

Oral sequelae and rehabilitation considerations for survivors of childhood cancer

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Key points

Provides deeper understanding of the effects of chemotherapy and radiotherapy on the developing oral and dental tissues.

Highlights long-term side effects of childhood head and neck cancer.

Demonstrates the complex nature of dental rehabilitation of childhood head and neck cancer patients.

Advances in the treatment of childhood cancer including chemotherapy, radiotherapy and surgery have resulted in increased numbers of survivors. Due to the side effects of oncology treatment, childhood cancer survivors are at risk of long-term medical problems. Children who have received chemotherapy or head and neck radiotherapy are at a higher risk of abnormal dental development, which can result in long-term complications regarding dental treatment and oral rehabilitation. Associated dental abnormalities include tooth agenesis, atypical tooth development and delayed eruption. This article describes long-term treatment planning implications for childhood cancer survivors highlighted by reference to three cases.

Introduction

The number of childhood cancer survivors is increasing due to the improvement of available treatment options including radiotherapy, chemotherapy and surgery. In the United Kingdom, the five-year survival rate for children presenting with malignant disease has increased from 25% in the 1960s to 75% in the 1990s; and around one in 715 young adults have had cancer in childhood.^{1,2} However, the side effects of oncology treatment in childhood increases the risk of long-term medical problems for survivors. These can include endocrine deficiencies, organ toxicity and surgical deformities, as well as an impaired quality of life due to consequences such as infertility, sensory impairment, educational difficulties and struggle with social relationships.^{3,4} Recognised long-term consequences of childhood cancer, particularly in head and neck cancer survivors, also

include anomalies to the dentition. This article describes the common dental anomalies associated with childhood cancer, as well as a report of three patients previously treated for childhood cancer which illustrate the long-term complications associated with oral and dental rehabilitation of such patients. The oral and dental care for the early side effects of chemotherapy and radiotherapy are not discussed in detail and further reading can be found elsewhere.⁵

Prevalence of dental anomalies in childhood cancer survivors

The prevalence of dental and maxillofacial abnormalities have been shown to be highest in children who receive head and neck radiotherapy, compared to those who receive chemotherapy alone.⁶ Furthermore, abnormalities are more severe in children who received radiation at an earlier age and at higher doses.^{6,7} One of the largest studies following head and neck childhood cancer patients is the Intergroup Rhabdomyosarcoma Study.⁸ This study followed a cohort of 4,292 patients diagnosed with rhabdomyosarcoma (RMS) of the head and neck who received systemic chemotherapy, with or without irradiation, and reported that a third of

survivors developed dental anomalies. Kaste *et al.* studied the dental panoramic tomograms of 22 long-term survivors of head and neck RMS and found radiographically identifiable dental abnormalities in 77% of patients.⁹ A similar study investigating the long-term craniofacial effects of ten patients treated for RMS reported that 80% of patients had clinical or radiographic dentofacial abnormalities.¹⁰

The prevalence of dental anomalies is also higher in children who have received treatment for childhood cancer in regions other than the head and neck. Avşar *et al.* followed 96 childhood cancer survivors treated with chemotherapy whose diagnoses included bone, blood, liver and muscle malignancies and reported that 70% had dental anomalies.¹¹ When compared to a group of healthy subjects, this prevalence was significantly higher in the survivor group. Maciel *et al.* compared 56 survivors treated for acute lymphoblastic leukaemia in childhood to 56 healthy controls and the prevalence of dental anomalies was significantly higher in the survivor group, with 80.4% presenting with at least one dental anomaly.⁷ In a similar study, survivors of childhood lymphoblastic leukaemia who received chemotherapy, alone or in combination with cranial irradiation, were followed and dentofacial abnormalities

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were reported in 94% of patients.¹² Therefore, it should be recognised that dental anomalies are a significant long-term side effect of childhood cancer treatment.

Why do dental anomalies occur in childhood cancer patients?

