Orofacial Development Changes in Children Following Cancer Treatment: A Comprehensive Review of Literature and Analysis of Current Data in Leeds Dental Institute.

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Submitted in accordance with the requirements for the degree of

Professional Doctorate in Paediatric Dentistry

The University of Leeds

School of Dentistry

Division of Child Dental Health

March 2024

The candidate confirms that the work submitted is his own and that appropriate credit has been given where reference has been made to the work of others.

I. Acknowledgements

I want to express my sincere gratitude to all of those who have contributed to this project. First and foremost, I extend my most profound appreciation to my parents, whose unwavering love, encouragement, and support have been the driving force behind my academic pursuit. My appreciation extends to my wife, Rahaf. Her enduring patience and unyielding support have been the bedrock upon which this research was successfully completed. My son, Khalid, has provided a constant source of joy and inspiration.

My supervisors, Professor Bernadette Drummond and Dr Kate Kenny, have been exemplary guides throughout the process. Their profound expertise, insight, and timely feedback have shaped my research and inspired me to strive for excellence.

I sincerely thank King Saud University and the Saudi Arabian Cultural Bureau in London for their financial sponsorship and support during my postgraduate course.

"To my parents, Rahaf and Khalid, I dedicate this thesis to you."

II. Abstract

Introduction: Childhood cancer survivors often experience various side effects after treatment, including dental and orofacial developmental conditions. According to the literature, the treatment for cancer in children can affect the development of teeth, the function of salivary glands, the development of facial structures, and the operation of the temporomandibular joint [TMJ]. Leeds Dental Institute [LDI] has accumulated a wealth of data while providing dental healthcare for cancer survivors. This extensive data has not been thoroughly explored or published. Thus, this study aims to investigate the long-term effects of cancer treatment on dental and orofacial structures from the literature and the available records in children at Leeds Dental Institute. **Methods:** This research is structured into two sections. The first is a comprehensive literature review of existing studies on the adverse effects of cancer treatments on oral and facial structures in children by searching six databases to establish a foundation for understanding the broader context of the issue. The second section is a retrospective data collection and analysis of paediatric patient data from the electronic records in LDI using a list of appointments attended by cancer patients in LDI. **Results:** Fifty-one articles were included in the comprehensive literature review following the database search and the inclusion criteria. Numerous studies concluded that chemotherapy and other anticancer treatments in children are linked to increased dental anomalies like microdontia and enamel defects, especially when treatment occurs at a young age. The findings have been summarised in tables. Of the 806 registered appointments identified, the clinical records of 85 childhood cancer survivors who met the inclusion criteria were included. The post-treatment identified conditions included microdontia, hypodontia and enamel hypoplasia. Demographics, cancer diagnosis and type of treatment, in addition to dental findings, were summarised in tables. The data were also categorised according to age at the cancer treatment time and type of treatment provided. **Conclusions:** The literature review and LDI patient data revealed that childhood cancer survivors commonly face serious long-term dental issues due to their treatments. These findings highlight the importance of a better understanding of cancer therapy's impact on orofacial development, requiring more attention and support from healthcare professionals, particularly dentists.

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VI. List of Abbreviations

ACS: American Cancer Society.

ALL: Acute Lymphoblastic Leukaemia.

COG: Children Oncology Group.

CRUK: Cancer Research UK.

DDA: Dental Developmental Anomalies.

DMFT: Decayed, Missing, and Filled Teeth Index for permanent teeth.

dmft: Decayed, Missing, and Filled Teeth Index for primary teeth.

DNA: Deoxyribonucleic Acid.

Gy: Grays.

HDI: Holtta's Defect Index.

LDI: Leeds Dental Institute.

NCI: the National Cancer Institute.

NHS: The national health services.

PHE: Public Health England.

SCT: Stem cell transplant.

TBI: Total-body Irradiation.

TMJ: Temporomandibular joint.

1. Chapter 1: Introduction

Before 1970, most children and young adults diagnosed with cancer had little chance of being cured. By the late 1990's, due to the early diagnosis methods and improved intensive multimodal modalities of cancer treatment, 5-year survival rates had risen to 78% (Smith and Ries, 2002). According to a recent publication by Cancer Research UK [CRUK], approximately 84% of individuals diagnosed with cancer during their childhood successfully lived for five years or more (CRUK, 2021b).

Although increased survival rates have been accomplished, treatment side effects frequently impair survivors' quality of life. According to the American Cancer Society [ACS], children receiving cancer treatment may experience various side effects while under treatment, including tiredness, vomiting, hair loss, oral sores, altered appetite, weight loss, anaemia, susceptibility to infection, skin alterations and emotional changes (ACS, 2017). Side effects of therapy can manifest in various ways, ranging from immediate to late effects. These late effects can affect different body organs, including the heart, the blood vessels, the brain, the spinal cord, and the digestive tract (ACS, 2017). At the same time, some adverse effects are specific to the oral cavity and the facial structures, including lack of salivary secretion (xerostomia), dental anomalies, dental caries and disturbances in craniofacial morphology (Dahllof, 1998, Epstein and Chow, 1999, Carrillo et al., 2014). According to Effinger et al. in their published Children Oncology Group [COG] report, it was evident in the literature that treatment for cancer in children can affect the growth of teeth, the function of salivary glands,

the development of facial structures, and the operation of the temporomandibular joint [TMJ]. This can lead to a higher chance of oral and dental health issues in those who have survived childhood cancer (Effinger et al., 2014).

In recent years, a combination of cancer therapy modes has been adopted to minimise and reduce the chronic toxicity of the treatment (Bayat Mokhtari et al., 2017). Chemotherapy and radiotherapy are currently considered the primary modalities to treat young cancer patients in addition to surgery, which is a successful modality for solid malignant cancers diagnosed in their early stages (Kattner et al., 2019). In the 1940s, the first Deoxyribonucleic Acid [DNA] alkylating agent was discovered, derived from nitrogen mustard gas used in the Second World War and was introduced as chemotherapy (Falzone et al., 2018). It was observed that these agents were toxic and caused the death of white blood cells. Chemotherapy agents can circulate in the bloodstream and reach cancer cells in any body part. They can be administered through various routes, such as intravenous, intraoral, and intramuscular routes (Falzone et al., 2018). It is challenging to assess the specific impact of chemotherapy on dental outcomes in children, as most of them also receive radiation therapy. Despite this, reports have linked dental abnormalities in childhood cancer survivors to vincristine and alkylating agents (Maguire et al., 1987, Kaste et al., 2009).

In 1895, the discovery of X-rays introduced ionising radiation as a cancer treatment modality. The primary goal of radiation therapy is to cause damage to the DNA of cancerous cells. It is a practical and essential treatment component

for localised tumours and is often combined with chemotherapy (Jaffray and Gospodarowicz, 2015). Radiation therapy treats various cancer types, including cancers of the head and neck, lung, brain, and sarcomas. Patients with leukaemia typically receive systemic chemotherapy as the primary treatment modality. Still, radiotherapy can benefit them when treating leukaemia that has spread to the brain and spinal fluid or testicles. Whole-body radiation is also necessary for these patients before bone marrow or stem cell transplant (Jaffray and Gospodarowicz, 2015).

