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# Role of Panoramic Radiography in the Identification of Dental Anomalies and Disturbed Development of the Dentition

Cabov Tomislav<sup>1</sup>, Legovic Asja<sup>2</sup>, Cabov Ercegovic Lucija<sup>3</sup>, Zulijani Ana<sup>4</sup>

## ABSTRACT

Aim and objective: This study aimed to determine the prevalence of dental anomalies and impaired dentition development by analyzing panoramic radiographs.

**Materials and methods:** The study included 1,317 orthopantomograms of children treated in an orthodontic practice. Regarding the development of the dentition, they were divided into five stages: (1) Eruption of the first permanent molars. (2) Replacement of the incisors. (3) Completed replacement of the incisors. (4) Replacement in the supporting zones. (5) Completed replacement of the teeth of the supporting zones.

**Results:** Dental anomalies were found in 9.5% of the subjects. In the first stage, M1 was found to resorb the crown of m2 in 7.1% of cases during the eruption. In the second stage, I1 resorbed the adjacent deciduous tooth during the eruption in 17.5% of the cases. In the third stage, impaired development of incisors was observed in 28.9% of cases in the maxilla and in 27.9% in the mandible. In the fourth stage, ectopic position and premature eruption of the germ in segments C-P2 were noted in 20.8% of teeth in the maxilla and 9.7% in the mandible. Late mineralization of P2 and ankylosis of m2 was noted in 3.4% of cases in the maxilla and 6.5% in the mandible. In the fifth stage, 11.9% of M3 germs were ectopically positioned in the maxilla and 29.5% in the mandible, 5.9% of M3 germs were absent in the maxilla, and 6.7% in the mandible.

**Conclusion:** Our study showed a similar incidence of various dental anomalies and disturbed dentition development as reported in the literature. The results of this study confirm that the analysis of orthopantomogram is an important and useful element in the diagnosis and treatment plans for a malocclusion.

**Clinical significance:** Orthopantomogram analysis can be used as a useful element in the diagnosis and treatment plans for a malocclusion. **Keywords:** Children, Dental anomalies, Developmental disorder, Panoramic radiograph, Prevalence.

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## INTRODUCTION

In addition to the clinical examination and the analysis of plaster casts, the analysis of radiographs is an essential part of orthodontic diagnosis, especially the analysis of the orthopantomogram. Certain findings obtained from the radiographic status (usually 20 intraoral retroalveolar radiographs) are more reliable than findings obtained from the panoramic radiograph.<sup>1,2</sup> By supplementing the findings of the panoramic radiograph with the findings of 3-4 intraoral radiographs, the reliability of such data approaches obtained from the radiographic status.<sup>3</sup> Conventional panoramic systems have been replaced by digital systems. There are no significant differences between these two systems in the diagnosis of dental anomalies and problems associated with the position of the third molar. Many factors of exogenous and endogenous origin can affect the occurrence of abnormalities of tooth position and occlusion in the mixed dentition. A radiographic examination can provide important information about dental anomalies in number (hyperdontia and hypodontia), size (microdontia and macrodontia), and crown shape (germination and fusion). Numerous authors have studied their prevalence.<sup>4-12</sup> Hintze et al. stated that 94% of children can be excluded from orthodontic therapy by analyzing the orthopantomogram and that it is possible to identify 97% of those in whom immediate orthodontic therapy is necessary.<sup>5</sup> Neal and Bowden attribute slightly less importance to the orthopantomogram for diagnosis and treatment planning.<sup>4</sup> They found significant data in the orthopantomogram for orthodontic diagnosis and treatment in 26.5% of 9–10-year-olds.

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Witcher et al. pointed out a possible insufficient precision in the detection of dental anomalies, such as supernumerary teeth in the anterior maxillary region due to a narrow focal trough or spinal overjet.<sup>13</sup> They reported significantly higher reliability of using upper anterior occlusal radiographs in this region. The purpose of this study was to determine the prevalence of dental anomalies and certain disturbances in development during different phases of the mixed dentition by analysis of the orthopantomogram.

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## MATERIALS AND METHODS

The cross-sectional study included 1,317 orthopantomograms (694 girls and 623 boys) of children treated in a private orthodontic practice in Poreč, Croatia, from 2014 to 2019. The age of the subjects ranged from 5 to 15 years, with a mean age of  $10.34 \pm 2.17$  years. The study was approved by the Ethics Committees of the Faculty of Medicine, University of Rijeka, and Clinical Hospital Center Rijeka, and written informed consent was obtained from the legal representatives/parents/guardians.