Development of the primary dentition commences at around eight weeks *in utero* and ends at around three years of age. The development of the secondary dentition commences at around three to four months post-partum and ends at around 16 years of age (excluding the third molars). Stages of tooth development alternate between: a) morphodifferentiation of ameloblasts (enamel forming cells), odontoblasts (dentine forming cells) and cementoblasts (cementum forming cells); b) matrix deposition; and c) calcification. The developing dentition is most susceptible to damage from radiotherapy and chemotherapy before morphodifferentiation and calcification, and oncological therapy at this stage may result in tooth agenesis.¹⁰ Irradiation or chemotherapy at a later stage in dental development, such as matrix deposition and calcification, may result in abnormal development of the dental tissues, resulting in microdontia, enamel hypoplasia, incomplete calcification of enamel and arrested root development.¹³

Radiation causes damage to cells by direct damage through the ionisation of cell structures (for example, DNA and RNA) and indirect damage through the ionisation of water molecules. This can interrupt the normal cell cycle, with cells most susceptible to damage during periods of increased mitotic activity. Direct irradiation to the developing tissues of the face causes osteocyte death, microvascular injury, periosteal damage, fibrous replacement of marrow spaces and can result in tissue hypoplasia.^{8,10,13,14,15,16} The site and severity of hypoplasia depends on the radiation dose, age of patient and tissues within line of radiation beam.^{10,15} Patients who have received irradiation to the head and neck have significantly poorer healing ability because of endarteritis obliterans and reduced tissue cellularity.¹⁷ The long-term sequelae of radiation damage of the oral and dental tissues are listed in Table 1.

When the radiation dose is sufficiently high it causes odontogenic cell death, regardless of their stage in the cell cycle. This leads to arrested tooth and tooth-root development,

Tissue	Long-term sequelae
Bone	Retarded bone development
	Impaired bone healing
Teeth	Tooth agenesis (hypodontia)
	Hypoplasia (enamel/dentine)
	Microdontia
	Atypical root morphology
	Taurodontism
	Delayed/arrested tooth development
	Delayed exfoliation of primary dentition
	Delayed eruption
Soft tissues	Abnormal occlusal relationships
	Xerostomia (salivary gland dysfunction)
	Trismus
	Taste disturbances (damage to papillae of tongue)
	Soft tissue necrosis
	Scar tissue formation
Facial deformities	

Box 1 Long-term sequelae of chemotherapy on the dentition

- Long-term sequelae
- Tooth agenesis (hypodontia)
 - Hypoplasia (enamel/dentine)
 - Microdontia
 - Atypical root morphology
 - Taurodontism
 - Supernumerary teeth



Fig. 1 Labial view of case one, showing mild crowding and class III occlusion

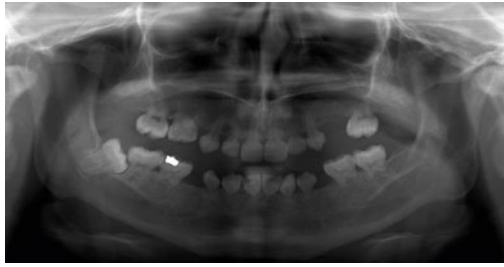


Fig. 2 Dental panoramic tomogram of case one, showing atypical root morphology of all teeth except 48



Fig. 3 Labial view following tooth whitening and composite build-ups



Fig. 4 Occlusal views of case two, showing distribution of maxillary teeth and palatal

as well as tooth agenesis. During tooth development radiation can affect amelogenesis, dentinogenesis and cementogenesis, causing disturbed tooth development.^{12,18} The minimum radiation dose to cause dental defects in humans is unknown, however, human tooth development is halted by 30 Gy. Mature ameloblasts can be damaged by 10 Gy of direct irradiation and late dental defects have been reported with as little as 4 Gy doses.^{9,15} In animal studies, doses ranging from two Gy to 50 Gy have been shown to cause dental defects.^{19,20}

Chemotherapy is targeted at rapidly proliferating cells in attempt to destroy malignant cells. There are many chemotherapeutic agents which have differing modes of action by targeting different stages of the cell cycle. Ameloblasts and odontoblasts are susceptible to damage from chemotherapy depending on their position in the cell cycle. Unlike radiotherapy, cells in non-proliferative phases are unaffected by chemotherapy. Dental defects attributed to chemotherapy include arrested root development, inhibition of dentin formation, and enamel defects.¹³ Chemotherapy received during the ages of dental development can cause dental anomalies, which are listed in Box 1.

