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Synovial Sarcoma: Effect of Treatment on Root Development and Eruptive Potential – A Case Report and Review

Abstract: Overall, the survival rate of people affected by childhood cancer is increasing. It is important for dental professionals to understand the effects cancer treatment can have on growth and dental development. The aim of this case report is to describe the effects of both chemotherapy and radiotherapy on dental development, dental appearance and oral health in a 6-year-old female patient treated for synovial sarcoma. The numerous theories of tooth eruption described in the literature are summarized and this case report shows how, although root development was arrested, tooth eruption still occurred.
CPD/Clinical Relevance: The skeletal and dento-alveolar effects of chemotherapy and radiotherapy for treatment of childhood cancers are explored and exemplified by the case reported. The numerous tooth eruption theories that have been described are also discussed. Interestingly in this case report, tooth eruption still occurred despite incomplete root formation.
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Case report

It is estimated that 1 in every 900 adults between 16 and 44 years is a survivor of cancer.[1] Treatment of cancer generally involves chemotherapy and/or radiotherapy, as well as possible surgical procedures. In general, radiotherapy and chemotherapy can have oral side-effects such as trismus (limited oral movements), ulceration and inflammation of the oral mucosal tissue and risk of bacterial, fungal or viral infections. In addition, it causes a dry mouth (xerostomia), increasing the caries susceptibility, and chewing, swallowing and taste can also be negatively affected. Following radiotherapy to the jaws, there is a risk of osteoradionecrosis. For children/adolescents undergoing such treatments there are additional sequelae such as disturbances in dental development and skeletal growth.

The 6-year-old patient presented to her general medical practitioner, in April 2003, with a painful swelling over her left cheek which had developed rapidly during the previous two weeks following four weeks of pain in the region. She was urgently referred to the Oral and Maxillofacial Department at Addenbrookes Hospital, Cambridgeshire. Clinical examination revealed a firm, smooth, diffuse swelling on the left cheek with drooping left lips and facial asymmetry (Figure 1). Intra-orally, she was in the early mixed dentition with first permanent molars erupted. A significant left lateral open bite extended anteriorly, providing only occlusal contacts on the right side (Figure 2). Radiographic examination showed an abnormal left coronoid process with displacement of the upper teeth towards

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Figure 1. Extra-oral views of patient at initial presentation at 6 years of age. Significant left facial swelling with drooping of left lips and facial asymmetry evident.

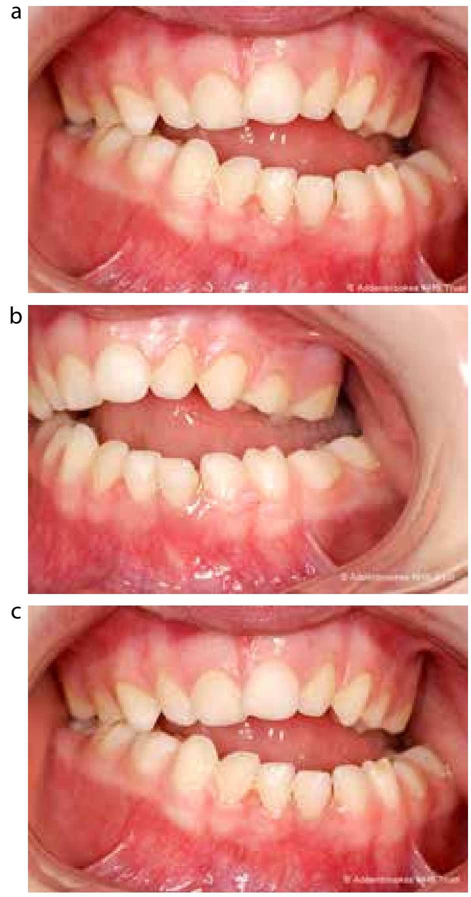

Figure 2. (a–c) Intra-oral views of patient at initial presentation at 6 years of age. All deciduous dentition present with fully erupted first permanent molars. In occlusion, a left lateral open bite extending to the anterior teeth is evident.