All radiographs were performed using Orthophos 3 Siemens panoramic device with the following parameters: 60–80 kV, 10 mA, 11.3 s. To minimize possible errors on orthopantomograms, it is most important to place the subject in the correct position in the focus well, exactly as indicated by the manufacturer.<sup>14</sup> All radiographs in which the contrast of the examined details was unsatisfactory were excluded from the study. Subjects with systemic or syndromal diseases, jaw fractures that affected the natural growth of the permanent dentition, or a history of previous orthodontic treatment were excluded from this study.

The subjects were divided into five stage groups according to the development of the dentition. The distribution of orthopantomogram in terms of sex, age, and stage of dentition development is shown in Table 1.

- On the orthopantomograms of the subjects in stage 1 of dentition development, the prevalence of resorption of the second deciduous molar by M1 in the eruption and the eruption of M1 in the space of extracted m2 (second deciduous molars) were studied.
- On the orthopantomograms of the subjects in the second stage of dentition development, the prevalence of the resorption of the lateral deciduous incisor by the central permanent incisor in eruption and the resorption of the deciduous canine by the lateral permanent incisor in the eruption were studied.
- On the orthopantomograms of the subjects at stage 3 of dentition development, the prevalence of crowding of incisors and diastema between all incisors was studied.
- On the orthopantomograms of the subjects at stage 4 of dentition development, the following prevalence was studied:
  - Ectopic position of the canine, first, and second premolars (C, P1, and P2). When subjects of the same age and sex had both homologous tooth germs misaligned on the orthopantomogram with respect to the position of the same tooth, bilateral dystopia was inferred. Unilateral ectopy was inferred if the tooth germ in sagittal position was significantly

different from that of the homologous tooth of the same jaw. For the maxillary canine, the ectopic position was inferred if the angle of the longitudinal axis of the tooth with the occlusal plane and the vertical distance of the incisal edge from the occlusal plane were significantly different from the homologous tooth of the same jaw. The ectopic position was also inferred when the crown of the canine was covered by the root of the lateral incisor.

- Premature eruption of a tooth (a situation in which the tooth had erupted and at least half of its root was not mineralized).
- Late mineralization of a tooth (the mineralization of the tooth was late in relation to the homologous tooth or other teeth of the C-P2 segment).
- Ankylosis of a deciduous tooth (the contour of the alveolar bone followed the cementoenamel junction, infraposition of the occlusal plane of the tooth in relation to the homologous tooth or adjacent teeth). After performing the panoramic radiograph during the clinical examination of the subject, the orthodontist noted the pathological features associated with the teeth and supporting structures and attached them to the radiograph. Thus, a record was made of the percussion of the teeth in infraposition.
- On the orthopantomograms of the subjects in the fifth stage of dentition development, the condition of the space after the extraction of the M1, the prevalence of the ectopic position of the M3, and the hypodontia of the M3 were studied.

The prevalence of dental anomalies in the number of teeth (hyperdontia and hypodontia, independent of M3 hypodontia), the size of teeth (microdontia and macrodontia), and the shape of the dental crown (germination and fusion) were studied for all subjects together.

All orthopantomograms were evaluated separately by two orthodontists with over 20 years of experience in evaluating panoramic radiographs. The orthopantomograms were evaluated on the monitor screen without any adjustment. The kappa coefficient was used to determine the degree of agreement. The values of the kappa coefficient ranged from 0.92 to 0.97. Each orthopantomogram in which there was disagreement in the findings of both examiners was examined separately, and agreement between the two examiners was achieved in a joint examination. The significance of the difference between the variables examined and the percentages between the maxilla and mandible at specific stages of dentition development was determined using a *t*-test for proportions. The level of statistical significance was determined at the level p < 0.05.