Radiation therapy can be delivered to patients in a total-body irradiation form [TBI], which is particularly beneficial for patients suffering from various types of blood and bone marrow cancers, such as lymphoma, leukaemia, myeloma, and myelodysplastic syndromes. TBI not only assists in eliminating cancer cells present in the bone marrow but also suppresses the immune system, which is crucial in preventing the rejection of the donor stem cells during transplantation (Paix et al., 2018). Another way of delivering external beam radiation therapy is targeted radiation (Stereotactic radiation therapy), which aims to focus a higher radiation dose on the tumour and minimise the radiation exposure on the surrounding tissues and organs. This is considered an effective way of treating smaller, well-defined tumours including brain tumours (Guckenberger et al., 2014).

According to the National Cancer Institute [NCI], stem cell transplant [SCT], also known as Haematopoietic Cell Transplantation, is a medical procedure that replaces blood-forming stem cells in patients who have had their cells destroyed

due to very high doses of chemotherapy or radiation therapy (NCI, 2015). SCT is a definitive treatment method for many diseases, including immune deficiencies, bone marrow failure, congenital metabolic diseases, and haematological malignancies (Yeşilipek, 2014).

This chapter aims to provide an overview of childhood cancer and the literature on the long-term adverse effects of cancer therapy on children's oral health and development and to outline the aim and objectives of the research.

1.1 Childhood Cancer Facts and Statistics

Childhood cancer is a group of diseases characterised by the uncontrolled growth and spread of abnormal cells. These cells can invade and damage surrounding tissues and organs and spread to other body parts through the bloodstream or lymph system, leading to secondary tumours or metastases (ACS, 2017).

Cancer is a multifactorial disease that affects individuals of all ages and is influenced by genetic and environmental factors. Moreover, paediatric tumours differ significantly from adult tumours in terms of their epidemiology, cellular origins, and response to therapy. Notably, environmental factors or lifestyle choices, often linked to adult cancers, do not play a significant role in the onset of most pediatric cancers. Furthermore, only a few such cancers are due to inheritable genetic alterations passed from parents to their children (Kattner et al., 2019). Paediatric cancers generally respond better to treatments, possibly due to differences such as children undergoing more rigorous treatment regimens (Kattner et al., 2019). Additionally, unlike adults, children usually do not

bear the burden of concurrent health conditions that could potentially worsen with cancer treatment. However, since children's bodies are in the growth phase, they may experience more side effects from some treatments. For instance, radiation therapy tends to impact children, particularly younger ones. Children display a greater vulnerability to radiation compared to adults, particularly displaying an increased relative risk for cancers such as leukemia, brain, skin, and thyroid following radiation exposure. This can be attributed to the radiosensitivity of their organs and tissues, which are still in development (Kutanzi et al., 2016). Also, many cancer therapies can trigger long-term side effects, and children who survive cancer require meticulous lifelong follow-up care (Kattner et al., 2019).

A study by Tomasetti and Vogelstein revealed that approximately 66% of cancer-causing mutations occur without an apparent external cause (Tomasetti and Vogelstein, 2015). Some medical conditions or genetic syndromes can increase the likelihood of certain types of cancers in children. For example, children with Down syndrome have a significantly increased risk of developing leukaemia and are ten to twenty times more likely to be affected than other children (Brown et al., 2019). Hereditary cancer, which accounts for only a small percentage of paediatric cancers, remains poorly understood. The factors driving malignancies in those cases are still unclear (Kattner et al., 2019).

Childhood cancer is rare. Approximately 300,000 children aged 0-19 years worldwide are diagnosed with cancer yearly (Steliarova-Foucher et al., 2017). In the UK, around 1900 children between 0-14 years are diagnosed with cancer yearly, which accounts for 1% of all cancer cases diagnosed. According to CRUK, the highest incident rates for childhood cancer are in children under five

years old, accounting for 46% of all childhood cancer cases in the UK (CRUK, 2021a).

The most common forms of cancer found in children in the UK are Acute Lymphoblastic Leukaemia [ALL], nephroblastoma (Wilms tumour), neuroblastoma, non-Hodgkin's lymphoma, and retinoblastoma (CRUK, 2021a). Table 1.1 shows the incidence rates of the most common childhood cancer types according to Public Health England [PHE] based on the average national statistics for the UK and Ireland (PHE, 2021).

Table 1.1 Incidence rates of the most common childhood cancer types based on the average national statistics for the UK and Ireland according to Cancer Research UK, 2021.

Type of childhood cancer	Percentage
Leukaemia	31%
Brain and spinal tumours	26%
Lymphomas	10%
Soft tissue sarcomas	7%
Neuroblastoma	6%
Kidney tumours	5%
Bone tumours	4%
Germ cell tumours	3%
Retinoblastoma	3%
Liver tumours	2%
Other tumours	4%

1.2 Medical Side Effects of Cancer Treatment

Children undergoing cancer treatment can suffer from various side effects impacting their physical, emotional, and social well-being. While most side effects that emerge during treatment disappear shortly after treatment, some late effects may persist or appear months or years later following the treatment.

Common medical side effects experienced during and after chemotherapy include fatigue, vomiting, hair loss, altered appetite, weight loss, anaemia, susceptibility to infections, skin alterations, and emotional changes (Altun and Sonkaya, 2018).

Radiation therapy can result in various tissue injuries, with symptoms varying based on the treatment site. Head and neck exposure can cause erythema, inflammation, and desquamation, leading to mucositis, ulcers, and trismus (Dörr et al., 2002). Irradiation of the salivary glands can lead to cell death and subsequent issues such as xerostomia and severe dental caries (Cooper et al., 1995). Neurological symptoms, ranging from headaches and fatigue to persistent neurocognitive effects, can follow cranial irradiation (Mehta et al., 2019, Cayuela et al., 2019). Exposure to the thorax can lead to complications like radiation pneumonitis and restrictive lung disease (Morgan and Breit, 1995). The heart may experience acute pericarditis, valvular dysfunction, and myocardial fibrosis (Taylor et al., 2018).

SCT can lead to a variety of side effects affecting multiple body systems. Gastrointestinal and hepatic complications may occur, including mucositis and venoocclusive disease, also known as sinusoidal obstruction syndrome. Pulmonary complications are also common and may encompass pulmonary edema, bacterial, fungal and viral infections, idiopathic pneumonia syndrome, and diffuse alveolar hemorrhage (Yeşilipek, 2014). Kidney-related complications, such as nephrotoxicity and haemolytic uremic syndrome-thrombotic microangiopathy, may arise, as well as hemorrhagic cystitis. Cardiac

complications, including cardiotoxicity, conduction disorders, and intracardiac thrombosis associated with catheters, can present significant challenges. Additionally, there can be delayed endocrine complications like hypothyroidism, adrenal insufficiency linked with steroid usage, testicular or ovarian insufficiencies, and developmental delays (Yeşilipek, 2014).

