

Occurrence of invasive cervical resorption after the completion of orthodontic treatment

PAULA PERLEA¹⁾, MARINA IMRE²⁾, CRISTINA-CORALIA NISTOR¹⁾, MIHAELA-GEORGIANA ILIESCU³⁾,
 IRINA-MARIA GHEORGHIU⁴⁾, ITZHAK ABRAMOVITZ⁵⁾, ALEXANDRU-ANDREI ILIESCU⁶⁾

¹⁾Department of Endodontics, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

²⁾Department of Removable Prosthodontics, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

³⁾Department of Orthodontics and Dentofacial Orthopedics, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

⁴⁾Department of Restorative Dentistry, Faculty of Dental Medicine, "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

⁵⁾Department of Endodontics, Hadassah School of Dental Medicine, Hebrew University, Jerusalem, Israel

⁶⁾Department of Oral Rehabilitation, Faculty of Dental Medicine, University of Medicine and Pharmacy of Craiova, Romania

Abstract

The invasive cervical resorption (ICR) is an irreversible and progressive loss of tooth hard tissues involving coronal and root dentine that usually affects single permanent teeth. The aim of this study was to present the pattern of ICR lesions detected in three patients with no contributory medical and dental anamnesis, at different time periods after orthodontic tooth movements. Conventional radiographs and cone-beam computed tomography (CBCT) images were obtained by X-Mind™ (Satelec), respective 3D Accuitomo (Morita). The present clinical study confirmed that orthodontic forces might be a key factor for generating an ICR and the risk of lesion occurrence is increased in long movements of the teeth because the orthodontic forces act continuously an extended time. However, it should not be overlooked the synergistic effect of additional factors such as traumatic injuries, periodontal inflammation, clenching, and grinding. The more advanced ICR lesions found in our study, described as Heithersay Class 3 and Class 4, appeared on conventional radiographs as irregular, diffuse, mottled radiolucencies extended both to the crown and deeply into the tooth root. CBCT proved to have a superior accuracy in detection and assessing the severity of ICR, since the conventional intraoral radiographs cannot afford an early and proper identification of the resorptive defect. Moreover, the CBCT image allows an accurate inspection of all surfaces of tooth due to the slices in sagittal, axial and coronal planes, and to avoid erroneous diagnostic conclusions. Currently, due to CBCT scan, the nature and extension of ICR lesion into the tooth structures can be exactly evaluated.

Keywords: invasive cervical resorption, orthodontic treatment, radiographic diagnosis, CBCT.

Introduction

The invasive cervical resorption (ICR) is an insidious pathological process of multifactorial etiology, usually affecting single permanent tooth that resides in the irreversible damage of mineralized tooth tissues, mainly cementum and dentine; sometimes, enamel may be also affected [1]. The mechanism of root resorption relies on odontoclastic action of locally differentiated multinucleated giant cells, odontoclasts and osteoclasts. Depending on the moment of diagnosis, rate of defect progression and appropriate treatment, this unwanted condition may finally result in tooth loss [1–3].

The numerous potential predisposing factors of ICR are either biological (age, nutrition, genetic and systemic factors, habits, developmental defects, position anomalies, dental trauma, intracoronary bleaching, root canal treatments, and restorations) or mechanical (orthodontic and periodontal treatment, orthognathic and dentoalveolar surgery). The factors that may initiate a root resorption act independently or in association and unfortunately are even now poorly understood; they can also be idiopathic [2, 4, 5].

The resorptive process is initially located below the epithelial attachment of the affected tooth. Later on, is extending coronally and apically along the root dentine. This condition does not involve the root canal, is slowly progressing and the tooth is painless. It takes years to be clinically diagnosed [1, 2, 6–8].

Usually, ICR is diagnosed by routine periapical radiographs because clinical features are highlighted in some cases only in advanced stages. The main sign consists in a pink discoloration of crown, visualized at the gingival margin [1, 6, 7]. Radiological, an asymmetrical radiolucency with irregular margins is located in tooth cervical area superimposed on the root canal [6, 7].

