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Child Cancers: Managing the Complications of Childhood Chemotherapy in the Adult Dentition

Abstract: Young children who are unfortunate enough to suffer from a malignant disease are often treated with chemotherapy. This selectively toxic treatment keeps them alive but, in many cases, the effects on the developing dental structures can be very serious. Robust evidence is limited on how to manage the dental issues of the surviving patients later on in their lives. This article demonstrates some interesting malformations of teeth produced by the malignant disease or by the chemotherapy early in life. It offers some pragmatic ideas on solving some of these dental problems without destroying the already much reduced tooth tissue.

CPD/Clinical Relevance: This article enables clinicians to appreciate the long-term effects of chemotherapy on the dental development of young cancer victims and outlines subsequent management using minimally destructive, pragmatic, bonded composite restorations.

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Chemotherapy and the developing dentition

Chemotherapy is the first line treatment employed in treating many childhood cancers such as leukaemia and lymphoma and has resulted in improved survival rates. A recent report found that predicted five-year survival rate for children and adolescents who were diagnosed with cancer has risen by up to 82%.[1]

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The severity of the malignant disease usually dictates the concentration, toxicity and duration of chemotherapy to which the child is subjected during treatment. Typically, this chemotherapy regimen can last from 1 to 3 years.

Previous studies have looked at children who were in long-term remission from cancers of different types. Hypodontia, as well as hypoplasia of the crowns of the teeth, were the most commonly reported dental abnormalities.[2,3]

The malformation of the crowns, pulps and roots of adult teeth are usually closely linked to the age of the child when the toxic, albeit life-saving, chemotherapy was commenced. This is due to its impact on the process of amelogenesis and dentinogenesis at the age at which the teeth are forming. For instance, the crowns of the deciduous dentition are completely developed very early on and, if chemotherapy starts after that, these teeth will not be affected, but the adult teeth developing will be.

Familiarity with the chronology of tooth development helps in the diagnosis of the time at which the chemotherapeutic insult(s) probably occurred and thereby caused the observed effects in teeth (Figures 1 and 2).

Chemotherapy interferes with many different cells in relation to their speed of manufacture and with various aspects of intracellular metabolism. Teeth may suffer delayed development or have reduced size, which is known as microdontia. They can also have persistently enlarged pulp chambers due to reduction in dentinogenesis and root stunting due to interference with the Sheath of Hertwig to varying degrees. The severity of malformation is usually correlated with the concentration of the drugs involved, their

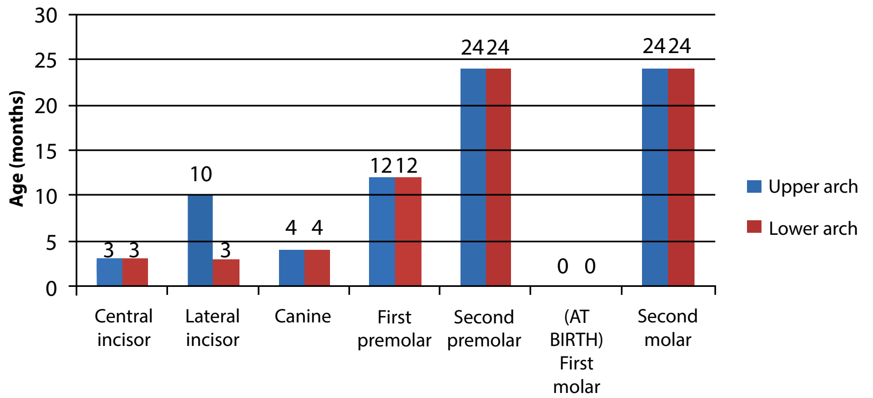


Figure 1. The average age at which calcification of the permanent dentition begins.[4]