 Table 1: Distribution of orthopantomograms by sex and stage of dentition development

| Developmen | nt of dentition   | Age range | Boys, N | Girls, N | Total, N |
|------------|---|-----------|---------|----------|----------|
| Stage 1    | Eruption of the first permanent molars in progress (M1)   | 5–8       | 76      | 78       | 154      |
| Stage 2    | Exchange of incisors in progress  | 5–9       | 114     | 114      | 228      |
| Stage 3    | Exchange of incisors complete, but the exchange of teeth in C-P2 segments not commenced (deciduous canine and deciduous molars) | 8–10      | 157     | 183      | 340      |
| Stage 4    | Exchange of incisors complete, exchange of teeth in C-P2 segments in progress   | 8–13      | 200     | 214      | 414      |
| Stage 5    | Exchange of teeth in C-P2 segments complete   | 11–14     | 76      | 105      | 181      |
| Total      |   |           | 623     | 694      | 1,317    |



### Results

The results of the study are presented in Tables 2 to 7. Table 2 shows the prevalence of dental anomalies. Dental anomalies were found in 9.5% of the subjects. The most common was hypodontia (6.3%), followed by hyperdontia (1.5%), microdontia (1.4%), germination (0.15%), and fusion (0.07%).

Table 3 shows the prevalence of impaired development of dentition in stage 1. It was found that the second deciduous molar was resorbed in 4.5% of the subjects in the maxilla and 2.6% in the mandible (p = 0.169) during eruption M1. The first permanent molar erupted into the space of prematurely lost m2 in 18.5% of the subjects in the mandible and 12.9% in the maxilla (p = 0.057).

Table 4 shows the prevalence of impaired development of dentition in stage 2. It was found that during the eruption, the permanent incisor resorbed the adjacent deciduous tooth in 13.6% of the subjects in the maxilla and 3.9% in the mandible (p = 0.003). This occurred more frequently in the maxilla during the eruption of the lateral incisor than during the eruption of the central incisor (8.3 vs 5.3%; p = 0.195).

Table 5 shows the prevalence of impaired development of the dentition at stage 3. Impaired development during the eruption of the incisors was observed in 28.9% of the subjects in the maxilla and 27.9% in the mandible (p = 0.772). Crowding of incisors was more common in the maxilla (15.6 vs 11.8%; p = 0.133), and spacing was more common in the mandible (16.2 vs 13.2%; p = 0.267).

Table 2: Prevalence of dental anomalies

| Dental anomalies | N   | %*   |
|------------------|-----|------|
| Hypodontia       | 83  | 6.3  |
| Hyperdontia      | 20  | 1.5  |
| Microdontia      | 19  | 1.4  |
| Germination      | 2   | 0.15 |
| Fusion           | 1   | 0.07 |
| Total            | 125 | 9.5  |

\*Percentage shares are determined in relation to the total number of subjects (N = 1,317)

Table 3: Prevalence of disturbed development of dentition in stage 1

|  | Maxillary |      | Ма | ındible |
|--|-----------|------|----|---------|
| Analyzed variables                               | Ν         | %    | Ν  | %       |
| M1 during eruption resorbed M2*                  | 7         | 4.5  | 4  | 2.6     |
| M1 erupted in the space of the<br>extracted M2** | 40        | 12.9 | 57 | 18.5    |

\*Percentage shares are determined in relation to the total number of subjects in stage 1 (N = 154)

\*\*Percentage shares are determined in relation to the total number of teeth in stage 1 (N = 308)

Table 4: Prevalence of disturbed development of dentition in stage 2

|   |           |      |          | -   |
|---|-----------|------|----------|-----|
|   | Maxillary |      | Mandible |     |
| Analyzed variables  | Ν         | %    | Ν        | %   |
| I1* During eruption resorbed i2 <sup>#</sup>                    | 12        | 5.3  |          |     |
| crown   |           |      |          |     |
| I2 <sup>\$</sup> During eruption resorbed c <sup>##</sup> crown | 19        | 8.3  | 9        | 3.9 |
| Total   | 31        | 13.6 | 9        | 3.9 |

11\* central permanent incisor, i2<sup>#</sup> lateral deciduous incisor, l2<sup>\$</sup> lateral permanent incisor,  $c^{##}$  deciduous canine

\*Percentage shares are determined in relation to the total number of subjects in stage 2 (N = 228)

Table 6 shows the prevalence of impaired dentition development in stage 4. The most common disorders of dentition development during tooth change in segments C-P2 were ectopic tooth position and premature eruption. Both disorders were more frequent in the maxilla (ectopic tooth position: 10.9 vs 5.6%; p < 0.001; premature eruption of teeth: 9.9 vs 4.1%; p < 0.001). Late mineralization of P2 was found in 3.1% of subjects in the mandible and 2.2% in the maxilla (p = 0.420), and ankylosis of m2 in 1.2% of subjects in the maxilla and 3.4% in the mandible (p = 0.035).