Sometimes, ICR is misdiagnosed as a form of internal resorption. The differential diagnosis is often very difficult on intraoral periapical radiograph. In last years, the cone-beam computed tomography (CBCT) is considered the examination of choice because with its three-dimensional (3D) high-resolution, this imaging investigation allows a much better topographic and volumetric assessment of the lesion [9–12].

Among the other risk circumstances of ICR, the

orthodontic treatment is also considered a putative onset factor because during the tooth movement the root cervical region is subjected sometimes to orthodontic forces that might compromise the tooth survival [13–16].

It seems that intrusion, torquing, round-trip movements, flaring, and intermaxillary self-ligating systems facilitate an ICR. However, no correlation has been found between a particular orthodontic technique of treatment and the lesion [3].

The objective of this case series study is to emphasize the value of CBCT investigation for early diagnosis in ICR after the completion of orthodontic tooth movement.

Case presentations

Case No. 1

A healthy 27-year-old female with noncontributory medical history attended a dental clinic for resolving a previous non-finalized root canal treatment in right lower first molar (tooth 46). The intraoral radiograph showed an ICR in distal root of the tooth (Figure 1). She reported that more than 10 years ago was in an orthodontic clinic to closing the space in right lateral side of mandible and no other family member had a similar resorptive process.



Figure 1 – Intraoral periapical radiograph of first lower molar (tooth 46) showing a Class 3 ICR lesion in the distal root. The irregular radiolucency involving both the coronal dentine and the cervical third of the root dentine has a moth-eaten appearance. It is also revealed a radiolucent area extended into the alveolar bone in the vicinity of root lesion. ICR: Invasive cervical resorption.

CBCT scan confirmed an ICR in distal root of right first lower molar (tooth 46), which was visualized in all 3D axes (sagittal, axial and coronal) (Figures 2–4). Accordingly, following Heithersay's four Classes' classification of ICR lesions this clinical case may be considered as Class 4, since the large destructive process progressed beyond the cervical third of root dentine. The treatment decision was in this case the tooth replantation due to the extensive and irregular resorption of distal root, which appears on CBCT in sagittal (Figure 2) and axial planes (Figure 3).

Though the intraoral periapical radiograph and CBCT in sagittal plane are performed in the same 3D sagittal axis, the imagistic information about the pathological condition (ICR) was more comprehensive in CBCT since it eliminated the superimposed bone structures.



Figure 2 – CBCT image in sagittal plane of tooth 46 showing a large ICR lesion in the distal root expanded beyond its coronal and middle third, and penetrating the root canal space. As compared to periapical radiograph it can be diagnosed as Class 4 ICR lesion. CBCT: Cone-beam computed tomography; ICR: Invasive cervical resorption.



Figure 3 – CBCT image of tooth 46 in axial plane. The ICR lesion actually destroyed the disto-lingual surface of the distal root. There are also confirmed the penetration of the distal root canal space and the bone loss adjacent to the root lesion. CBCT: Cone-beam computed tomography; ICR: Invasive cervical resorption.

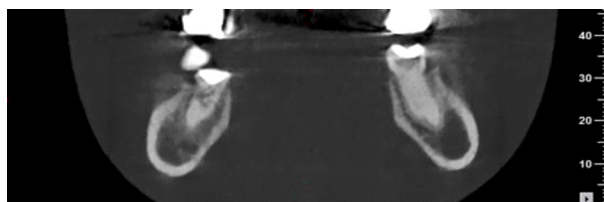


Figure 4 – CBCT image of tooth 46 in coronal plane showing in this sectional representation an irregular ICR lesion situated in buccal area of coronal half of the distal root, having two lingually directed extensions. The condition seems to be less destructive than in sagittal and axial planes. However, it is confirmed the Class 4 category of ICR. CBCT: Cone-beam computed tomography; ICR: Invasive cervical resorption.

Moreover, as compared to the intraoral periapical radiograph, CBCT examination demonstrated in this case that exactly captures the 3D shape and location of ICR. However, it has to be considered that the same condition may have different appearance according to the sagittal, axial or coronal sectional images.