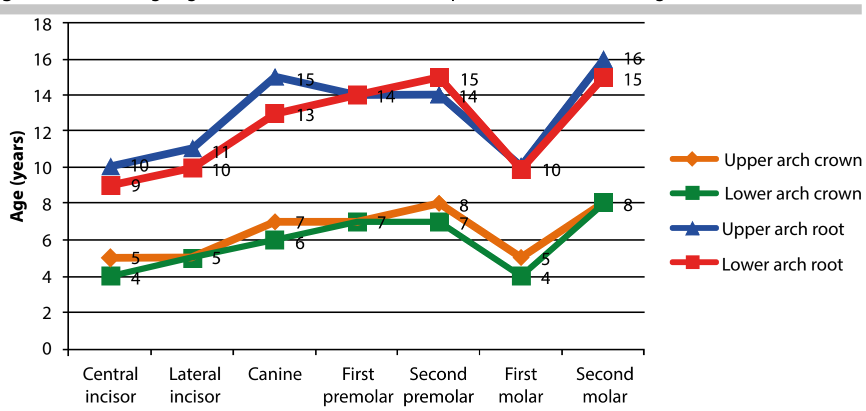


Figure 2. The average age at which crown and root development is normally completed in the permanent dentition.

toxicity and timing.

Dental abnormalities are reported to be more frequent in surviving patients who have had leukaemia and solid tumours, but can also occur with other malignant diseases treated with chemotherapy only or with chemotherapy and radiotherapy. Acute lymphoblastic leukaemia is the most common malignancy, accounting for 24% of childhood malignancies and many reports in the literature are on dental malformations presenting in these individuals.

There is a view that the developing dentition will be affected to some degree due to a combination of the malignancy itself, irradiation and chemotherapy. It can be difficult, however, to be certain whether it was the radiotherapy or chemotherapy that actually caused the dental malformation.[3]

Chemotherapeutic agents

Cyclophosphamide is a cytostatic agent used in cancer therapy that acts as an alkylating agent that cross-links the guanine bases in double-stranded DNA, thus inhibiting cell division. Such an effect on the sensitive odontogenic mesenchymal cells can interfere with normal dentine formation and, if the effect is sufficiently severe, also interfere with ameloblasts and therefore with enamel formation, as described by Koppang.[5] The effects of other chemotherapeutic agents, such as vincristine, vinblastine, and doxorubicin in animal studies were found to cause dental abnormalities similar to those in cyclophosphamide.[6,7]

Should a group of ameloblasts become disturbed, the resultant enamel secreted at that precise time may be defective or hypoplastic. In cases of more severe disturbance, the whole tooth may fail to form. This outcome can be seen in patients who, as a result of their selectively toxic treatment, present later with tooth agenesis.

It is important to remember that the tooth abnormalities seen in childhood cancer survivors can also be attributed to either their disease and/or their chemotherapeutic treatments. Jaffe *et al* stated that developmental abnormalities could also, or alternatively, be attributed to systemic disturbances, childhood fever, antibiotics or poor nutritional habits in a very young patient group.[8]

The most common dental findings of a patient subject to chemotherapy at a young age are:

- Delayed eruption;
- Hypodontia;
- Hypoplasia;
- Microdontia;
- Thin roots with enlarged pulps and root canal systems;
- Arrested tooth development;
- Tooth agenesis.

Table 1 shows the findings of studies into the effects of childhood chemotherapy on the developing dentition.

Management of the effects of childhood chemotherapy

Case study

Thorough history-taking and examination

This 34-year-old male presented to the Restorative Assessment Clinic at King's College Dental Institute, London, after being referred by his general dental practitioner with regards to repeated failed restorations and malformed teeth.

He presented with a generalized pattern of tooth surface loss in his adult dentition, with the incisal surfaces being particularly affected. Microdontia and enamel hypoplasia were noted at his upper right and left first and second premolars and lower left first premolar. The formation of the premolars occurs between 2–3 years of age, and this finding helped to identify that the drug treatment occurred at about this time (Figure 3).

Detailed history-taking was important in trying to ascertain the probable causes of the tooth surface loss. This included open questions and more focused questions about dietary and regurgitation issues. However, the reasons for the curious malformations of the teeth required further lines of enquiry.

The tooth surface loss of the dentition was suggestive of a combination

Authors	Year	Sample	Sample Size	Age Range	Dental Health	Radiographic Findings
Welbury *et al*[9]	1984	Leukaemia + solid tumours	64	3–20y	No variation from normal	Hypodontia and enamel hypoplasia
Jaffe *et al*[8]	1984	Leukaemia + solid tumours	23	5–28y	Not assessed	Acquired amelogenesis microdontia and taurodontism
Rosenberg *et al*[10]	1987	Leukaemia	17	7–14y	Not assessed	Short and thinning of roots
Maguire *et al*[3]	1987	Leukaemia + solid tumours	82	3–22y	All dental parameters normal except more malocclusions and enamel opacities in treated group	Lack of development Microdontia Enamel hypoplasia Abnormal root development
Purdell-Lewis *et al*[11]	1988	Leukaemia + solid tumours	45	7–13y	Higher prevalence of caries and enamel opacities	Delayed eruption Malformed roots

Table 1. The findings of studies into the effects of childhood chemotherapy on the developing dentition.