Table 7 shows the prevalence of impaired dentition development at stage 5. The extraction spaces of M1 were narrow or closed in 19% of the subjects in the mandible and in 14.2% in the maxilla (p= 0.292). The germ of the lower M3 was more frequently positioned dytopically in the mandible than in the maxilla (29.5 vs 11.9%; p= 0.001). The germ of the mandibular M3 was absent in 6.7% of subjects and that of the maxillary M3 in 5.9% of subjects (p = 0.806).

#### DISCUSSION

In this study, the prevalence of dental anomalies and certain growth disorders during the mixed dentition was investigated by analyzing the orthopantomogram. Dental anomalies were found in 9.5% of the subjects. Stahl et al. and Thongudomporn and Freer

Table 5: Prevalence of disturbed development of dentition in stage 3

|                            | N  | Maxillary |    | Mandible |  |
|----------------------------|----|-----------|----|----------|--|
| Analyzed variables         | Ν  | %         | Ν  | %        |  |
| Crowding of incisors*      | 53 | 15.6      | 40 | 11.8     |  |
| Diastema between incisors* | 45 | 13.2      | 55 | 16.2     |  |
| Total                      | 98 | 28.9      | 95 | 27.9     |  |

\*Percentage shares are determined in relation to the total number of subjects in stage 3 (N = 340)

 Table 6: Prevalence of disturbed development of dentition in stage 4

|   | Maxillary |      | Mandible |     |  |
|---|-----------|------|----------|-----|--|
| Analyzed variables                                | Ν         | %    | Ν        | %   |  |
| Ectopic position of the teeth of C-P2** segment   | 270       | 10.9 | 139      | 5.6 |  |
| Premature eruption of the teeth of C-P2** segment | 247       | 9.9  | 102      | 4.1 |  |
| Late mineralization of P2*                        | 9         | 2.2  | 13       | 3.1 |  |
| Ankylosis m2*                                     | 5         | 1.2  | 14       | 3.4 |  |

\*Percentage shares are determined in relation to the total number of subjects in stage 4 (N = 414)

\*\*Percentage shares are determined in relation to the total number of teeth in stage 3 (N = 2,484)

Table 7: Prevalence of disturbed development of dentition in stage 5

|   | Maxillary |      | Ма | andible |
|---|-----------|------|----|---------|
| Analyzed variables                          | Ν         | %    | Ν  | %       |
| Space of the extracted M1 narrow or closed* | 38        | 14.2 | 51 | 19.0    |
| Ectopic position of germ**                  | 32        | 11.9 | 79 | 29.5    |
| Agenesis M3*                                | 8         | 5.9  | 9  | 6.7     |

\*Percentage shares are determined in relation to the total number of subjects in stage 4 (N = 134)

\*\*Percentage shares are determined in relation to the total number of teeth in stage 3 (N = 268)

found significantly higher prevalence (40.8 and 30.8%) and studied more dental anomalies than the present study.<sup>8,11</sup> Pallikaraki et al. found anomalies of teeth and jaws in 18.8% of subjects by analyzing panoramic radiographs.<sup>15</sup> They found 224 developmental dental anomalies on 1,200 radiographs. Considering amelogenesis imperfecta, which was not investigated in this study, Altug-Atac and Erdem found a significantly lower prevalence of dental anomalies in a Turkish population, 5.6%.<sup>16</sup> The wide variation may be attributed to different sample size, age range, and included dental anomalies.

The findings of hyperdontia, germination, and fusion obtained in this study confirm the findings of other authors.<sup>17,18</sup> Hyperdontia was 1.5% of all subjects, which is in the same range (1.2-3%) in the review study by Anthonappa et al.<sup>19</sup> According to Laganà et al. and Stahl et al. mesiodens was the most common form of supernumerary teeth in non-orthodontic and orthodontic patients, with a higher prevalence in orthodontic patients.<sup>11,20</sup> Regarding the prevalence of hypodontia (6.3%), a higher prevalence was found by Vahid-Dastjerdi et al. than in the study, 9.1%, in a retrospective study of 1,751 subjects.<sup>21</sup> In a review by Rakhshan, the prevalence of hypodontia in the permanent dentition, excluding M3, ranged from 0.15 to 16.2%.<sup>22</sup> Baccetti significantly associated second premolar hypodontia with dental anomalies and disorders of dentition development, microdontia of maxillary lateral incisors, ankylosis of deciduous molars, enamel hypoplasia, and palatally displaced teeth.<sup>23,24</sup>