Case No. 2

A 25-year-old female patient came to the dental office for presenting a buccal abscess in the region of left upper canine and first premolar. The preoperative radiograph (Figure 5) revealed a chronic apical periodontitis in left upper first premolar (tooth 24) that generated the abscess and additionally an ICR in the former impacted canine (tooth 23).

We learned from anamnesis that she was born with agenesis of left upper lateral incisor. Twelve years ago, she started an orthodontic traction treatment of the impacted left upper canine (Figure 6). The left upper first premolar (tooth 24) was identified as causal tooth of the abscess and an appropriate endodontic treatment was performed (Figure 7).

Regarding the pattern of resorptive lesion in left upper canine, this involved a large area of the root surface. Due to the multiple areas of root resorptions in tooth 23, extended beyond the coronal third of root

dentine, this lesion was estimate as belonging to ICR Class 4.

Since it was considered as impossible to conserve the canine, the treatment decision was tooth extraction, which was accomplished having the informed consent of the patient. After six months of alveolar bone healing, an implant was inserted. The 6-month follow-up showed on same radiograph that the healing of chronic apical periodontitis in left upper first premolar was in progress, avoiding the risk of inflammation in the proximity around the dental implant (Figure 8).



Figure 5 – Preoperative radiograph of symptomatically left upper first premolar (tooth 24). Incidentally, an ICR lesion was discovered in canine (tooth 23). The multiple areas of root resorptions in tooth 23, extended beyond the coronal third of root dentine, estimate this lesion as belonging to ICR Class 4. ICR: Invasive cervical resorption.



Figure 6 – Orthopantomogram at the beginning of orthodontic treatment 12 years ago. Agenesis of upper left lateral incisor (tooth 22) suggested the uprighting traction of impacted canine (tooth 23).



Figure 7 – Postoperative radiograph of left upper first premolar (tooth 24). Due to the pattern of ICR lesion in left upper canine, which involved a large area of the root surface, there was decided the canine extraction followed by an implant insertion after six months of alveolar bone healing. ICR: Invasive cervical resorption.



Figure 8 – Control periapical radiograph of implant site and apical status in upper left first premolar (tooth 24) at one year. Healing of chronic apical periodontitis in first premolar is in progress.

Case No. 3

A 39-year-old female undergoing an orthodontic treatment for uprighting the right upper wisdom tooth (Figure 9) complains of tooth slight mobility. We learned from anamnesis that to getting a corrected occlusion years ago the patient underwent two times orthodontic treatments. Unfortunately, those previous treatments failed. She was unable to specify neither the type of orthodontic appliances that were used nor the duration of those treatment attempts.

At inspection, no coronal or root caries were clinically detected. It was present only reduced gingival recession.

The intraoral periapical radiograph shows an ICR in right upper wisdom tooth (Figure 10).

CBCT scans both in coronal (Figure 11) and sagittal plane (Figure 12) revealed an ICR that expanded coronally and broadly undermined the enamel, without to involve the pulp chamber. According to Heithersay's classification, this pretty advanced ICR lesion illustrating the clinical case may be still considered as Class 3.

Discussion

In healthy status, the root dentine is covered by protective surface of cementum and no resorptive process can affect it. A defect or damage of the outermost cementum or cementoid layer after trauma or surgery is a prerequisite to starting the resorption of the underlying exposed root dentine [17, 18].

ICR is a poorly understood pathological condition with still uncertain etiology and extensive type of root dentine destruction [19]. ICR is a localized and progressive lesion that involves the bulk of dentine in the cervical area of the tooth without to affect the external root surface and pulp chamber or root canal [1].

It is proved that the ICR is initiated through a portal of entry in the cementum layer, at the root surface bellow the epithelial attachment [20]. Although usually the starting point is the cervical area of the tooth root, the lesion could be located in some other regions, depending on position change of the epithelial attachment in different clinical conditions of the marginal periodontium and depth variation of the periodontal pockets [3, 21, 22].