Surgical effects primarily depend on the malignant tumour's location, size, and type. In some instances, minor surgery may be sufficient to remove the tumour. At the same time, more extensive procedures may be necessary to eliminate malignant masses, resulting in the removal of parts or all of an organ or limb. According to CRUK, cancer surgeries may lead to several potential complications. Pain post-surgery is common and can be controlled with regular painkillers, though sometimes patients may experience long-term or phantom pain. The risk of blood clots or deep vein thrombosis is also a concern, particularly if the patient's mobility is reduced. Chest and breathing problems can occur, including serious chest infections like pneumonia. Wound complications can also arise, including infections or internal blood or tissue fluid collection, causing swelling (haematoma or seroma). Bruising around the operation area is often seen but typically resolves over time. Finally, lymphoedema, or swelling due to fluid build-up, often in an arm or leg, can occur if lymph nodes have been damaged or removed during surgery. Early detection and treatment of these complications can help mitigate their impacts (CRUK, 2022).

1.3 Dental and Orofacial Side Effects of Cancer Treatment

1.3.1 Immediate Side Effects

Oral complications associated with cancer treatment can appear during the course of the treatment itself. This was illustrated in a longitudinal study by Fayle and Curzon in 1991, which investigated the occurrence of dental issues in children receiving cancer treatment. The study tracked 43 children, aged from 2 to 14 years, from their initial diagnosis for periods between 8 and 30 weeks, noting the development of dental and oral problems. The research found that oral mucosal ulcers were the most prevalent, impacting 28 of the 43 children (Fayle and Curzon, 1991).

It is common for patients to experience oral side effects during their treatment, leading to discomfort, pain, and an increased likelihood of oral infections. Childhood cancer survivors may exhibit a higher incidence of conditions such as oral mucositis, fungal infections, xerostomia, and dental abnormalities later in life (Gawade et al., 2014).

Up to 80% of children who receive chemotherapy may suffer from some level of mucositis. However, the rate at which oral mucositis occurs can differ depending on the cancer type and the treatment plan (Cheng, 2007). It is noteworthy that children with haematologic malignancies have a higher frequency of mucositis compared to those with solid tumors (Miller et al., 2012). This condition often leads to difficulties in speaking, eating, and swallowing due to the accompanying burning or tingling sensations (Belfield and Dwyer, 2004). Various studies have put the incidence of oral mucositis in children receiving cancer treatment at 50–

54% (Chen et al., 2004). Despite oral lesions in children and adolescents healing faster than in adults, the incidence of oral mucositis post-chemotherapy is higher in children, possibly due to a faster rate of epithelial cell division (Sonis, 1998). Children undergoing cancer treatment are more susceptible to oral fungal infections, as a result of factors like the use of broad-spectrum antibiotics, steroids, poor oral hygiene, and inadequate nutrition (Quindós et al., 2019).

One common side effect of both chemotherapy and head and neck radiotherapy is xerostomia, also known as dry mouth. The condition arises due to damage to the acini of the salivary glands as a consequence of the cancer treatment, altering the quantity and consistency of saliva in the oral cavity. This alteration makes the oral environment more acidic, increasing the risk of dental caries (Belfield and Dwyer, 2004). Individuals with xerostomia often struggle with unpleasant alterations in taste and difficulties in speaking, chewing, and swallowing (Belfield and Dwyer, 2004). Even though damage from radiotherapy to the head and neck area tends to be more severe and permanent compared to chemotherapy, some paediatric patients may experience some return of normal salivary function within 4–12 months post-radiotherapy (Belfield and Dwyer, 2004).

1.3.2 Late Side Effects of Cancer Treatment

Some effects of cancer treatment may only become apparent later in life and are considered late effects of treatment. Defects in developing teeth may be caused at the time of treatment, however, these are usually not noticeable until the teeth erupt into the oral cavity but can be diagnosed with dental radiographs in the

dental clinic. These may vary in nature and severity depending on various factors such as the type of cancer, the age of the child during treatment, the stages of tooth development, the child's overall health before cancer treatment and their genetic makeup (Altun and Sonkaya, 2018).

According to a systematic review published in 2014 by Gawade et al., which reviewed the literature for late dental effects following childhood cancer treatment, dental caries, dental developmental abnormalities, including dental agenesis, dental hypoplasia, root stunting, and enamel hypoplasia, were reported in childhood cancer survivors who underwent cancer treatment early in life (Gawade et al., 2014).

Case studies have observed changes in facial development in children receiving cancer treatment, including micrognathia (small mandible), maxillary hypoplasia and facial disproportion (Kaste and Hopkins, 1994).

1.3.2.1 Chemotherapy and Late Dental Effects

Determining the independent effects of chemotherapy on dental outcomes in children undergoing cancer treatment is challenging due to the overlapping use of radiation therapy, suggesting further research is required. However, certain chemotherapy drugs like vincristine and alkylating agents have been linked with dental abnormalities in childhood cancer survivors. Notably, vincristine has been associated with the appearance of pronounced incremental lines in dentine due to its inhibitory effect on collagenous dentine matrix secretion by odontoblasts (Macleod et al., 1987, Maguire et al., 1987, Kaste et al., 2009). A multivariable

analysis revealed a dose-dependent risk of dental abnormalities in survivors treated with alkylating agents (Kaste et al., 2009). Furthermore, a strong association was found between cyclophosphamide and dental anomalies, including hypodontia, microdontia, and reduced root-to-crown ratios (Hsieh et al., 2011).

Chemotherapy has also been associated with dental caries, often reflected in increased number of restorations and higher DMFT and DMFS scores (Pajari et al., 1988). Some studies reported a lower salivary flow rate and higher prevalence of cariogenic bacteria, resulting in a higher prevalence of dental caries among survivors (Purdell-Lewis et al., 1988, Avsar et al., 2007).

Dental developmental abnormalities, including dental agenesis, dental hypoplasia, root stunting, and enamel hypoplasia, have been strongly associated with chemotherapy in various child cancer cohorts (Maguire et al., 1987, Purdell-Lewis et al., 1988). The severity of dental abnormalities post-chemotherapy is influenced by younger age at treatment and concomitant radiation (Cubukcu et al., 2012). Higher prevalence and number of dental abnormalities, including delayed development, microdontia, malformed roots, and enamel hypoplasia, have been reported in patients treated at a younger age and those undergoing combined chemotherapy and radiation treatments (Minicucci et al., 2003).

1.3.2.2 Radiotherapy and Late Dental Effects

Radiation can affect odontogenesis (teeth formation) by affecting the mitotic activity of odontoblasts (Collett and Thonard, 1965). It also indirectly impacts

amelogenesis (enamel creation) by inducing osteodentine that substitutes normal dentine, which restricts enamel crystal nucleation and results in deficient enamel mineralisation (Arsenault and Robinson, 1989). It is reported that tooth development can be affected at a radiation dose of 30 Gray [Gy] (Kaste et al., 1994).

Radiation causes damage to tooth buds in early developmental stages, leading to dental developmental abnormalities such as partial agenesis or hypodontia, dental hypoplasia, root stunting, and enamel hypoplasia (Cubukcu et al., 2012). The age at the time of radiation and the radiation dose influence the risk of these abnormalities. A study by Kaste et al. found a higher prevalence of dental abnormalities in survivors treated when younger than eight years of age and those treated with radiation than those who were not (Kaste et al., 1997).