Case reports

Case one

An 18-year-old female presented to a joint orthodontic and restorative dentistry clinic concerned about the appearance of her crowded dentition. At ten months of age she was diagnosed with stage IV neuroblastoma in the thorax with liver metastases. She received systemic chemotherapy (busulphan) followed by a stem cell transplant. Side effects of her childhood cancer treatment included hearing loss, bronchiectasis, and hypothyroidism. She had received regular dental examination and oral disease prevention care by a paediatric dentistry department before referral to the restorative dentistry department.

Mild crowding was present in the maxillary and mandibular anterior dentition and she had an edge-to-edge, class III malocclusion (Fig. 1). All premolars and second molars were missing and the second deciduous molars were still present in the upper right, lower right and lower left quadrants. All erupted teeth had normal crown morphology, colour and enamel consistency. Radiographic examination revealed atypical root morphology affecting all mandibular and maxillary teeth with

exception of the 48 (Fig. 2). Less than 10% root development was present in the mandibular dentition and the maxillary molars. The maxillary canines and incisors had narrow roots, with 50–70% normal root length.

Orthodontic treatment was contraindicated due to the atypical root morphology. Instead, tooth whitening and direct composite veneers were provided. The dentition was whitened from a shade A3 to a shade A2. Alginate impressions were taken for study models and the 12, 11, 22 and 32 were waxed up to improve aesthetics. A suck down stent of the prescribed wax up was used to build up the 12, 21, 22 and 32 with shade A2 composite (Fig. 3). The patient has since been kept under regular review.

Case two

A 15-year-old male with a history of head and neck RMS presented with mobility of his maxillary lateral incisors and concerns regarding the prognosis of his dentition. At three years of age, he was diagnosed with left paranasal RMS which was treated with pre-operative chemotherapy (epirubicin, radiotherapy 54 Gy). Surgical excision of the tumour was followed by nasal reconstruction. Aside from regular review with plastics, ENT and oncology specialities, there was no other relevant medical history. He had received regular dental examination, oral disease prevention advice and simple restorations by a paediatric dentistry department before referral to the restorative dentistry department.

All erupted teeth had normal crown morphology, colour and enamel consistency. The 12 and 22 were Millers grade II and II mobile respectively (Fig. 4).²¹ There was bleeding on probing and suppuration at the gingival margin of the 22 with a 5 mm periodontal pocket affecting the palatal aspect. On radiographic examination, the entire maxillary dentition had atypical root morphology with less than 10% normal root length developed (Fig. 5). The mandibular dentition displayed atypical root morphology, affecting the 46, 47 and 36 with approximately 40–50% root length developed along with narrow, tapered roots. The 17, 47, 23 and 38 were present but unerupted, with no evidence of development of the 28, 18 and 48. There was widening of the periapical periodontal ligament of the 22 and it responded negatively to sensibility testing. Diagnoses included atypical root morphology, delayed eruption and perio-endo lesion of the 22.



Fig. 5 Dental panoramic tomogram of case two, showing atypical root morphology of 46, 47, 36 and entire maxillary dentition



Fig. 6 Extracted 22, showing degree of root shortening as a side effect of radiotherapy to the maxilla in childhood



Fig. 7 Gingival veneer replacing 22 and 23



Fig. 8 Maxillary partial cobalt-chrome denture with occlusal load and clasp spread between all maxillary teeth