In the study, microdontia and peg-shaped lateral incisors were considered as anomalies and were found in 1.4% of the subjects. Both anomalies were found in 5.2% of children by Albashaireh and Khader.<sup>25</sup> Hua et al. reported the average prevalence of peg-shaped teeth in the general population to be 1.8%, similar to our study, and the most affected were the maxillary lateral incisors, concluded Altug-Atac and Erdem.<sup>16,26</sup> The prevalence of microdontia was reported in the range of 0.5–2.6% and also the most affected were the maxillary lateral incisors by Kjær.<sup>16,27–29</sup>

Ectopic eruption of M1, in which this tooth resorbs the crown of the second deciduous molar during the eruption, was found in 7.1% of the subjects, with an insignificant prevalence in the maxilla relative to the mandible. This impaired tooth development shows a variable prevalence from 2 to 6%.<sup>30-32</sup> The largest study on a sample of 8,041 children, conducted by Salbach et al. diagnosed this disorder in a significantly lower number of subjects (1.3%) and more frequently in the maxilla, in agreement with the data of other authors, without preference for the left or right side.<sup>32–35</sup> Chintakanon and Boonpinon reported ectopic eruption of M1 in a significantly smaller number of subjects (0.75%) with similar prevalences for M1 in the mandible and maxilla.<sup>35</sup> Barberia-Leache et al. found ectopic eruption of M1 with resorption of the m2 crown in 4.3% of children, citing incorrect direction of eruption and also increased mesiodistal diameter of the M1 crown as the main reason.<sup>30,32–35</sup> Other etiologic factors that may lead to ectopic eruption have been reported in the literature to be the inadequate length of the dental arch and a growth deficit in the posterior region.<sup>33</sup> Bjerklin et al. and Baccetti relate this disorder to other genetically determined disorders in dentition development.<sup>24,34</sup> Bjerklin et al. link this to infraocclusion and ankylosis of m2 and ectopic eruption of the upper canine, and Baccetti mentions rotation of the upper lateral incisor in addition to the above.<sup>24,34</sup> In addition, the study by Salbach et al. found a significant association of ectopic eruption of the maxillary first molar with crowding,

lateral malocclusion, and mandibular prognathism.<sup>33</sup> A relationship between ectopic eruption and one or more other dental anomalies may be inferred. In Istria and other regions, premature loss of deciduous teeth of the supporting zone is common.<sup>36,37</sup> In 12.9% of maxillary segments and 18.5% of mandibular segments, M1 erupts in its place due to premature loss of m2. Apart from the fact that the premature loss of m2 due to the mesial eruption of M1 destroys the harmony of the area and width of the crowns of C, P1, and P2, it also provokes an earlier eruption of M1 teeth in the Istrian region is poor, and therefore they are often extracted prematurely.<sup>37</sup> The consequences are reflected in the position of the adjacent teeth, where they are more pronounced in the maxilla and also in the occlusion.<sup>40</sup>

The normal position of the incisor in the dental arch depends on many factors that have long-term effects. Some act before the replacement of the incisors, some act during the replacement, and some act after the replacement of the incisors, when the normal symmetrical positioning of the incisors should take place.<sup>38</sup> Often, disproportions of the space in the dental arch and the width of the crown of the erupting incisors result in a situation where the tooth resorbs the adjacent tooth during the eruption. These phenomena were found to be significantly greater in the maxilla than in the mandible (p = 0.003). In the maxilla, I2 resorbed the crown of the deciduous canine during eruption insignificantly more often than I1 resorbed the crown of the lateral deciduous incisor (p = 0.195). These disturbances are predictors of crowding in the incisor region. Although in the literature, data on crowding of incisors show a wide variation in prevalence (28.4–52.1%) depending on the measured spatial discrepancies, it is considered to be the most common anomaly with the increase in permanent dentition.<sup>41-45</sup> In the present study, crowding of incisors was found to be insignificantly more frequent in the maxilla relative to the mandible (p = 0.133). Other authors found more frequent crowding of incisors in the mandible.<sup>8,43,45</sup> However, Keski-Nisula et al., Borzabadi-Farahani et al., and Gelgör et al. found a lower prevalence of crowding in mandible but significantly higher in the maxilla.<sup>44,46,47</sup> Spacing between incisors was found to be insignificantly lower in the maxilla than the mandible (p = 0.267). Thilander et al. arrived at similar data, and a significantly greater prevalence of spacing was found by Bässler-Zeltman et al.<sup>42,48</sup>