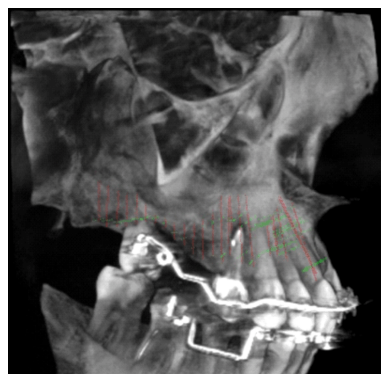


Figure 9 – Right upper wisdom tooth (tooth 18) mesially tipped. Uprighting attempt. CBCT – 3D reconstruction. CBCT: Cone-beam computed tomography.



Figure 10 – Intraoral periapical radiograph of mesially tilted right upper wisdom tooth (tooth 18) showing an ICR lesion that expanded coronally, broadly undermined the enamel. However, the pulp chamber is not affected by resorptive process and the tooth is still vital. ICR: Invasive cervical resorption.



Figure 11 – CBCT scan of tooth 18 in coronal plane revealing an asymmetrical radiolucency that could be diagnosed as ICR Class 3 during its last stage of evolution. Note also the 90° curvature of apical third of the tooth root. CBCT: Cone-beam computed tomography; ICR: Invasive cervical resorption.



Figure 12 – CBCT scan of mesially tilted tooth 18 in sagittal plane showing a large ICR lesion mesially located in tooth crown, which undermined the enamel and progressed in the coronal root dentine. The ICR Class 3 estimation of the asymmetrical radiolucency in coronal plane is confirmed in sagittal plane as well. CBCT: Cone-beam computed tomography; ICR: Invasive cervical resorption.

Regardless the etiology once initiated, the ICR progression is stimulated by orthodontic treatment due to the continuous mechanical forces [23]. Later on, the destructive lesion penetrates the dentine pulpward, frequently spreading in coronal and apical direction around the root canal, without to open it [19, 20].

The typical circumferential manner of ICR spreading without to affect the pulp demonstrates that actually the pulp tissue is not involved in the pathogenesis of invasive cervical resorption. Often, the radiographic images reveal a radiopaque border line between the lesion and the root canal [1–3, 6, 8] as the resorptive process stops in the innermost layer of dentine and predentine and the pulp tissue remains uninfamed for a time [1, 2, 8].

The resorption process does not penetrate the pulp tissue due to the protective effect of a mineralized layer surrounding the root canal, which is referred as pericanalar resorption-resistant sheet (PRRS) [23].

The insidious resorption process does not pass the so-called pericanalar resorption-resistant sheet, as the lack of extracellular arginine-glycine-aspartate proteins in predentine and cementum reduces the clastic cells potential of binding to these mineralized tooth tissues. It is thought that actually this sheet is not true dentine but rather cementum-like or bone-like tissue [24].

Though initially it was considered that PRRS occurs as a result of a resorptive process, presently is thought to also be a repair place since in some circumstances may undergo a reparative process by apposition of osteodentine at its borders [24].

PRRS consists mainly of predentine and dentin and its thickness was reported to be approximately 200 µm, ranging from 70 µm up to 490 µm [23, 24]. However, it was also described apposition of reparative bonelike tissue resembling trabecular bone, sometimes combined with woven bone. Simultaneously, the pulp tissue undergoes diffuse calcifications associated with a decrease of cells number [23]. Accordingly, it seems that ICR induced by orthodontic treatment is a more complex process than it was previously thought due to the potential reapposition of osteodentine [24].

Gunst *et al.* (2013) noticed that owing to its reduced thickness the PRRS may be identified exclusively *ex vivo* on micro-computed tomography (micro-CT), but not visualized *in vivo* on conventional radiographs or CBCT [24]. However, recent studies highlight that the progress in *ex vivo* 3D imagistic by nano-computed tomography (nano-CT) enable to comparably reproducing the hard tissue structure at histological level and provide an excellent tool of investigation [20, 23].