Figure 3. **(a–e)** The 34-year-old patient showing malformations, including microdontia, hypodontia, hypoplasia, as well as generalized tooth wear.

of erosion and attrition, but the rate at which the teeth were wearing away was not consistent with his history. On further open-ended questioning, the patient reported that he had always had malformed teeth since childhood and that he had been seen at Great Ormond Street Hospital when he was one year old, where he was treated for stomach cancer. He subsequently underwent chemotherapy and was seen in the hospital until the age of five. Based on his probable dental development during the period of life when he was undergoing chemotherapy, the reasons why he might have had these particular malformations became clearer.

Medically, the patient was fit and healthy and was not taking any medications. He denied having any gastric regurgitation type problems and was not a vegetarian. Further questioning about his diet revealed no present or abnormal intake of particularly erosive fluids or unusual dietary habits. He was working as an engineer and did not reveal any parafunctional habits.

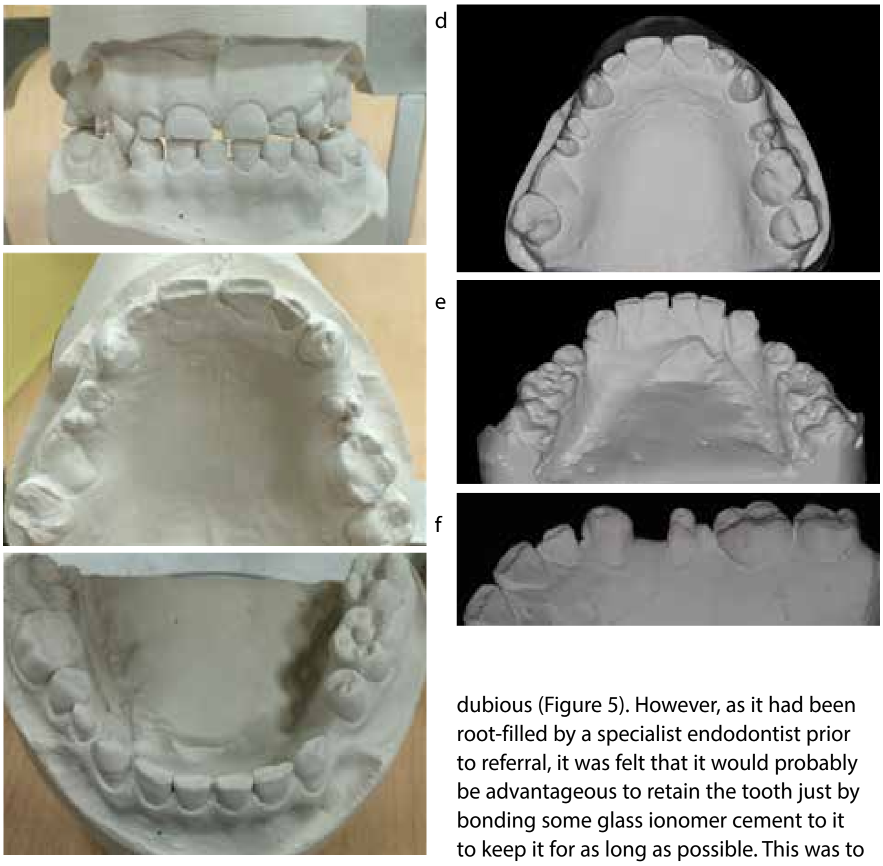
There was no obvious active caries and signs of significant periodontal disease were limited. Positive results were gained from sensibility testing of his remaining dentition with ethyl chloride and electric pulp testing, apart from his UR6.

