result in negative effects on dental structure, such as changes in enamel crystalline structure, enamel hardness, and dentin-enamel junction. The radiation in deciduous teeth affected longitudinally the microhardness of the enamel and dentine as the dose of radiation grew, depending on the region that was hitten. There was a change in the enamel and dentine structure, resulting in an amorphous appearance of the surface, making it difficult to visualize the prismatic structure of the enamel and the dentinal tubules in the dentine.[6]

MARANGONI-LOPES et. al described the reduction of the hardness of the enamel surface after a 2160cGy dose of radiation, which was less than the values observed after a 1080 and 3060cGy dose. The hardness of the dentine surface reducted after a 1080cGy, and even more after a 2160cGy dose. And after a 3060cGy dose intermediary values were observed. About the composition of dentine and enamel, there was a significant decrease of phosphate v2, carbonate, amide, and hydrocarbon after 3060cGy. In dentine, phosphate v2, amide, and hydrocarbon significantly decreased after a 1080cGy and a 2160cGy dose. Significant and progressive changes in morphology were observed in both enamel and dentine. Enamel presented crackles in its surface after 2160cGy. And dentine after a 1080cGy, degradation of the peritubular structure was observed, resulting in a progressive obliteration of the dentinal tubules during the experiment.[17]

Radiotherapy and chemotherapy can decrease the proliferation of cells during odontogenesis and/or rhizogenesis. Depending on the dental development stage of the patient, size, shape, number, or structural alterations can occur. Any disturbance during the dental morph differentiation period can result in microdontia. An interruption in odontogenic proliferation or some impediment on his beginning can lead to hypodontia. Root anomalies were the most present anomaly in patients that survived cancer, probably because of the high sensitivity of the Hertwig root sheath proliferative cells, that were affected by radio and chemotherapy. Shortened roots can result from premature apexification, which culminates in prejudice of mitosis in that area. Dental impaction can be caused by a complication in the action of odontoblasts in reason of radiation and chemotherapy through the dental follicular cells, which results in cellular disorganization. A patient treated with head and neck, both chemo and radiotherapy, is more susceptible to developing a huge number of dental anomalies than patients that only received one of these treatments.[4,18]

Many antineoplasic treatments need an integrated therapy with chemo and radiotherapy, which makes it difficult to know the etiology of the dental abnormality.4 Salivary glands can also be affected during antineoplasic treatment with the decrease of saliva and the changes in saliva composition. The dysfunction of the gland is going to depend on the dose and volume of glandular tissue irradiated. The duration of hyposalivation affects directly each patient, and his recovery can occur in months, or the gland can be permanently compromised. Saliva has it's potential decreased, which is important to contain the advance of dental demineralization. So, studies reported that the salivary flow leads to a weak oral heath, once it increases the cariogenic bacterias, which can culminate in excessive caries lesions and pH alterations, increasing in the evolution of this oral disease.[2,19]

The teeth of patients who are undergoing cancer treatments are more susceptible to erosion due to the action of radiation and also to the reduction in the amount of saliva. The effect of radiation on dental elements depends on the organic composition of enamel and dentin. Deciduous teeth are more susceptible than permanent teeth to suffer from caries lesions. This occurs by the different characteristics between them, such as smaller thickness[17].

The dental organ is in a constant process of demineralization and remineralization. When more demineralization occurs, it can generate tooth cavitation. Remineralization occurs mainly in the face of two substrates: calcium and phosphate, both present in saliva. It is known that some chemotherapy agents, opioid analgesics, and antidepressants may cause hyposalivation, however, radiation has a more impact on salivary gland changes. Although the radiation knowledge about the tooth is still controversial, in vitro studies have confirmed that radiotherapy causes changes in a direct way in the dental structure and morphological changes in both dentin and enamel[20].

Radiation caries has a different clinical pattern since it mainly affects smooth surfaces. In addition to developing rapidly, they can lead to the destruction of the dental element, as they often affect the cementoenamel junction, leading to the amputation of the crown. Therefore, the management of these carious lesions is more complicated. The progressive and rapid destruction of this lesion can affect the pulp and lead to an infectious process in the dental alveoli. Teeth that are in and out of the radiation field have the same potential to develop rapidly progressing carious lesions[19].

Radiation caries are easily differentiated clinically, since the teeth may have a brownish-black coloration, change in translucency, and can affect all surfaces of the teeth, even the root. This condition is motivated by several factors, from dental fragility, hyposalivation, and other salivary changes such as pH change, lower buffering capacity, increased viscosity, the proliferation of cariogenic bacteria, increase in calorie-rich diets due to great weight loss. Of these patients and compromised oral health, due to trismus, mucositis, and misinformation[2,3,22].

Until now there is no exact dosimetry that aims at destroying the tumor cells and not affecting the dental tissues, although it is already known that radiation can generate considerable and irreversible damage to these structures[22].