Heithersay claims that in an early stage the invasive cervical resorption is broadly a resorptive process exclusively aseptic, free of acute inflammatory cells [1]. At a later stage, the resorption area could be invaded with microorganisms from the periodontal pocket [1, 2, 8].

The destroyed cementum and dentine are replaced by highly fibrovascular granulomatous tissue and chronic inflammatory cells consisting in lymphocytes, histiocytes, plasma cells and. The clastic cells, osteoclasts, differentiate locally from blood macrophages and border the dentine on the resorption front within the resorption bays, or Howship's lacunae [2, 8]. The histological feature of the lesion is comparable to external inflammatory resorption [2, 6, 21].

According to literature, the main intimate reason of external root resorption might be the osteoclasts over-

activation. The secreted extracellular receptor osteoprotegerin (OPG) as component of osteoprotegerin/receptor activator of nuclear factor κ B ligand/receptor activator of nuclear factor κ B (OPG/RANKL/RANK) pathway is a key inhibitory factor of osteoclasts differentiation and maturation. Hence OPG protective effect for root cementum. Loss of OPG results in osteoclastogenesis and malmineralization of cementum, which cooperate to the onset and progress of ICR [25].

The resorptive and reparative phenomena may develop simultaneously at different areas of the affected root [23]. Sometimes, in advanced stages occurs an attempt of repairing the dentine resorption bays with poorly organized bonelike tissue. These calcificated deposits can be ectopic or in direct contact with previously resorbed dentine [6, 8].

Mavridou *et al.* (2016) observed that in all vital teeth with external root resorption occurs a repair process based on substitution of the resorbed hard tissues by reparative bonelike tissue that undergoes an active remodeling. Occasionally, a layer of newly generated cementum and periodontal ligament are also associated proving that the ICR destructive and reparative nature could be combined [23].

Clinical diagnosis of ICR is challenging since the signs and symptoms occur pretty late. Of remarkable help are visual inspection based on an operating microscope and CBCT as an adjunct to conventional intraoral radiography [24].

Often, ICR is detected unexpectedly on intraoral radiographs, either periapical or bitewings. The resorption lesions can be challenging to diagnose accurately the pathological process on conventional radiograph and this is a serious impediment in caring out a predictable conservative management. Early lesions are usually revealed when they are located proximally. Merely, in advanced lesions is possible a clinical detection [2, 3, 6, 10, 11].

The common radiographic image in early stage of root destruction is cloudy radiolucency with irregular borders, asymmetrically situated in the cervical segment of the affected tooth. In more advanced evolution stages, if fibro-osseous tissue is generated to fill the resorption lacunae, frequently the mottled picture is depicted [2–4].

Typical in Class 1 invasive cervical resorption is depicted as a small radiolucency superimposed to the clinical lesion. In Class 2 is revealed radiolucency with poorly defined borders, often projected over the root canal. In Class 3, the radiological image is mottled, with irregular margins. In Class 4, the lesion image is diffuse and characterized by translucent lines extending along the root canal into the apical third of the tooth root [1, 3].

With conventional radiographs, there are limitations to appropriate identification of the lesion [15]. Often, the differential diagnosis oscillates between internal root resorption [1, 2, 6, 10, 12], burnout effect [2, 26], and infrabony periodontal defect [26].

Usually, the intraoral periapical radiograph cannot fully assess its true ICR nature and location [19]. Particularly, the condition is simultaneously destructive and reparative, creating in various areas of the same tooth a 3D structure that can be properly evaluated only by CBCT imagistic

examination [20]. Furthermore, the CBCT evaluation is with 30% more accurate due to the reduction of anatomic noise and 3D nature of image [19].

Over the past years, a bulk of evidence emphasizes the more accurate diagnostic value of CBCT because the conventional intraoral radiograph failed to demonstrate the real size and location of resorptive defect [2, 3, 6, 8–12, 27–28]. Using intraoral periapical radiography, in incisors and premolars can be correctly diagnosed only 60% of lesions and in molars maximum 25% of the lesions, as opposed to CBCT scan that demonstrated a 30% more accurate ICR diagnosis [19].