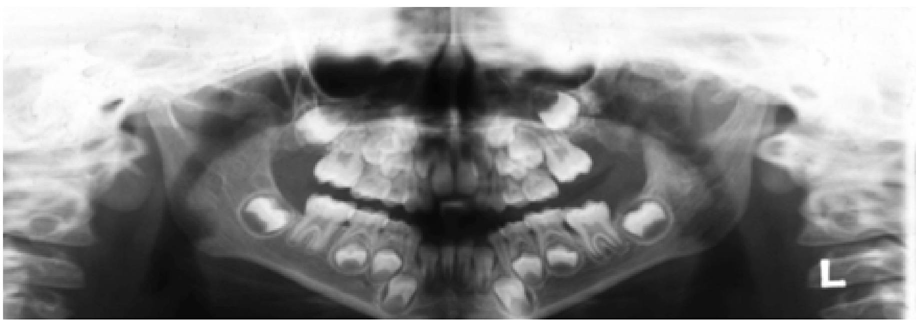

Figure 3. OPG taken in 2003: pre-radiotherapy/chemotherapy. This confirms the patient's early mixed dentition stage with lower central and lateral permanent incisors erupting. The developing permanent dentition shows a normal staging of crown and root development for the patient's age. There seems to be a short left coronoid process and abnormal radio-opacity area on the upper left maxillary buttress region displacing UL7 tooth germ.

the midline (Figure 3). A CT scan confirmed the presence of a large soft mass in the left infra-temporal fossa, which had caused thinning of the zygomatic arch, anterior bowing of the posterior wall of the maxillary sinus, medial displacement of the left pterygoid plate and deformity of the anterior aspect of the mandibular ramus. The alveolus and unerupted maxillary teeth on the left side were also displaced. The diagnosis of synovial sarcoma of the left infra-temporal fossa was made based on the bony deformity and incisional biopsy results.

Treatment involved an initial course of chemotherapy (MMT 953) which provided approximately a 10–20% reduction in tumour size as well as a change in its texture consistent with central necrosis. Owing to the relatively poor response to chemotherapy, resection of the synovial sarcoma was undertaken in September 2003 followed by a course of radiotherapy. The surgical procedure required both a posterior approach via a coronal flap and an anterior approach via a Weber Ferguson 2 incision. Radiotherapy was applied to the whole margin of the operative site in two phases: 50.4 Gy in 28 fractions and the second 9 Gy in 5 fractions for a total of 59.4 Gy in 33 fractions. This involved most of the left mandible, maxilla, eye, pituitary gland, optic chiasm and parotid gland. The side-effects the patient experienced included: xerostomia, trismus and mild erythema of the skin on her face and neck. The latter responded well to 1% hydrocortisone and emolients. An MRI confirmed opacification of the mastoid and left maxillary sinus due to mucosal thickening, which caused congestion and copious gelatinous discharge when she had a cold. On completion of the treatment, severe trismus due to ankylosis of the left TMJ made eating and talking difficult. A bilateral coronoidectomy and peri-articular steroid injections followed by jaw exercises were undertaken in November 2005. On subsequent reviews, the limited mouth opening remained but reasonable mandibular movements were achieved. The severe disruptive effects of radiotherapy and chemotherapy on dental development and growth were also monitored. Although dental eruption occurred, root development, particularly of the lower left premolars, was compromised (Figures 4–7). The UL2 was extracted when approximately 12 years old because of resorption of this tooth by the unerupted UL3 (Figure 6), which allowed for further eruption of UL1 and UL3. Skeletal and soft tissue growth was also affected leading to pan-facial asymmetry (Figure 8).