Damage to the salivary glands following radiation reduces salivation, makes saliva more acidic, and encourages the growth of cariogenic bacteria such as *Streptococcus mutans* and *Lactobacilli* (Dreizen et al., 1976).

1.3.2.3 Stem Cell Transplants and Late Dental Effects

There is inconsistency in the literature regarding the long-term impact of SCT on dental caries. Two studies involving children aged 4 to 12 years found no significant difference in the average number of decayed and filled surfaces among survivors treated with SCTs with 10 Gy TBI and cyclophosphamide compared to a control group. This lack of association might be attributed to preventive measures like fluoride prophylaxis, chlorhexidine rinse, and dental

care education for parents (Nasman et al., 1994, Dahllöf et al., 1997). However, another study by Uderzo et al. reported contrasting results, noting higher DMFT scores among SCT survivors compared to those treated with chemotherapy alone (Uderzo et al., 1997).

Nasman et al.'s study in 1994 found that SCT survivors conditioned with 8-10 Gy of TBI and cyclophosphamide had a significantly higher mean number of teeth with halted root development two years post-SCT compared to survivors treated with chemotherapy alone. This group also showed increased rates of enamel hypoplasia, microdontia, and hypodontia, while no dental abnormalities were noted in the control group (Nasman et al., 1994).

1.3.2.4 Late Dental Effects Reported in Case Reports

Case reports published by Bektaş-Kayhan et al. in 2013 described three male patients, aged 13, 14, and 15 years, diagnosed with nasopharyngeal carcinoma. The radiation therapy doses received differed across the cases - 66 Gy for the first patient at the age of 10 years, 70 Gy for the second at the age of 12 years, and 68 Gy for the third at the age of 10 years. They all sought treatment in dental clinics due to the dental and TMJ complications. They experienced caries in their permanent dentition, trismus, and significant xerostomia, indicating the long-term effects of radiotherapy (Bektas-Kayhan et al., 2013).

A case report by Cetiner and Alpaslan in 2004 reported root malformations in second molars (Short, blunted, tapered, and V-shaped), and rotated canines, in an eight year old female patient diagnosed with Burkitt's Lymphoma who

received chemotherapy when she was six years of age including cyclophosphamide, ifosfamide, vincristine, methotrexate, etoposide, and adriamycin, along with a total of 20 Gy of radiation (Cetiner and Alpaslan, 2004). Chang et al. reported a case of a seven year old boy who was diagnosed with rhabdomyosarcoma with intracranial extension. The patient received chemotherapy involving various drugs and localised radiotherapy with a total dose of 50.4 Gy. During the treatment, the boy suffered from radiation-induced caries, trismus and painful radiation-induced oropharyngeal mucositis. Three years post-treatment, numerous issues were found in his primary and developing permanent teeth, including caries, residual roots, hypoplasia, foreshortened and blunted roots, premature root closure, and V-shaped roots. The boy developed facial asymmetry as he aged due to prominent atrophy of his right cheek. A comparison of cephalometric tracings at ages 11 and 17 years showed reduced craniofacial development. His orthodontic diagnoses included skeletal and dental Class III malocclusion with mandibular prognathism, but by the age of 32 years, 25 years post-cancer therapy, the patient had lost multiple teeth and experienced severe facial deformity (Chang and Lin, 2021).

Hernandez et al. reported a case in 2019 that involved a boy who exhibited numerous dental irregularities at the age of nine. The patient had received chemotherapy for acute myeloid leukaemia when he was 15 months old in addition to SCT. A thorough clinical and radiographic assessment revealed several dental anomalies six years following SCT. These included the absence of the second permanent molars and three of the four second premolars, microdontia of first premolars, and stunted root growth of the central incisors and first premolars. The first permanent molars lacked roots and there were enamel

defects, specifically affecting the permanent incisors and canines. (Hernandez et al., 2019).

Hoogeveen et al. 2020 reported cases of children who underwent radiotherapy to the head and neck area in addition to chemotherapy. They reported hypoplastic mandibular ramus, an abnormally formed condyle, altered anatomy of the pterygomaxillary fissure, short roots of the second premolars, and a rootless right lower second molar in a patient who received chemotherapy and targeted radiotherapy with a dose of 50.4 Gy (Hoogeveen et al., 2020). Another case was of a patient who received chemotherapy for rhabdomyosarcoma at the age of 3 years. The patient presented later with smaller crowns in the upper left and right second premolars and maxillary second molars. These anomalies can be attributed to these teeth being in an early developmental stage during the therapy (Hoogeveen et al., 2020). Moreover, a survivor diagnosed with rhabdomyosarcoma and treated at three years and four months old with radiation therapy up to 50.4 Gy with chemotherapy, suffered from the absence of the second molars (Hoogeveen et al., 2020).

Kaste et al. reported two case studies in 1994 highlighting alterations in dental and orofacial development following chemotherapy and radiation. These changes included hypoplasia of the jaw, incomplete tooth development, microdontia, changes in tooth eruption patterns, stunted root growth, and disruptions in enamel formation (Kaste et al., 1994).

Recently, Bousserouit et al. reported a case of a 20 year old male who had recieved chemotherapy at age 6 for Hodgkin’s lymphoma. They reported a

narrow and high-arched palate, multiple carious lesions, and inflamed gingiva. The radiograph revealed dental anomalies including short roots in certain teeth and small third permanent molars (Bousserouit et al., 2022).

Zulijani et al. reported a case of a 9 year old girl who was treated for anaplastic ependymoma using chemotherapy agents including cyclophosphamide, vincristine, methotrexate, etoposide, and carboplatin. The clinical examination revealed an abnormaly shaped right maxillary lateral incisor, unilateral posterior crossbite. The radiographs revealed maxillary retrognathia and six microdontic teeth (Zulijani et al., 2022).

1.4 Summary and The Rationale for this Research

The orofacial changes that may occur after cancer therapy can have profound implications for a child's quality of life, growth, and overall development. Orofacial modifications like mandibular and maxillary hypoplasia, hypodontia, microdontia, altered eruption patterns, root stunting, and altered amelogenesis may substantially affect a child's ability to speak, eat, and engage in social interactions, which can lead to psychosocial distress and lowered self-esteem (Kaste et al., 2009). Furthermore, these changes can impact the child's physical growth and development. For instance, maxillofacial growth retardation can result in skeletal disharmonies and malocclusions requiring extensive orthodontic and surgical interventions (Paulino et al., 2000). Also, dental anomalies such as hypodontia and microdontia can affect masticatory function. Hence, understanding the late effects of cancer treatment on orofacial development is

crucial to ensure the well-being of paediatric cancer survivors and to provide the most appropriate care to manage the potential problems.

1.5 The Role of Leeds Dental Institute

The Leeds Dental Institute [LDI] plays a critical role in providing dental health care to children in Yorkshire, UK. It serves children undergoing cancer treatment and those who have survived childhood cancers. The Institute has accumulated a wealth of data while providing dental healthcare for cancer survivors. It is essential to acknowledge, however, that as far as is known, this extensive data has not been thoroughly explored or published. This suggested a significant opportunity to explore and compare such data with what is already known from the literature and could potentially be instrumental in enhancing healthcare services for these children.