One of the most popular CBCT equipment, 3D Accutomo (Morita), delivers an effective radiation dose of 7.3 μ Sv. As compared to effective dose of 6.3 μ Sv in conventional orthopantomography and 5 μ Sv in intraoral periapical radiography, it seems that in CBCT scanning the patient irradiation is equivalent [11].

However, in order to be a useful diagnostic tool, the beneficial contribution of CBCT scan should outweigh the risk of irradiation. Accordingly, because the effective dose of a CBCT scan is higher than of a conventional radiograph it is highly recommended to establish the working parameters for CBCT according to ALARA (as low as reasonably achievable) principle [19].

CBCT scan may detect incipient external root resorptions before to be visualized on conventional intraoral radiographs. Moreover, CBCT allows an accurate volumetric evaluation of the resorptive process and its linear axial extension, which is extremely important for an adequate conservative treatment and an improved prognosis [29].

CBCT also technically provides a better visualization approach, by illustrating 3D the normal and pathological morphology of the root, as opposed to currently used radiograph, which reproduce the anatomical structures on two-dimensional image. Moreover, the anatomical noise and geometrical position of the film holder typical for intraoral periapical radiographs are eliminated [10]. Another advantage is provided by CBCT software. The dentist may select the most favorable orthogonal views and also adjust the thickness of slices and interval between them [10].

Presently, CBCT became widespread as it provides radiological images that definitely influence the choice of treatment planning. The reliability of CBCT diagnostic imaging to revealing the external root resorption depends on ability limits to detecting the loss of mineralized tooth tissue. The condition is clearly observed in the axial, coronal, and sagittal sectional images. Unlike the not attainable information provided by panoramic or conventional radiographs, CBCT images in ICR are critical to decide the appropriate diagnosis and therapeutic intention [11].

CBCT is not always necessary in correctly diagnosing both internal and external root resorption. Patel *et al.* (2009) underlines that although the intraoral periapical radiograph is reasonably accurate, CBCT scans provide a perfect diagnosis of any type of root resorption. However, the CBCT scans sensitivity and specificity should not be overestimated because the treatment decisions were only 80% correct [10].

Despite this level of sensibility, it has to be highlighted that in particular cases of severe external ICR, the CBCT scan is very useful because by conventional radiograph, the real relationship between the lesion and the normal anatomical structure cannot be exactly outlined [10].

In order to outweigh the potential risks is recommendable to use a small field of view CBCT scanner. A CBCT scanner with high resolution guarantees the maximal benefit of imagistic examination [19].

The level of radiation using a focused CBCT is very low. In the upper anterior teeth is almost the same as for conventional intraoral periapical radiographs. However, the diagnostic value for a successful treatment is increased because in extended resorptive lesions can indicate if an endodontic approach is mandatory or should be avoided.

However, as aforementioned CBCT images have their limitations in identifying the morphological complexity of resorption border since fails to detect the reparative bonelike tissue. To date the detailed visualization of the area is provided solely by nano-CT, a newcomer of *in vitro* imagistic investigation [20].

The literature widely reported differences in the quality of CBCT images when field of view (FOV) or the voxel size was changed. In external root, resorption was also demonstrated that using small voxel sizes can be achieved images with high diagnostic power. In order to get the real volume of the lesion, the standardization of imaging protocols based on adequate CBCT acquisition parameters is of utmost importance [30].

da Silveira *et al.* (2015) reported that using 0.300-mm voxel were achieved under-dimensioned images of lesion volume compared to 0.200–0.250 mm voxel. The image definition provided by larger voxel size was poorer due to the increased anatomical noise. However, the noise is also higher when reducing voxel size below 0.200 mm [30].

According to ALARA principle, an appropriate diagnostic CBCT image has also to comply with a low radiation exposure dose. Therefore, exposing small areas like a resorption defect, is recommendable to be used a restrict FOV due to the lower radiation [30].

da Silveira *et al.* (2015) substantiate the necessity of voxel size standardization in CBCT image acquisition in order to avoid any under- or overestimation of the ICR volumetric dimension [30].