At 12 years of age, the patient's concern was the appearance of the upper left central incisor and canine on smiling. Orthodontic treatment was avoided as the

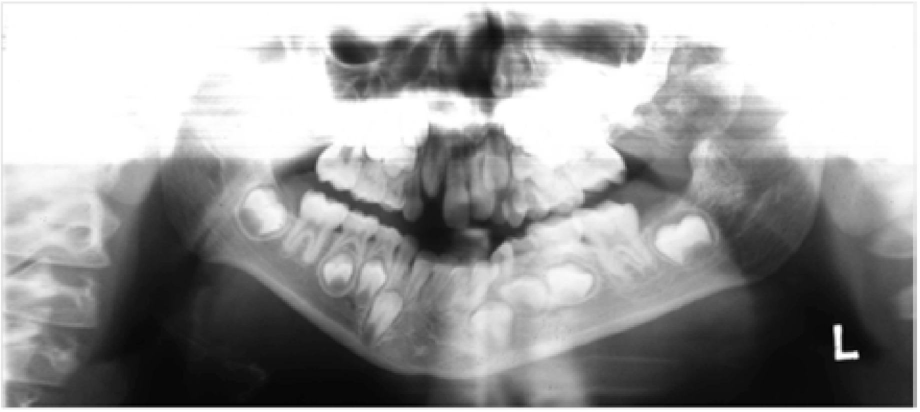

Figure 4. OPG taken in April 2004: post chemotherapy/radiotherapy. The OPG, of grade 2 quality, shows the lower incisors have erupted and root development is progressing. The roots of the lower right canine and premolars are starting to form with apical elongation noted; however, this is not occurring on LL45. Crown formation is complete to the CEJ for lower second molars.

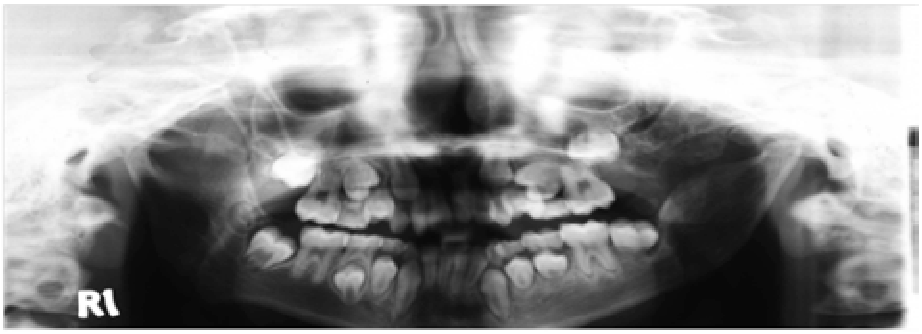

Figure 5. OPG taken in May 2007; 10 years of age. This reflects coronoidectomy has been undertaken already. The incisors and first permanent molars are erupted but have shortened roots. UL12 have not reached the same occlusal level as UR12. Further root development is noted on the lower canines and lower right premolars, albeit in a shortened and pipette-shaped manner, yet lack of development on LL5 root is present. UR8 and LR8 tooth germs are visible.

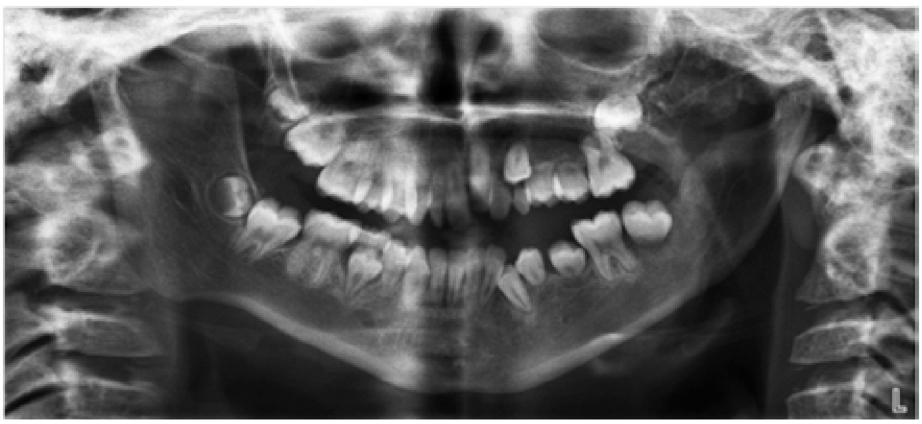

Figure 6. OPG taken in January 2009; 12 years of age. This shows the late mixed dentition stage with only LRE and ULC retained. A left lateral open bite is evident. Generalized shortened and pipette-shaped roots are evident on the permanent dentition. LL45, UL5 and LL7 have erupted despite lack of root formation. UL3 is unerupted and has caused resorption of UL2. UL7 remains high and ectopic.