Within the supporting zone, two teeth appear very frequently ectopically in the dental arch due to either genetic instability-P2, or complications during eruption-upper canine, or whose mineralization and eruption time deviate from normal.<sup>49</sup> The ectopic position of the tooth germ was found significantly more frequently in the maxilla than in the mandible (p < 0.001). Bjerklin et al. found atypical germ position in 12.2% and displaced teeth in 7% of subjects.<sup>34</sup> Stemm also found frequently malpositioned lower premolars (P1 14.67%, P2 41.0%).<sup>50</sup> The author reported that many of them were spontaneously upright in normal occlusion during development. According to literature data, the upper canine is ectopically placed in 0.92–4.3% of subjects.<sup>51</sup> In addition to space loss due to premature loss of supporting zone teeth, permanent successors also erupt prematurely due to periapical processes on deciduous teeth. Also, in this study, there was a significantly higher percentage of a premature eruption of teeth of the C-P2 segments of the maxilla compared with the percentage in the mandible (p < p0.001). Late mineralization of the P2, decreased mesiodistal diameter



of the dental crown, the ectopic position of the germ, late eruption, decreased vertical growth of the alveolar process of the segment, infraocclusion of the deciduous tooth, and atypical position of the adjacent teeth are microsymptoms of hypodontia.<sup>49,52</sup> Ankylosis of the deciduous molars was found in 4.5% of subjects, with significant prevalence in the mandible (3.4 vs 1.2%; p = 0.035). Kurol found deciduous molar infraocclusion in 8.9% of subjects, with a tenfold higher incidence in the mandible.<sup>53</sup> A similar incidence has been reported in previous studies, with significant variations likely due to the different ages of subjects at inclusion criteria.<sup>54,55</sup> A significant association of deciduous molar infraocclusion in the mandible and atypical maxillary canine position was reported by Laganà et al.<sup>20</sup> Shalish et al. suggested infraocclusion as an early marker of dental agenesis and palatally displaced canines.<sup>56</sup> Increased prevalence of ectopically placed maxillary canines was found in correlation with hypodontia of the maxillary lateral incisor, but even more frequently in correlation with hypodontia of the mandibular P2.<sup>57</sup>

The ectopic position of the M3 germ is significantly more frequent in the mandible (p < 0.001). According to some authors, with the development of M3, there is a possibility that the ectopic position will be corrected.<sup>58,59</sup> In the absence of space, the ectopic position of the germ is the main reason for M3 impaction, the prevalence of which ranges from 9.5 to 39%.<sup>6,58,60</sup>

Agenesis of M3 was evaluated in this study after the age of thirteen years, although in the literature its initial mineralization was found as early as seven years.<sup>61</sup> In the subjects of this study, it was found in 12.7%, 5.9% in the maxilla, and 6.7% in the mandible. In the other studies, the prevalence was reported between 12.7 and 41%, varying according to the population and age of the subjects. In addition, agenesis showed a greater incidence in the maxilla.<sup>62</sup> There have been studies suggesting associations between agenesis and other dental anomalies, reduced size, and hypodontia of other permanent teeth.<sup>63,64</sup>

## CONCLUSION

Our study showed a similar incidence of various dental anomalies and disturbed dentition development as reported in the literature. The results of this study confirm that the analysis of the orthopantomogram is an important and useful element in the diagnosis and treatment plans for a malocclusion.

## **C**LINICAL **S**IGNIFICANCE

Orthopantomogram analysis can be used as a useful element in diagnosis and treatment plans for dental anomalies and malocclusion.

## **E**THICS **D**ECLARATIONS

This study was approved by the Ethics Committees of Faculty of Medicine, University of Rijeka, and Clinical Hospital Center Rijeka.

"All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5). Informed consent was obtained from all patients for being included in the study."

The study included children and adolescents ages below 18 years. Written informed consent was obtained from the legally authorized representatives/parents/guardians. Legally authorized representatives/parents/guardians could refuse their child's participation, and participation was voluntary. All obtained data were kept strictly confidential.

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