During the orthodontic treatment, ICR often occurs mainly apical as a consequence to the inflammatory process associated with tooth movement. Although the goal of induced orthodontic forces is the guided bone resorption facilitating the tooth movement, sometimes cementum and even underling dentine are also involved in the resorptive process.

Various biological and mechanical risk factors may influence root resorption during therapeutically tooth movement. It should be also highlighted the synergistic effects of additional traumatic injuries, inflammation, clenching and grinding, which relying on chronic local hypoxia generated by continuous mechanical compressive stress of the periodontal ligament (PDL) during the orthodontic treatment finally can result in an ICR lesion [20].

Definitely, the mechanical forces induced by activated orthodontic appliances are the key factor. Among the mechanical factors should take into account the level of

applied force, magnitude and duration of orthodontic force, type of tooth movement, *e.g.*, intrusion, torque or bodily movement, and long movement distances as well. Regarding the biological factors, the genetic inheritance, gender, tooth morphology, systemic diseases and medication have to be considered.

To avoiding the severe root resorptions in patients of increased risk, a careful plan of orthodontic treatment has to be established, depending on dental and medical history. Heithersay found that ICR may be diagnosed along an extended period of time, between 1½–33 years after the completion of orthodontic treatment [4].

To early detection of the orthodontic induced ICR should be mandatory a 6-month radiographic follow-up. In patients of increased risk, the time limit is shorter, at three months visits. It should be noted that panoramic radiographs overestimate the root resorption degree because the magnification of the image X-rays is up to 20%. Moreover, these types of radiographs are pretty unreliable due their low level of reproducibility [31].

As compared to the surface resorption in the cervical area of the tooth root that occurs frequently during the course of orthodontic tooth movement, ICR is definitely a rare lesion. Another issue, which differentiates these two lesions, is a radiological one. The surface resorption lesions are revealed as self-limiting radiolucent concavities in contrast to extensive radiolucent image with poorly defined borders of ICR [13].

Most frequently after an orthodontic treatment, the upper anterior teeth and lower first molars are affected by ICR. If for upper incisors and canines no correlation was found with the used technique or appliance, in case of lower molars it could be an explanation because the orthodontic bands might mechanically damage the cervical area of the tooth.

It seems that long movement distances during the course of orthodontic treatment, that implies continue and long duration action of orthodontic forces, are rendering the tooth prone to progressively developing an ICR [13].

However, is still inquiring why usually the ICR occurs several years after the conclusion of treatment, as opposed to surface resorption detected during the course of the orthodontic treatment and never later [2].

✎ Conclusions

The present clinical study confirms that orthodontic forces might be a key factor for generating an ICR. The risk is increased in long movements of the teeth because the orthodontic forces act continuously an extended time. It should not be overlooked the synergistic effect of additional traumatic injuries, inflammation, clenching, and grinding. Typical for ICR of orthodontic etiology is the occurrence in some still non-elucidated circumstances many years after the completion of orthodontic treatment. To avoiding the severe root resorptions in patients of increased risk, a careful plan of orthodontic treatment has to be established, depending on dental and medical history. Since it has superior imagistic accuracy than the intraoral periapical radiographs, CBCT is an extremely useful diagnostic aid in assessing the lesion severity. Based on CBCT imagistic effectiveness, the early detection and appropriate management of ICR presently are highly improved.

Conflict of interests

The authors declare that they do not have any conflict of interests.

Author contribution

Authors #1 (PP) and #2 (MI) have equal contributions to this paper.

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Corresponding author

Irina-Maria Gheorghiu, DDS, PhD, Department of Restorative Dentistry, Faculty of Dental Medicine, “Carol Davila” University of Medicine and Pharmacy, 19 Plevnei Avenue, 050051 Bucharest, Romania; Phone +40744–305 591, e-mail: igheorghiu@hotmail.com