roots of the existing teeth were already shortened and there was a risk of ankylosis of UL13. Instead, she was referred to a specialist restorative team who provided her with composite build-ups of the UL1 and UL3, disguising UL3 as UL2, improving her smile aesthetics without jeopardizing the longevity of the existing dentition (Figure 9).

Discussion

Synovial sarcoma, radiotherapy and chemotherapy effects

Synovial sarcoma is a rare form of cancer which most commonly occurs in the soft tissues of the extremities near to large joints, eg arms and legs. It has also been found to occur in the head and neck, lung, heart, mediastinum and abdominal wall. It accounts for approximately 8% of all soft tissue sarcomas in the young and approximately 15–20% of cases in adolescent and young adults,[2] affecting males more than females. Despite its name, it does not arise from synovial tissue. The cause is unknown but has been associated with a genetic origin: chromosomal translocation of t(X;18)(p11;q11). It is a serious condition requiring a combination of surgery, radiation and/or chemotherapy and long-term follow up. In a multi-centre retrospective analysis of 62 patients followed up for at least 10 years, a tendency to developing late metastasis with high mortality was noted hence >10 years follow-up advised.[3]

Oral side-effects of radiotherapy and chemotherapy can include infections (eg candidiasis), trismus and reduced salivary flow, which in turn increase the risk of caries. In addition, they can lead to retardation of growth, disturbances in dental development and the rate of craniofacial growth, the latter effects being more significant if treatment is undertaken during peak times of growth and development. Abnormal dental development is characterized by hypodontia, microdontia, enamel hypoplasia, taurodontism, over-retention of primary teeth, increased prevalence of malocclusion and decreased TMJ mobility.[4] Disturbances in root formation are mostly seen when patients are exposed to chemotherapy, radiotherapy or both, at the time of root development. Root development of the permanent dentition is completed approximately 2.5–3 years after eruption. Root formation of the central incisors and first permanent molars starts at approximately 3.5 years of age, with the second permanent molars starting at 7.5 years of age.[5] Disturbances can include: failure of root formation, short roots, V-shaped tapering and blunting of the apical area.[6] Root shortening in survivors, especially when moderate to severe, can have a significant impact on the long-term prognosis of the teeth.[6] However, if a patient has a reasonable occlusion with good oral hygiene and no periodontal disease, minor root shortening may not affect the tooth's lifespan.[6] Therefore, optimal oral health is critical for these patients and often the treatment principle is to preserve what is present and avoid any harm to any teeth or mucosal tissues. Survivors undergoing orthodontic treatment may have risk factors which would need consideration, such as abnormal root morphology, root resorption, increased