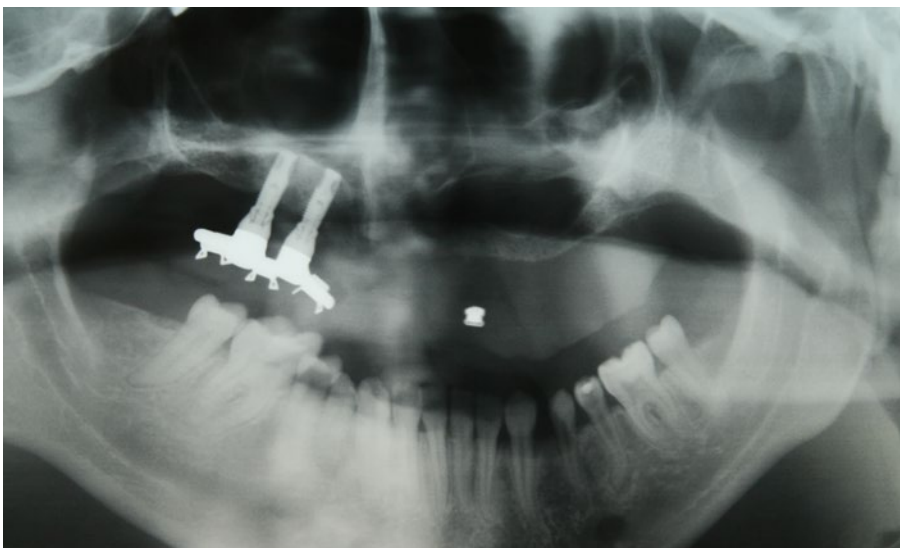


Fig. 9 Dental panoramic tomogram of case three, showing original distribution of implants and implant-retained bar

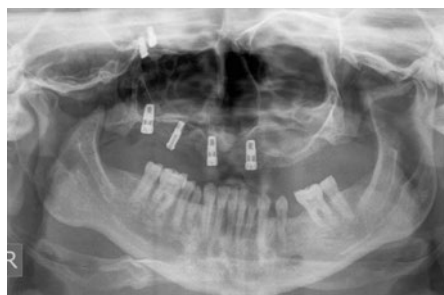


Fig. 10 Dental panoramic tomogram following the placement of two implants in anterior maxilla and two orbital implants

The 22 was extracted under local anaesthetic prophylactic antibiotic cover (amoxicillin 500 mg PO stat plus amoxicillin 250 mg tds seven days) (Fig. 6). Immediate replacement of 22 was provided using a cantilever fibre-reinforced composite (FRC) resin retained bridge (RRB) using the 21 as the abutment. A labial FRC splint plus composite restorations splinting the 13, 12 and 11 were provided to stabilise the 12. At a one-year review, there was no evidence of further eruption of the 23. To prevent overloading of the already compromised maxillary dentition, a gingival veneer was constructed with 22 and 23 pontics incorporated into the design (Fig. 7). Although the patient was satisfied with the aesthetics, the gingival veneer did not fulfil his functional requirements during mastication. Therefore, a maxillary partial cobalt-chrome denture overlaying and clasping all posterior teeth was constructed to replace 22 and 23 (Fig. 8). The overlays provided an increase in occlusal vertical dimension to allow restoration of the 22/23 space, as well as distribution of occlusal forces between all posterior teeth to prevent overloading. Multiple clasping of all posterior tooth units distributed denture and occlusal loads between posterior teeth. He was warned of the uncertain prognosis of his remaining maxillary teeth and remains under regular review.

Case three

A 20-year-old female presented with poor denture stability. She had been treated previously at another specialist unit who provided her with an implant-retained overdenture. At ten months old she was diagnosed with RMS of the right ocular muscle and was treated at three years old with systemic chemotherapy (vincristine, actinomycin D, and cyclophosphamide), surgical excision of the tumour, and head and neck radiotherapy (54 Gy). As a result of the treatment for RMS she developed focal epilepsy.

On examination, she had a right orbital prosthesis retained by glue. Her maxillary dentition had failed to develop, however, her mandibular dentition had developed normally with all teeth present except for missing third molars. Gross caries was present in 35 and radiographic examination revealed periapical pathology. She had two endosseous implants in the right maxilla with an implant-retained cast bar and clip-retained overdenture (Fig. 9). The denture was loose due to the unilateral distribution of implants and the

fulcrum around the implant-retained bar. Diagnoses included aplasia of the maxillary dentition, caries and asymptomatic periapical periodontitis 35, and loose denture.