1.6 Aims and Objectives

1.6.1 Aims

- Investigate the long-term effects of cancer treatments on dental and orofacial development in children in epidemiological studies in the literature.

- Investigate the long-term effects of cancer treatments on developing dental and orofacial structures in children at LDI from available records.

1.6.2 Objectives

- Provide a comprehensive review of the existing knowledge in the literature about the long-term effects of cancer treatments on the development of dental and orofacial structures.

- Data collection and analysis to investigate the long-term effects of cancer treatments on dental and orofacial development in cancer patients treated in the paediatric dental department at Leeds Dental Hospital.

1.6.3 Hypothesis

Children who underwent cancer treatments and were seen in LDI will exhibit significant long-term developmental anomalies in dental and orofacial structures. This hypothesis is based on existing studies suggesting that cancer treatments, such as chemotherapy and radiation, can interfere with the normal development of dental and orofacial structures due to their impact on rapidly dividing cells, which are prevalent in growing children.

2. Chapter 2: Methodology

This research project is divided into two sections; the first part is a comprehensive literature review of the long-term adverse effects of cancer treatments on oral and facial structures in children. The second part is a retrospective analysis of paediatric patients records treated at LDI following anticancer therapy. The secondary data collection was registered as part of a service evaluation project in LDI's clinical audit database (Service evaluation No. SE0031). This section details the methods followed to achieve the research aim and objectives.

2.1 Comprehensive Literature Review

There are various types of literature reviews, including, narrative reviews, scoping reviews, and qualitative reviews. A comprehensive review incorporates methods from different categories to conduct an exhaustive and precise analysis of existing literature, thereby minimising outcome bias (Stratton, 2016). A comprehensive literature review method was selected for this research to systematically and scientifically review the literature to limit outcome bias.

The findings could influence policy-making in LDI, encouraging the implementation of comprehensive and multidisciplinary follow-up programmes for paediatric cancer survivors.

2.1.1 Inclusion Criteria for Studies

Epidemiological studies that reported long-term dental adverse effects of cancer treatment in childhood cancer survivors were considered eligible for the review. These included cross-sectional, case-control, cohort, and clinical trials published

in English from 1990 until November 2023. Studies that do not fulfill the criteria were excluded from the research.

2.1.2 Search Methods for Identification of Studies

A search strategy was developed by the research team to search six databases related to the field: Cochrane Library, Web of Science, Scopus and Ovid databases, including MEDLINE, Embase, and Embase classic. The search strategy for the Ovid databases was used to perform searches using medical subject headings and keywords with a combination of controlled vocabulary and terms, including the most common side effects of cancer treatment, to identify relevant studies. The relevant databases were selected, and the data search strategy was developed in collaboration with a specialist librarian from the University of Leeds' library and was adjusted for other database searches. The strategy included specific terms related to the type of anticancer treatment (chemotherapy, radiotherapy, and stem cell transplant) with other words to specify the age at cancer treatment of participants in the studies, such as (children, paediatrics, and juvenile). The entire search strategy is included in Appendix 1. EndNote x9 was used to manage references and eliminate duplicates.

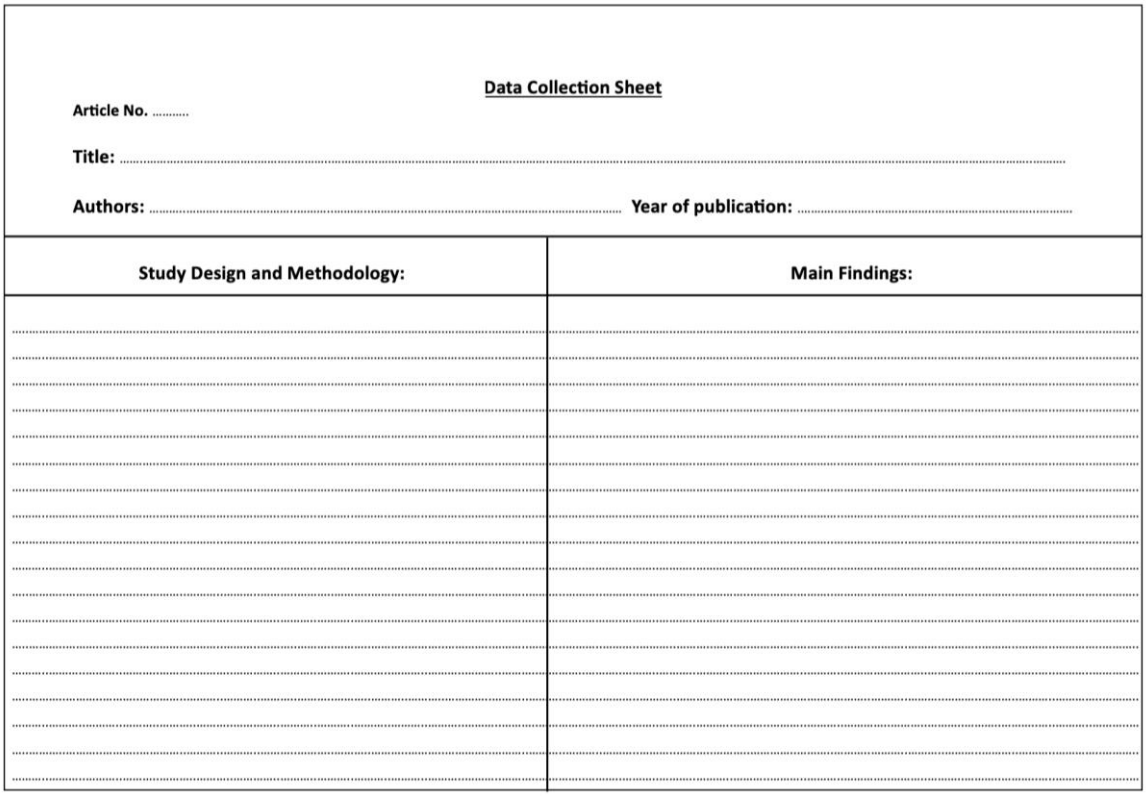
2.1.3 Data Collection and Analysis

The data were collected from the included studies using a data collection sheet developed by one reviewer, Talal Alghamdi (TA), to obtain the following information from each article: Authors, title, year of publication and study design, summary of the study methodology and main findings.

Figure 2.1 shows the data collection sheet used for the included articles.

Included articles' findings were summarised in tables according to the type of treatment provided to the cancer survivors in each study. Critical Appraisal Skills Programme (CASP) checklists and the Appraisal Tool for Cross-Sectional Studies (AXIS) were utilised to assess the included literature.

Figure 2.1 Data collection sheet used for the included articles.



Data Collection Sheet

Article No. .....

Title: .....

Authors: ..... Year of publication: .....

Study Design and Methodology:	Main Findings:

2.2 Service Evaluation

According to the National Health Service [NHS] service evaluation aims to assess and quantify the current practices within a particular service. The outcomes of this evaluation are used to generate internal recommendations for enhancements, Thus, a service evaluation is focused on determining the level of

standard achieved by the service in question (NHS, 2018). The data collection was registered as part of a service evaluation project in LDI's clinical audit database (Service evaluation No. SE0031).