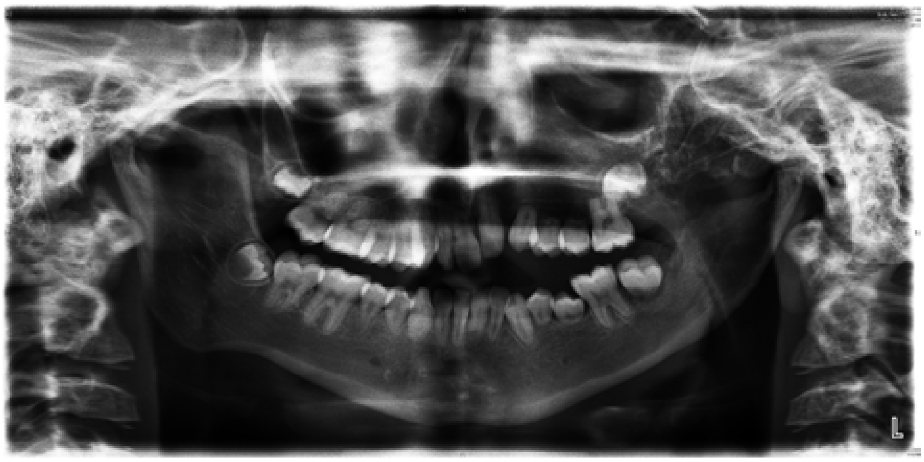

Figure 7. OPG taken in January 2011; 14 years of age. Permanent dentition stage with a marked left lateral open bite and asymmetric growth features; small left condyle, mandibular ramus height and width and angle definition compared to the right side. The UL2 has been removed and UL13 have erupted though still not reached the occlusal plane, possibly ankylosed.

caries risk, periodontitis, cranio-mandibular disorders and pulpal effects.[7] Often, owing to the latter and/or general health factors, orthodontic treatment is avoided. However, when provided, orthodontic treatment should be undertaken 2 years after completion of active cancer treatment or re-occurrence.[1] In addition, the treatment mechanics should aim at minimizing the risk of root resorption; employing simple mechanics, low forces, considering early debond, if necessary, and avoiding the lower arch.[1] A study reported no harmful side-effects of orthodontic treatment in long-term survivors of childhood cancer.[8]

Review of tooth eruption process

Tooth eruption has been defined as the developmental process where a tooth moves in an axial direction from its alveolar crypt to its position of function within the oral cavity.[9] Despite extensive research, the exact mechanism of tooth eruption remains unknown.[9–14] The complex nature of the eruptive process is possibly responsible for this, in addition to the lack of understanding of the biological nature of the mineralized tissue in comparison to other tissues.[15] The rate of tooth eruption varies between the five main stages (Table 1). It is usually slow in the intra-osseous phase, accelerates as the tooth penetrates the mucosa and then decreases as the tooth approaches the occlusal plane. The rate of tooth movement is also reflected on the root formation stages; eruption accelerating as the root forms and slowing as the apical foramen narrows.Theories of tooth eruption include the following.

1. Root growth theory

This supports the view that, as the root grows, it produces the eruptive force. However, eruption of rootless teeth is seen clinically in patients who have dentine dysplasia Type I and following irradiation of the head and neck region.[16] A 4-year-old patient who received irradiation following a diagnosis of embryonal rhabdomyosarcoma in the submandibular region experienced cessation of root development but normal mandibular tooth eruption.[17] Therefore, root formation *per se* may not be essential but it may speed tooth eruption.

2. Periodontal ligament formation/fibroblast theory

The periodontal ligament (PDL) has been viewed as a major contributor by many studies.[12,18,19,20] In theory, the cross-linking and shrinkage of collagen fibres and fibroblast contraction within the PDL lead to tooth eruption. The direction of PDL fibres and high metabolic turnover, found in the PDL during tooth eruption in rats, further supports this concept.[21,22,23] However, rodent teeth erupt continuously throughout life and extrapolation to humans may not be appropriate. Rootless teeth have, by definition, little or no periodontal ligament present, yet they still erupt. It may be that periodontal ligament is not the sole factor but may play a role in the process.

3. Alveolar bone remodelling

This theory bases tooth eruption on the opposing deposition and resorption of alveolar bone surrounding the tooth. Without bone resorption via osteoclasts occlusal to the erupting tooth, eruption does not occur. In osteopetrotic rats where there is failed/

a b c

Figure 8. Extra-oral views of patient when 14 years old upon completion of anti-cancer treatment. A significant left-sided pan-facial asymmetry affecting the hard and soft tissues in the regions of the eyes, nose, ears, lips and mandibular angle evident.

a b c


Figure 9. Intra-oral views of patient when 14 years old upon completion of anti-cancer treatment. All permanent teeth present except for the UL2. UL1 and UL3 have had composite build-ups to improve smile aesthetics. A significant upper dental centerline shift to the left-hand side and left lateral open bite was accepted.