Exploring treatment options

Before commencing any active treatment, it was important to discuss the causes, options and possible or expected outcomes with different approaches, in order to plan for the risks and to gauge and manage the patient's expectations. The obvious issues that needed to be considered included what he felt were his priorities and whether or not it would be possible to restore all the spaces and restore all the teeth. There were understandable concerns about the amounts of tooth tissue remaining and the degree of spacing between the teeth.

Study casts were mounted on a Denar Mk 2 articulator with the aid of a face bow and an inter-occlusal record in ICP (Figure 4). A diagnostic wax-up was done to assess various issues in more detail, but this was of limited help.

It was felt that, while the problems were interesting, the significant



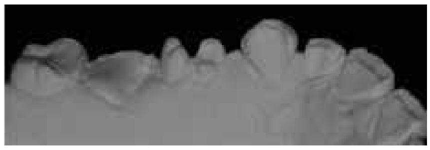


Figure 4. **(a–g)** Study models used to examine occlusion and malformations of teeth closely.

tooth surface loss and the hypoplasia might be amenable to being managed with minimally destructive, pragmatic restorative techniques, for example, using direct composite with a 3-bottle system (eg All-Bond 2® by Bisco) and fibre (eg EverStick® Stick Tech) to reinforce the composite as required. The addition of direct-bonded composite resin onto the incisal surfaces of the teeth was to be utilized to increase the patient's anterior vertical dimension and restore the appearance without further damage being done to the worn teeth. The space created anteriorly to improve the appearance on a pragmatic basis would then help the restoration of the posterior dentition. Burke *et al* demonstrated a series of case reports where worn teeth were restored with direct bonded composite resin, which helps protect teeth from further wear as well as improving aesthetics as an added bonus.[12] The marked improvement in aesthetics resulted in many satisfied patients.

The prognosis of the upper right first molar was assessed as being very dubious (Figure 5). However, as it had been root-filled by a specialist endodontist prior to referral, it was felt that it would probably be advantageous to retain the tooth just by bonding some glass ionomer cement to it to keep it for as long as possible. This was to avoid extraction and doing so would help to preserve bone in that region, which could be important for the patient later in life, as a possible implant site.

Restoring teeth

The use of direct composite resin to restore the worn anterior dentition is a concept that has been used over time with much success. This technique offers the most obvious advantage of not having to reduce tooth tissue in order to accommodate the additive, rather than destructive restorations. It is particularly useful in wear cases, where the composite material gets worn rather the tooth tissue, therefore serving as a preservative and protective material (Figure 6).

There are numerous reports in the literature of follow-ups from cases that have undergone such treatment, which have supported this principle in restoring the worn dentition. A study by Al-Khayatt *et al*,[13] which expanded on a previous study by Poyser *et al*,[14] showed that direct composite restorations bonded to the worn anterior dentition had 85% survival at the 7-year follow-up. Gulamali *et al* also supported the use of composite restoration resin to open the anterior vertical dimension as a viable treatment option for wear cases over a ten-year period.[15]

It has to be accepted by everyone involved that there will be some degree of maintenance required. The mechanical properties of composite and its physical characteristics mean that some deterioration of the restorations in the medium term should be expected, especially as there was evidence of attrition. This must be part of the discussion with the patient prior to undertaking elective treatment.

Some of the more common minor failures associated with composite restorations are wear, chipping and marginal discoloration. These can be dealt with quickly by simply polishing, or by the addition of composite resin. 'Loss of restoration' can potentially occur where enamel quality is poor and secondary caries are more occasional complications associated with composite resin restorations. The patient must be aware that the surface of composite is rougher than enamel and will naturally accumulate more plaque. As a consequence, oral hygiene must be meticulous and the patient should be shown how to use interdental and interspace brushes for effective cleaning.

It can be seen that the benefits of using composite resin as a method of restoring worn teeth far outweigh the risks. For instance, there is no destruction of the remaining sound tooth tissue or of subjecting healthy pulps to hazards, as is the case with many of the popular ceramic materials. When one considers the options of indirect restorations by the use of crowns in restoring the worn dentition, the biological price is significantly greater in comparison to composite resin restorations. Not only when providing conventional crowns is there a loss of tooth structure, but also 19% of teeth develop endodontic complications, as demonstrated by Saunders and Saunders.[16]

Figure 5. **(a, b)** Upper first molar with little remaining coronal tooth.

Large scale epidemiology studies are increasingly questioning the outcome for the teeth after they are crowned.