2.2.1 Inclusion Criteria for Participants

The inclusion criteria for patients were as follows:

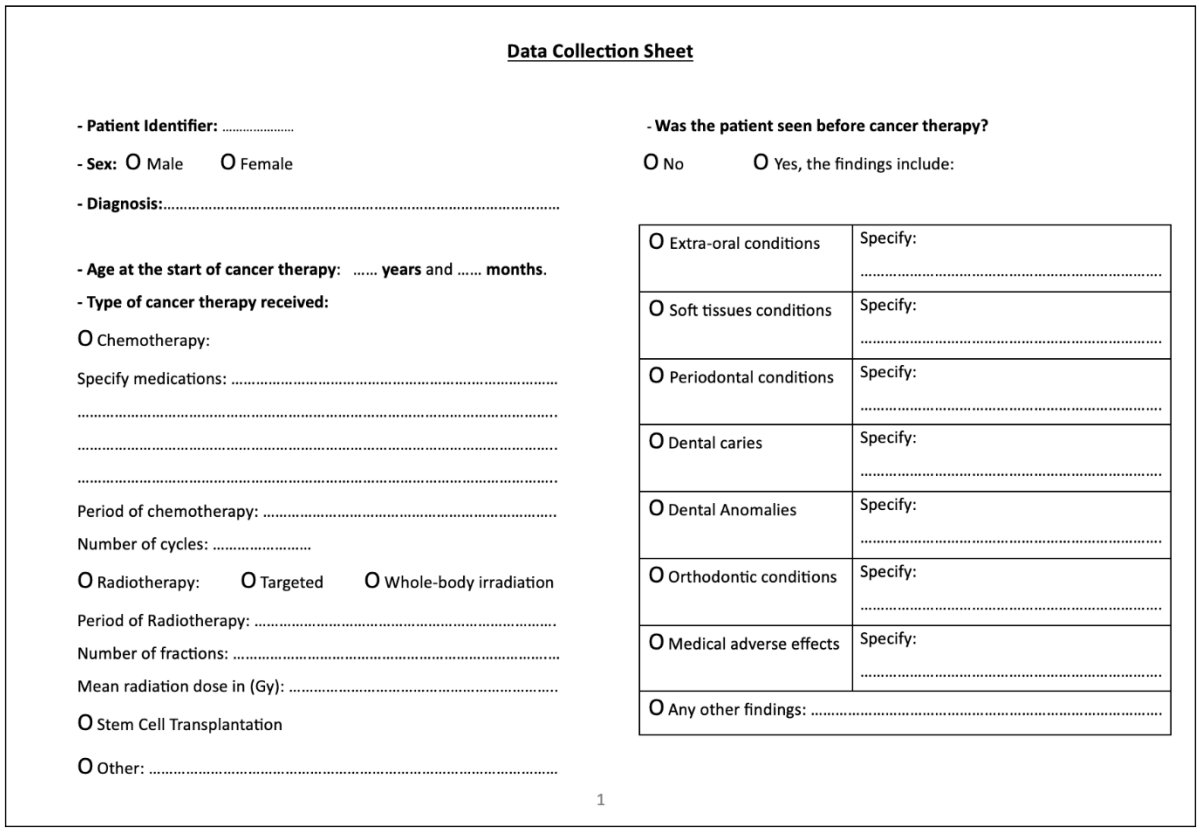
- Childhood cancer survivors or other patients with diseases who had received any type of cancer treatment, including but not limited to chemotherapy, radiation therapy and SCT.
- Children aged up to 18 years at the time of cancer treatment who had been followed up after completion of cancer treatment in the paediatric dental clinic with available medical and dental records at LDI.

Patients who did not fulfil the criteria were excluded from the research.

2.2.2 Data Collection

A data collection sheet was developed by TA following a pilot review of the literature, which explored the most common adverse effects of anticancer therapies on orofacial structures in childhood cancer survivors in Figures 2.2 and 2.3.

Figure 2.2 First page of the data collection used for the service evaluation.



Data Collection Sheet

- **Patient Identifier:** .....
- **Sex:** O Male O Female
- **Diagnosis:**.....

- **Age at the start of cancer therapy**: ..... **years** and ..... **months**.
- **Type of cancer therapy received:**

O Chemotherapy:

Specify medications: .....
.....
.....
.....

Period of chemotherapy: .....
Number of cycles: .....

O Radiotherapy: O Targeted O Whole-body irradiation

Period of Radiotherapy: .....
Number of fractions: .....
Mean radiation dose in (Gy): .....

O Stem Cell Transplantation

O Other: .....

- **Was the patient seen before cancer therapy?**

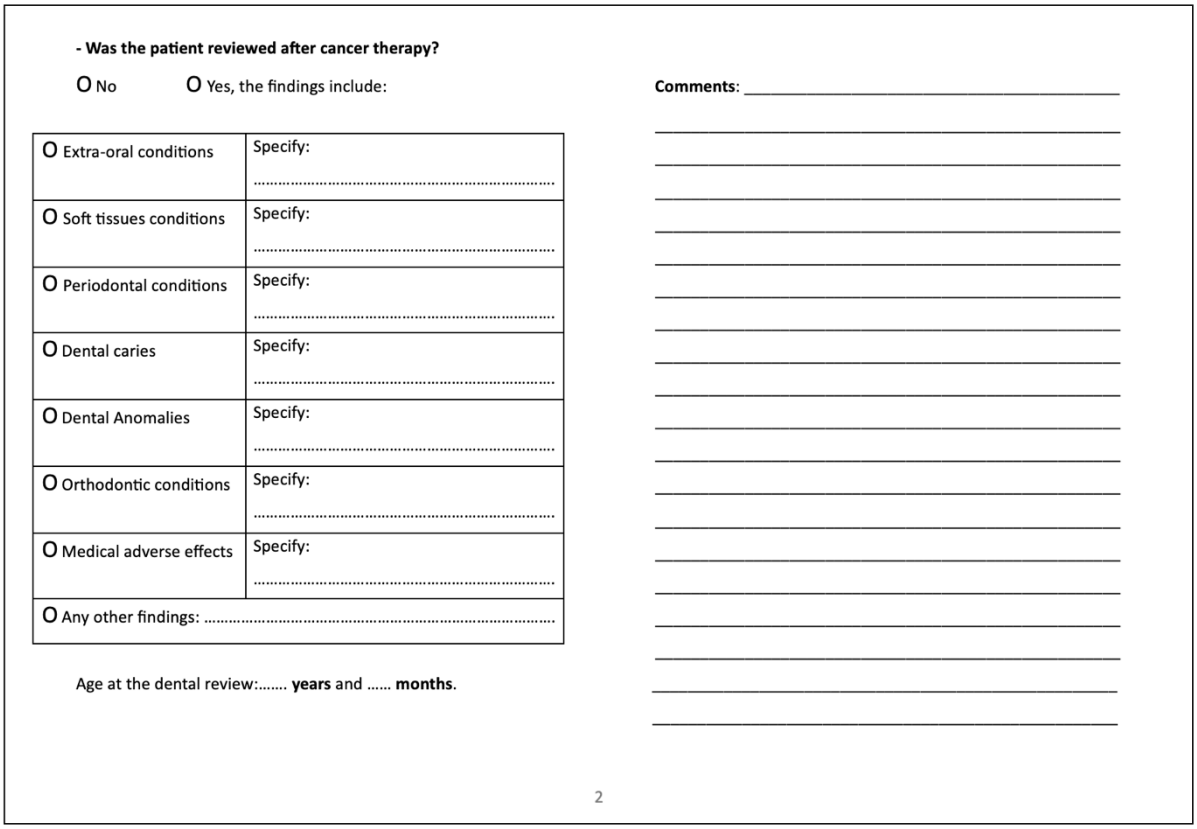
O No O Yes, the findings include:

O Extra-oral conditions	Specify: .....
O Soft tissues conditions	Specify: .....
O Periodontal conditions	Specify: .....
O Dental caries	Specify: .....
O Dental Anomalies	Specify: .....
O Orthodontic conditions	Specify: .....
O Medical adverse effects	Specify: .....
O Any other findings:	

1

Patients were identified from a list of cancer patients' appointments obtained from the department of paediatric dentistry at LDI of paediatric cancer patients who attended appointments in LDI's paediatric dental clinics from January 2009 until January 2021. Data from 806 appointments were reviewed and investigated through the electronic dental management system Salud, the medical management system PPM+ and the radiology system Infinitt.

Figure 2.3 Second page of the data collection used for the service evaluation.



- Was the patient reviewed after cancer therapy?

O No O Yes, the findings include:

Comments: _____

O Extra-oral conditions	Specify: .....
O Soft tissues conditions	Specify: .....
O Periodontal conditions	Specify: .....
O Dental caries	Specify: .....
O Dental Anomalies	Specify: .....
O Orthodontic conditions	Specify: .....
O Medical adverse effects	Specify: .....
O Any other findings:	

Age at the dental review:..... **years** and ..... **months**.

2

2.2.3 Data Analysis

Data were recorded on a Microsoft Excel™ spreadsheet. For each patient, the following data were recorded: gender, diagnosis, age at diagnosis and treatment, type of cancer therapy, length of treatment, treatments provided: chemotherapy (which medication), radiotherapy (targeted, whole-body radiation), oral conditions following the treatment including extraoral findings such as facial growth deficiencies, intraoral findings such as dental anomalies, dental caries and the periodontal conditions and any other general medical side effects secondary to cancer therapy. The data were analysed using SPSS software, and the results were presented in tables featuring descriptive statistics.

3. Chapter 3: Results

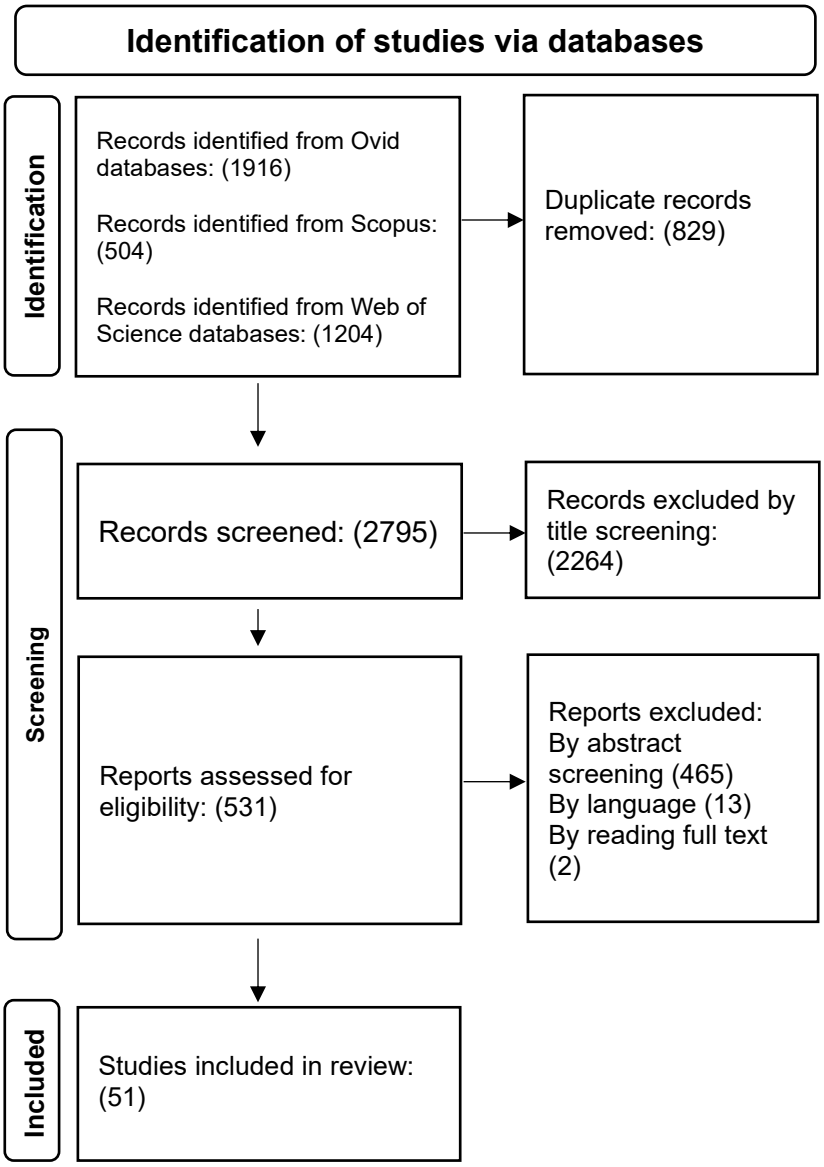
3.1 Review of the Literature Results:

3.1.1 Results of the databases search

This study identified 3624 records from Ovid databases, Scopus, and Web of Science, with no records found in the Cochrane Library. After eliminating duplicates, we proceeded to screen the results based on titles and abstracts. Fifty-three records were selected for full-text review following the specific inclusion and exclusion criteria outlined in Chapter 2. Two articles were excluded after reading the full texts; both articles aimed to study the long-term adverse effects of cancer in patients who were treated during their adulthood (Khojastepour et al., 2012, Hamilton et al., 2022). A detailed flow diagram of the database search results is provided in Appendix 1. Figure 3.1 shows a detailed flow diagram of the database search results.

Of the 51 studies included in the analysis, 68.6% (35) were cross-sectional studies, 2% (1) were a cohort study, and 29.4% (15) were case-control studies.

Figure 3.1 Flow diagram of the database search results.



3.1.2 Summary of the Findings

3.1.2.1 Chemotherapy Studies

In 1999, Alpaslan et al. studied 30 children who had been in remission from lymphoma and had undergone chemotherapy. The children were compared to 20 age-matched healthy controls. The findings indicated a higher prevalence of dental anomalies among the children who had received chemotherapy, including root malformations, enamel hypoplasia, and teeth agenesis. The chemotherapy

agents included Procarbazine, Cyclophosphamide, Vincristine and Prednisolone (Alpaslan et al., 1999).

Similar findings were observed in other studies; a 2007 study by Avsar et al. involving 96 childhood cancer survivors reported enamel disturbances in 69.8% of the participants. Arrested root development with short V-shaped roots was the most frequent root malformation, and microdontia was detected in lateral incisors and premolars in 5.2% of the survivors (Avsar et al., 2007).