Initial treatment consisted of the provision of a milled implant-retained bar with two locator attachments, with the aim to improve denture retention. Unfortunately, no improvement in retention was gained, therefore two further endosseous implants were placed in the anterior maxilla (Fig. 10). Furthermore, two endosseous implants were placed in the supraorbital margin of the frontal bone to provide an implant-retained orbital prosthesis. Magnetic abutments were placed on the oral implants and new magnet-retained overdenture was provided (Fig. 11). A new magnetic-retained orbital prosthesis was also provided (Fig. 12). The patient has since been kept under regular review.

Discussion

There is a paucity of available literature regarding the oral rehabilitation of childhood cancer survivors, and therefore treatment planning should be conducted on a case-by-case basis. Likewise, there is currently no long-term evidence regarding the prognosis of teeth with atypical root morphology or significantly shorted roots and therefore close review of such patients is recommended.

These three cases outline the late side effects of chemotherapy and radiotherapy to the dentition and the clinical implications of restoring such dentitions. In case one, atypical root morphology meant orthodontic treatment was contraindicated due to the susceptibility of pathological mobility and further root resorption. Instead, a simpler treatment plan was followed to meet the patient's needs and limit potential complications. In case two, reduced periodontal support left the dentition susceptible to pathological mobility from occlusal forces and periodontal disease progression, which led to the unpredictable loss of teeth. Furthermore, the remaining teeth were poor abutments due to significantly reduced root length; therefore, restoration of edentulous spaces was complicated. Although resin bonded bridgework was successful in the short term to replace one tooth unit, when designed to replace two tooth units the bridge failed, due to occlusal interferences. Both removable options (gingival veneer and removable partial denture) were designed to apply minimal forces to the remaining dentition and prevent overloading of



Fig. 11 Maxillary occlusal view of implants with magnet housing



Fig. 12 Magnetic implant-retained overdenture in situ

abutments. In case three, the maxillary alveolar ridge was atrophic with unfavourable anatomy as a result of tissue hypoplasia and tooth agenesis from radiotherapy treatment in childhood. Therefore, endosseous implants were placed to provide the patient with retention for a removable dental prosthesis. It is important to recognise that patients who have received irradiation to the head and neck have significantly poorer healing ability due to hypoxia and hypocellularity of the tissues.²² Although there are no studies reporting the success of implants placed for survivors of head and neck cancer, implant survival in patients

who have received radiation for head and neck cancer in adulthood have a significantly lower success rate.²³ Furthermore, dental implant placement can lead to compromised healing, reduced osseointegration and serious infection such as osteoradionecrosis. It is, therefore, important that such patients are appropriately referred to a restorative dentistry specialist or consultant for treatment and restoration.

Conclusions

Childhood cancer survivors are likely to have significant long-term oral and dental

complications because of oncology treatment. Oral and dental treatment can be complex due to the presence of dental anomalies and reduced vascularity of the bone and soft tissues as a consequence of radiotherapy. Due to the paucity of evidence regarding the oral rehabilitation of childhood cancer survivors, individualised treatment planning is required for every case. In children who have received head and neck radiotherapy, the long-term success of implant-retained prostheses is unknown and carries a small but significant risk of osteoradionecrosis. It is important that the multidisciplinary care for childhood cancer survivors includes early input from a restorative dentistry specialist or consultant to plan any potential long-term oral and dental rehabilitation.