Patients find this treatment regimen attractive owing to its non-destructive nature and having 'self preservation' benefits, its general painlessness, the procedural simplicity, the immediate improvement in function, as well as the aesthetics and the relative ease of repair should failures occur. For clinicians and patients this can only be seen as a 'win-win' situation. There is, however, the issue of it being technique sensitive and the fact that it takes time to do it reasonably well, but the minimally destructive nature of the treatment means that it can be re-polished, 're-pointed', re-surfaced or redone anytime that it is required. This can help avoid and delay the need to provide conventional restorations, which are a much higher biological risk to the patient's teeth, as well as having big financial implications.

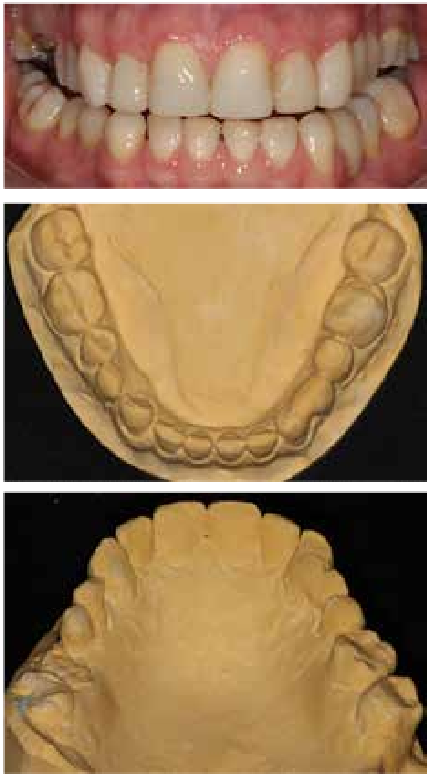


Figure 6. **(a–c)** Post-treatment dentition and study models, following composite build-ups to augment affected teeth.

Edentulous spaces

The management of edentulous spaces that the patient presented with can be considered first by assessing the absolute need to restore the edentulous space and possible risks and benefits of restoring the spaces. The options considered were to do nothing, or to provide fixed prostheses of various designs or to use removable prostheses.

While the recent boom in implants is now seen as the first choice for some clinicians and patients, it is important to realize the complications that can occur in the long-term, such as peri-implantitis, which has been reported by Alani *et al*.[17] It is worth noting that, when considering replacing missing teeth, it is wise to ascertain the reasons why teeth were lost in the first place, and it is often the usual causes of caries, smoking and periodontal disease. If one were to place implants in patients who have lost teeth as a result of the periodontitis, one should not be surprised to find patients returning in the medium term, as the implants themselves develop problems of different types.

The provision of fixed minimally destructive prostheses and removable prostheses can often be more appropriate and, in many cases, they should be considered first. In this case, resin-retained bridges could be used to replace the edentulous spaces owing to their longevity and clinical success over numerous years.

A well-known study by Djemal *et al* looked at the survival of such restorations over 15 years and described the success of these restorations over the long-term.[18] These types of restoration are one appropriate way to restore edentulous spaces and provide adequate function and reasonable pragmatic improvement in the aesthetics for many individuals.

In this case, StickTech fibre reinforcement was considered to be a reasonable alternative to conventional metal-based adhesive prostheses, and the bridges were fabricated at chairside. Such materials increase the range of minimally invasive options for the patient (Figure 6).

Risk management

The management of such a case requires appropriate risk assessment and planning. The majority of such cases first present in the NHS general dental practice setting, where there are increasing pressures as a result of the UDA remuneration system. A fairer and more sensible system would help dentists to provide ethical treatments that are in the patient's best interests in the longer term. A simple 'daughter test'[19] can help clinical decision-making, whereby one asks 'Would I carry out this procedure on my own daughter, knowing what this would involve for the teeth in the long term?'

The well-known Montgomery vs Lanarkshire case can be used as an example highlighting the importance of informed consent whereby the patient is made aware of all risks and alternative treatments. It is recognized that a pragmatic direct bonding approach using fibre reinforcement has limitations and is neither 'perfect' nor 'permanent'. In this case, after various discussions, the patient declined ceramic veneers, crowns or implants, partly because these are neither 'perfect' nor 'permanent', which some claim them to be .

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