	Eruption Stages	Carlson's study findings for human premolar root development and its relation to eruption
1	Pre-eruptive movements before crown completion	Tooth eruption commences only after formation of the crown is complete
2	Intra-osseous stage	Root development starts without movement of the crown and at the expense of basal bone
3	Mucosal penetration	
4	Pre-occlusal eruption: just before reaching functional occlusion	Root growth occurs throughout pre-occlusal eruption right up to occlusal plane Cessation of root formation occurs at the expense of basal bone
5	Post-occlusal eruption: continuation of eruption throughout	Continuation of tooth eruption occurs with alveolar process growth, which occurs throughout life

Table 1. Tooth eruption stages matched with phases of human premolar root development statements drawn from the radiological findings by Carlson.[32]

decreased bone resorption, fully formed teeth fail to erupt.[24] However, which tissue initiates and controls bone remodelling is not clear. It has been suggested that the dental follicle may be responsible via ecto-mesenchymal interactions with the enamel organ, once crown formation is complete.[25]

4. The follicular theory

This proposes that the dental follicle co-ordinates tooth eruption via osteoclastic activity occlusally and bone formation apically to the erupting tooth. This regulatory function was proved, as removing the coronal part of the dental follicle was shown to prevent alveolar bone resorption and removing the basal part prevented alveolar bone formation.[26] Furthermore, when the crowns of permanent mandibular premolars in dogs were removed and replaced with crown shells or metal or silicone replicas in the follicles, the crowns/substitutes still erupted.[27] Even when no substitute was placed, if the follicle was preserved, characteristic features of tooth eruption still occurred. Most experimental studies where the role of the dental follicle has been explored have had reduced enamel epithelium attached to it.[28] The latter is tightly bound to the follicle and separated from alveolar bone surfaces by loose vascular connective tissue epithelium. However, one study was able to remove the dental follicle on 13 mandibular premolars in dogs by the use of EDTA.[29] The crowns with the enamel organ but without the dental follicle did not erupt; crowns from which only the enamel organ was removed and replaced in the crypt did erupt and so the enamel organ does not appear to cause tooth eruption on its own. The dental follicle is essential for tooth eruption to occur.[29]

5. The gubernaculum canal theory

The gurbernacular canal links the tooth follicle with the overlying gingiva behind the deciduous dentition and it may aid the eruption of the permanent successor by providing an eruptive pathway. However, Cahill and Marks studied its role with histological and radiographic examinations in nine beagle dogs and concluded that the dental follicle was the only structure required for both the eruption process and bone formation at the base of the bony crypt.[16] However, some controversy still exists.[30]

6. The hydrostatic theory and pulpal growth

Hydrostatic forces are generated within the pulp or by the apical vasculature as a result of differential pressures, which could aid tooth eruption. However, eruption still occurs when pulp is removed and drugs reducing blood pressure seem to have no effect on eruption.[14]

7. Genetic components

Disturbed dental eruption is observed in numerous disorders known to affect bone remodelling, enamel formation, gingival overgrowth and certain syndromes. Some links have been established between the genetic aetiologies of some of these conditions and eruption, eg cleidocranial dysplasia caused by mutation of Cbfa1. At a molecular level, the ostoblast-osteoclast signalling via the RANKL/OPG pathway, and factors affecting this, are likely to be a key in tooth eruption regulation. The osteoblast transcription factor, Cbfa1 (Runx2), is expressed at high levels by the dental follicle cells and has been shown to have a role in tooth eruption.[31]

Tooth eruption theories in relation to the case report

In this case, dental eruption occurred for all permanent teeth expected for her age (except for UL7), in spite of incomplete or lack of root formation. Although radiotherapy was targeted to the left side of the face, teeth on the right side were also affected, though not as extensively. The lower left premolars had absent roots, whereas the lower right premolars and canine developed shortened and pipette-shaped roots. A significant left lateral open bite and facial asymmetry developed following the chemotherapy and radiotherapy, most likely caused by retardation of alveolar and skeletal growth. From the summary table (Table 2), exploring the relevance of the different eruption theories discussed, it appears that the major contributors in this case were alveolar bone growth and the follicular theories and the minor contributors; the periodontal formation, root growth and hydrostatic theories.