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References

1. Kroll M E, Passmore S J, Stiller C A *et al*. Childhood Cancer. In Toms J R (ed) *Cancerstats monograph 2004: cancer incidence, survival and mortality in the UK and EU*. pp 63–72. London: Cancer Research UK, 2014.
2. Campbell J, Wallace W H B, Bhatti L A *et al*. *Childhood Cancer in Scotland: Trends in Incidence, Mortality, and Survival, 1975–1999*. Edinburgh: Information & Statistics Division, 2004.
3. Stevens M C, Mahler H, Parkes S. The health status of adult survivors of cancer in childhood. *Eur J Cancer* 1998; **34**: 694–698.
4. Hudson M M, Mertens A C, Yasui Y *et al*. Health status of adult long-term survivors of childhood cancer: a report from the Childhood Cancer Survivor Study. *JAMA* 2003; **290**: 1583–1592.
5. Hancock P J, Epstein J B, Sadler G R. Oral and dental management related to radiation therapy for head and neck cancer. *J Can Dent Assoc* 2003; **69**: 585–590.
6. Jaffe N, Toth B B, Hoar R E *et al*. Dental and maxillofacial abnormalities in long-term survivors of childhood cancer: effects of treatment with chemotherapy and radiation to the head and neck. *Pediatrics* 1984; **73**: 816–823.
7. Maciel J C, de Castro C G Jr, Brunetto A L, Di Leone L P, da Silveira H E. Oral health and dental anomalies in patients treated for leukemia in childhood and adolescence. *Paediatr Blood Cancer* 2009; **53**: 361–365.
8. Raney R B, Maurer H M, Anderson J R *et al*. The Intergroup Rhabdomyosarcoma Study Group (IRSG): Major Lessons From the IRS-I Through IRS-IV Studies as Background for the Current IRS-V Treatment Protocols. *Sarcoma* 2001; **5**: 9–15.
9. Kaste S C, Hopkins K P, Jenkins J J. Abnormal odontogenesis in children treated with radiation and chemotherapy: imaging findings. *AJR Am J Roentgenol* 1994; **162**: 1407–1411.
10. Estilo C L, Huryn J M, Kraus D H *et al*. Effects of therapy on dentofacial development in long-term survivors of head and neck rhabdomyosarcoma: the memorial sloan-kettering cancer center experience. *J Paediatr Hematol Oncol* 2003; **25**: 215–222.
11. Avşar A, Elli M, Darka O, Pinarli G. Long-term effects of chemotherapy on caries formation, dental development, and salivary factors in childhood cancer survivors. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2007; **104**: 781–789.
12. Sonis A L, Tarbell N, Valachovic R W, Gelber R, Schwenn M, Sallan S. Dentofacial development in long-term survivors of acute lymphoblastic leukemia: a comparison of three treatment modalities. *Cancer* 1990; **15**: 2645–2652.
13. Goho C. Chemoradiation therapy: effect on dental development. *Paediatr Dent* 1993; **15**: 6–12.
14. Guyuron B, Dagsy A P, Munro I R, Ross R B. Effect of irradiation on facial growth: a 7- to 25-year follow-up. *Ann Plast Surg* 1983; **11**: 423–427.
15. Fromm M, Littman P, Raney R B *et al*. Late effects after treatment of twenty children with soft tissue sarcomas of the head and neck. Experience at a single institution with a review of the literature. *Cancer* 1986; **57**: 2070–2076.
16. Shetty K, Tuft H. Dental management of the paediatric post radiation therapy—rhabdomyosarcoma patient: Case reports and review of literature. *Oral Oncol Extra* 2005; **41**: 242–248.
17. Marx R E, Johnson R P. Studies in the radiobiology of osteoradionecrosis and their clinical significance. *Oral Surg Oral Med Oral Pathol* 1987; **64**: 379–390.
18. Gawade P L, Hudson M M, Kaste S C *et al*. A systematic review of dental late effects in survivors of childhood cancer. *Paediatr Blood Cancer* 2014; **61**: 407–416.
19. Lindvall A M, Omnell K A, Schildt B E. The effect of roentgen irradiation on the formation of enamel and dentin in maxillary rat incisors. *Scand J Dent Res* 1972; **80**: 253–263.
20. Collett W K, Thonard J C. The effect of fractional radiation on dentinogenesis in the rat. *J Dent Res* 1965; **44**: 84–90.
21. Miller S C. *Textbook of periodontia - oral medicine*. 1st ed. London: Henry Kimpton, 1938.
22. Marx R E, Johnson R P, Kline S N. Prevention of osteoradionecrosis: a randomized prospective clinical trial of hyperbaric oxygen versus penicillin. *J Am Dent Assoc* 1985; **111**: 49–54.
23. Chambrone L, Mandia J Jr, Shibli J A, Romito G A, Abrahao M. Dental implants installed in irradiated jaws: a systematic review. *J Dent Res* 2013; **92 (Spec Iss)**: 1195–1305.