DISCUSSION

There are several adverse effects associated with antineoplastic treatment. However, the changes in dental tissues are scarcely described, despite their high prevalence in patients who are underneath chemotherapy and/or radiotherapy during childhood. Nevertheless, it is already described in the literature that these individuals are more susceptible to damage to teeth, including changes in number and shape. Among the alterations described in the literature, the most frequently reported are rhizogenesis disorders, hypodontia and anodontia.

Nemeth et al. and De Mattos et al. conducted studies with children who were underneath chemoradiotherapy treatment. In their findings, both authors reported dental disorders, the most commonly found ones being: root malformations, hypodontia and anodontia[13,23].

The correct etiology of the alterations is still unknown because there are several treatment protocols and, many times, the therapies are combined. Among the findings, it is known that some drugs are cytotoxic during tooth development, causing defects in enamel and dentin.

Some studies suggest that chemotherapeutic agents, such as vincristine and vinblastine, act to disrupt ameloblast microtubules and their calcium transport, causing enamel defects and subsequently affecting tooth morphology[10]. And these drugs were commonly seen in many studies, where they were related to many dental anomalies.

Furthermore, one of the possible etiologies is the radiation dose received during the cancer treatment. However, there is still no dosimetry protocol to combat the tumor cells and minimize the alterations in the dental tissues. It was observed by OWOSHO et al. that 10 Gy is enough to damage the ameloblasts, while 30 Gy leads to completely disrupted tooth development. In their study, the patients who developed changes were those who received more than 10 Gy, and those with more site impairment received more than 30 Gy in the treatment. In addition, KASTE et al. observed that the higher was the dose of radiation, the greater was the chance of developing dental anomalies, characterizing a dose-dependence about the consequences. In that study, only microdontia and enamel hypoplasia were shown to be related to chemotherapy associated with radiation therapy. And the children that received the treatment reported a higher frequency of dental abnormalities than the control group, including microdontia (9.2% vs 3.3%) and hypodontia (8.2% vs 5.3%). It was seen that patients who were under doses greater than 20 Gy had 4 to 10 times increased risk of having dental anomalies. This study then showed that pediatric patients, who are exposed to high doses, have a higher risk of developing dental anomalies[3,24](table 1).

Table 1. Staging and treatment strategies of BRONJ according to AAOMS[4].

Main dental anomalies		
Microdontia	Hypodontia	Root anomalies
Radiation dose associated with dental anomalies	**Chemotherapeutic agents associeated with dental anomalies**	
From 10 Gy	Vincristine and vinblastine	

The main dental alterations found were: microdontia, hypodontia and root changes in children who underwent antineoplastic treatment between 0.8 and 15 years. And dental alterations were observed from 10 Gy, and chemotherapy patients most associated with the alterations were:Vincristine and vinblastine. But it is known that the stage of development has an important influence on late dental effects.

MARANGONI-LOPES et al. reported that radiotherapy caused a reduction in the surface microhardness of both enamel and dentin, reduced the mineral components of enamel, phosphate, carbonate, amide, and hydrocarbons, and increased the amount of phosphate v2, amide, and hydrocarbons of dentin after 2160 and 1080 cGy, respectively. It was also possible to observe the presence of enamel cracks and obliteration of dentinal tubules[17].

One of the most common late effects present in pediatric patients who were underneath cancer treatment is radiation caries, which has difficult management, since it can lead to the loss of dental elements within one year, in severe cases. About this alteration, the etiology is still unclear, if it is a secondary effect due to alteration in the salivary glands, causing hyposalivation and change in the oral microbiota, or if it is a direct effect of radiation on the dental elements. But it is known that the developmental stage has an important influence on the effects of the radiotherapy. If a patient is treated in the dental bud stage, the bud can be destroyed or it's development can be affected. So, children in dental development are more susceptible to have more severe consequences because of the higher radiosensitivity[25].

Studies have reported that children who have survived cancer are more likely to develop caries lesions, with the influence not only of the antineoplastic treatment but also other factors surrounding the care of teeth by these patients. AVŞAR et al. studied a group of children who survived cancer, obtaining an 82% caries prevalence rate in these individuals, while the control group showed 54%. It is suggested that children who survived cancer should be considered a risk group, and should receive greater attention in oral health concerning caries, dental abnormalities, and other disorders. Therefore, caries control measures should be taken as soon as possible, such as preventive therapy, fluorotherapy, dental restoration, and when necessary, exodontia[20].

CONCLUSION

When pediatric patients are exposed to radiation during dental development, anomalies such as taurodontia, hypodontia, enamel hypoplasia, and root underdevelopment may occur, but they do not occur in adults. Such effects depend on the dose, duration of treatment and age of the patient. We already know that children who are subjected to chemotherapy and radiotherapy have different effects on dental development. Therefore, it is important that those responsible for the child are aware of this information. The implementation of protocols aimed at oral care during and after treatment is crucial to reduce the incidence and severity of such complications[1,2,3,27].

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