Theories	Case Report Relevance
Alveolar bone remodelling	Overall skeletal growth was affected, as is evident by the small condyle and mandible on the left and panfacial asymmetry that ensued, also leading to a marked left lateral open bite. Teeth still erupted.
Periodontal fibroblast theory	Since root development was severely disrupted, it is assumed that reduced periodontal fibres also developed, yet even the rootless teeth still erupted.
Root growth theory	Rootless teeth erupted. Hence root growth may not necessarily be required for eruption.
Follicular theory	Need histological studies for a definite answer. This theory cannot be excluded.
Hydrostatic theory	Cannot determine its effect with radiographic analysis. However, the pulp was not fully formed on some teeth (eg LL5), yet they erupted.

Table 2. Summary table of eruption theories and their relevance in case reports.

Conclusions

Several eruption theories have been proposed. However, owing to the complex nature of the process, the mechanism of tooth eruption is likely to be multi-factorial.Both radiotherapy and chemotherapy can have effects on tooth structure (crown and root development) and the surrounding tissues of the oro-facial region. They can lead to abnormal dental development, usually characterized by hypodontia, microdontia, hypoplasia and abnormal root development. This case report demonstrated that tooth eruption can occur despite incomplete root formation caused by chemotherapy and radiotherapy treatment in a patient with a developing dentition. The age of the patient when receiving this treatment may be a key factor when predicting its effect on tooth development.

Acknowledgements

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References

1. Dahllöf G, Huggare J. Orthodontic considerations in the pediatric cancer patient: a review. *Semin Orthod* 2004; **10**: 266–276.
2. Weiss SW, Goldblum J. *Malignant Soft Tissue Tumours of Uncertain Type: Enzinger and Weiss's Soft Tissue Tumours*. St Louis, Missouri: CV Mosby, 2001: pp1483–1571.
3. Krieg AH, Hefti F, Speth BM *et al*. Synovial sarcomas usually metastasize after >5 years: a multicenter retrospective analysis with minimum follow-up of 10 years for survivors. *Ann Oncol* 2011; **22**: 458–467.
4. Kaste SC, Goodman P, Leisenring W *et al*. Impact of radiation and chemotherapy on risk of dental abnormalities. A report from the childhood cancer survivor study. *Cancer* 2009; **115**: 5817–5827.
5. Haavikko K. The formation and the alveolar and clinical eruption of the permanent teeth. An orthopantomographic study. *Suom Hammaslaak Toim* 1970; **66**: 103–170.
6. Holtta P, Holvi L, Saarinen-Pihkala UM, Peltola J, Alaluusua S. Disturbed root development of permanent teeth after paediatric stem cell transplantation. Dental root development after SCT. *Cancer* 2005; **103**: 1484–1493.
7. Thilander BL. Complications of orthodontic treatment. *Curr Opin Dent* 1992; **2**: 28–37.
8. Dahllöf G, Jönsson A, Ulmner M, Huggare J. Orthodontic treatment in long-term survivors after pediatric bone marrow transplantation. *Am J Orthod Dentofacial Orthop* 2001; **120**: 459–465.
9. Schour I, Massler M. Bureau of public relations. The development of human dentition. *J Am Dent Assoc* 1941; **28**: 1153–1160.
10. Magnusson B. Tissue changes during molar tooth eruption. *Trans R Sch Dent Stockh Umea* 1968; **13**: 1–122.
11. Ten Cate AR**.** The mechanism of tooth eruption. In: *Biology of the Periodontium*. Melcher AH, Bowen WH (eds). New York: Academic Press Inc, 1969: pp91–103.
12. Berkovitz BK. The effect of root transection and partial root resection on the unimpeded eruption rate of the rat incisor. *Arch Oral Biol* 1971; **16**: 1033–1043.
13. Marks SC, Cahill DR. Experimental study in the dog of the non-active role of the tooth in the eruptive process. *Arch Oral Biol* 1984; **29**: 311–322.
14. Sandy JR. Tooth eruption and orthodontic movement. *Br Dent J* 1992; **172**: 141–149.
15. Gorski JP, Marks SC Jr. Current concepts of the biology of tooth eruption. *Crit Rev Oral Biol Med* 1992; **3**: 185–206.
16. Cahill DR, Marks SC Jr. Tooth eruption: evidence for the central role of the dental follicle. *J Oral Pathol* 1980; **9**: 189–200.
17. Carl W, Wood R. Effects of radiation on the developing dentition and supporting bone. *J Am Dent Ass* 1980; **101**: 646–648.
18. Berkovitz BK, Thomas NR. Unimpeded eruption in the root – resected lower incisor of the rat with a preliminary note on root transaction. *Arch Oral Biol* 1969; **14**: 771–780.
19. Pitaru S, Michaeli Y, Zajicek G, Weinreb MM. Role of attrition and occlusal contact in the physiology of the rat incisor: the part played by the periodontal ligament in the eruptive process. *J Dent Res* 1976; **55**: 819–824.
20. Michaeli Y, Pitaru S, Zajicek G. Localized damage to the periodontal ligament and its effect on the eruptive process of the rat incisor. *J Periodontal Res* 1982; **17**: 300–308.
21. Melcher AH, Correia MA. Remodelling of periodontal ligament in erupting molars of mature rats. *J Periodontal Res* 1971; **6**: 118–125.
22. Perera KA, Tonge CH. Fibroblast cell population kinetics in the mouse molar periodontal ligament and tooth eruption. *J Anat* 1981a; **133**: 281–300.
23 Perera KA, Tonge CH. Metabolic turnover of collagen in the mouse molar periodontal ligament during tooth eruption. *J Anat* 1981b; **133**: 359–370.
24. Cotton WR, Gaines JF. Unerupted dentition secondary to congenital osteopetrosis in the Osborne-Mendel rat. *Proc Soc exp Biol Med* 1974; **146**: 554–561.
25. Marks SC Jr, Schroeder HE. Tooth eruption: theories and facts. *Anat Rec* 1996; **245**: 374–393.
26. Cahill DR, Marks Jr SC. Regional control by the dental follicle of alterations in alveolar bone metabolism during tooth eruption. *J Oral Pathol Med* 1987; **16**: 164–169.
27. Cahill DR, Marks SC Jr. Chronology and histology of exfoliation and eruption of mandibular premolars in dogs. *J Morph* 1982; **171**: 213–218.
28. Andreasen JO, Petersen JK, Laskin DM. *Textbook and Colour Atlas of Tooth Impactions. Diagnosis Treatment and Prevention*. Chapter 1: Theories and mechanisms of tooth eruptions. Copenhagen, Denmark: Munksgaard, 1998: p29.
29. Larson EK, Cahill DR, Gorski JP, Marks Jr SC. The effect of removing the true dental follicle on premolar eruption in the dog. *Arch Oral Biol* 1994; **39**: 271–275.
30. Ferreira DCA, Fumes AC, Consolaro A, Nelson-Filho P, De Queiroz AM, De Rossi A. Gubernacular cord and canal – do these anatomical structures play a role in dental eruption? *RSBO* 2013; **10**: 167–171.
31. Wise GE, Frazier-Bowers S, D'Souza RN. Cellular, molecular and genetic determinants of tooth eruption. *Crit Rev Oral Biol Med* 2002; **13**: 323–334.
32. Carlson H. Studies on the rate and amount of eruption of certain human teeth. *Am J Orthod* 1944; **30**: 575–588.