Khojastepour's 2014 research on children treated for ALL compared to healthy children showed a high frequency of dental anomalies like taurodontism, short roots, and tooth agenesis in ALL patients (Khojastepour et al., 2014). Similarly, in 2016, Krasuska-Slawinska et al. found that children who had received chemotherapy had a significantly higher incidence of dental defects, including enamel defects, tooth agenesis, microdontia, root resorption, and taurodontism, than controls (Krasuska-Slawinska et al., 2016).

Another study by Lauritano and Petruzzi in 2012 focused on children who survived leukaemia. Their results indicated that these children were at a higher risk for dental caries and experienced a greater severity of dental anomalies when compared to the control group (Lauritano and Petruzzi, 2012).

Research conducted on children treated for specific types of cancer, like Wilms tumours, also confirmed these findings. Marec-Berard et al.'s 2005 study revealed that 70% of children treated for Wilms tumour developed dental

abnormalities, including root stunting, enamel hypoplasia, microdontia, and hypodontia (Marec-Berard et al., 2005).

Studies have also shown the implications of chemotherapy on salivary gland function, as noted in Nemeth et al.'s 2014 study. They found that children post-chemotherapy had a higher caries rate and reduced saliva flow (Nemeth et al., 2014).

In contrast, Nunn's 1991 study highlighted that dental anomalies were common among children after cancer treatment; however, the dental caries experience was similar between treated children and controls in England (Nunn et al., 1991). It is worth mentioning that according to PHE 2023, the national prevalence of caries in 5 year old children is 29.3% (PHE, 2023) . This suggests that a considerable proportion of young children in England have dental caries, regardless of cancer treatment.

Research from Jodlowska and Postek-Stefańska indicated the importance of the developmental stage of tooth formation during chemotherapy. Their studies suggested that while specific chemotherapy agents like cisplatin might be associated with dental developmental changes, the timing of chemotherapy relative to dental development might be another significant factor (Jodłowska and Postek-Stefańska, 2021).

In 2011, Hsieh and his team conducted a study involving 106 patients who had undergone treatment before the age of 16 years, and who had been in remission for over five years. The study highlighted a dose-dependent relationship between

the dose of cyclophosphamide and dental disturbances. Specifically, those administered with high doses showed an increased tendency towards dental anomalies and reduced salivary flow (Hsieh et al., 2011).

Lastly, Pedersen's 2012 study emphasised the association between chemotherapy at an early age and dental abnormalities. The study showed that children exposed to chemotherapy before eight years of age had a significantly higher incidence of microdontia and hypodontia than healthy children (Pedersen et al., 2012).

In conclusion, the studies mentioned above collectively highlight the profound implications of chemotherapy on paediatric dental health.

3.1.2.2 Summary of Mixed Treatment Modalities Studies

Combined Chemotherapy and Radiotherapy treatment

Kupferman et al. conducted a retrospective case review study in 2010 to report treatment outcomes among cancer survivors. The study involved 61 patients who underwent radiotherapy, chemotherapy and surgery. Notably, permanent facial paresis and xerostomia were documented in 12% and 4% of the patients, respectively (Kupferman et al., 2010). A 2003 study by Minicucci et al. on paediatric patients with acute lymphoblastic leukaemia found that 82.9% of the participants displayed at least one dental anomaly post-chemotherapy. The study emphasised on the importance of age of treatment in influencing these dental abnormalities (Minicucci et al., 2003).

In 2004, Alberth et al. conducted research involving 45 long-term cancer survivors who had undergone antineoplastic treatments, including chemotherapy and irradiation. The DMFT scores for these survivors were notably higher than their age and sex-matched controls, signifying a clear association between treatment and dental decay. Moreover, this study uncovered various dental anomalies, such as short V-shaped roots predominantly in the lower incisors and enamel hypoplasia. The mode of treatment, whether solely chemotherapy or a combination of chemotherapy and radiotherapy, did not show significant differences in dental outcomes (Alberth et al., 2004).

Further corroborating these findings, numerous other studies from researchers such as Atif, Cubukcu, Estilo, Halperson, et al. consistently highlighted that childhood cancer survivors showed an elevated incidence of dental anomalies, including microdontia, enamel defects, tooth agenesis, and abnormal root developments. Additionally, many of these studies highlighted a greater susceptibility to these dental anomalies among children who had undergone anticancer therapies at younger ages. White enamel opacities were especially frequent among these survivors (Estilo et al., 2003, Cubukcu et al., 2012, Halperson et al., 2022, Atif et al., 2022)

Kaste et al.'s research in 1998 and 2009 further emphasised the profound dental effects of combined anticancer therapies. Childhood cancer survivors, especially those diagnosed before age five, exhibited dental abnormalities like microdontia, hypodontia, root abnormalities, and severe gingivitis. Radiation exposure amplified these risks (Kaste et al., 1998, Kaste et al., 2009).

The effects are not limited to dental anomalies alone. Karsila-Tenovuo et al. highlighted deviations in craniofacial structures due to antineoplastic therapies (Karsila-Tenovuo et al., 2001). Mattos et al. noted significant dental and craniofacial alterations, mainly when treatment was administered before age five. These include facial asymmetry, reduced facial depth, and short mandibles (Mattos et al., 2019).

Other studies like those from Nishimura et al., Owosho et al., Quispe et al., and Sonis et al., focused on the dental and craniofacial anomalies in childhood cancer survivors, highlighting the susceptibility of younger patients, especially those treated before the age of five (Sonis et al., 1990, Nishimura et al., 2013, Owosho et al., 2016, Quispe et al., 2019, Defabianis et al., 2023).

Combined Chemotherapy, Radiotherapy and SCT

The impact of combined treatment, including total body irradiation and stem cell transplantation following chemotherapy, on dental development has been the focus of various studies. Nasman et al., in their 1994 study, evaluated the oral health and dental development disturbances in children who are long-term survivors after receiving antineoplastic therapy. A sample of 57 children were treated with chemotherapy, and 19 were treated with total body irradiation before bone marrow transplantation. Children who underwent total body irradiation were found to have a noticeably reduced salivary secretion rate. Moreover, disturbances in root development were more pronounced in the chemotherapy-treated group (Nasman et al., 1994).

Holtta et al. published two studies in 2005. First, they examined the relationship between total body irradiation, age at stem cell transplantation, and the prevalence of agenesis and microdontia in permanent teeth. The study included 55 patients, categorised based on their total body irradiation status and age at transplantation. One of the findings of this study was that younger recipients at the time of transplantation had a heightened likelihood of manifesting missing and microdontic teeth (Holtta et al., 2005a).

The second study by Holtta et al. focused on dental root development in 52 stem cell transplant recipients who underwent treatment before the age of ten years. Panoramic radiographs were employed to measure the crown-root ratios of fully matured permanent teeth. These ratios were subsequently compared with teeth from gender-matched controls. The research found that 77% of fully developed permanent teeth exhibited anomalies. Furthermore, teeth from the group exposed to total body irradiation demonstrated more pervasive abnormalities compared to the non-irradiated group. This was mainly in patients who underwent transplantation between the ages of three and five, with their teeth showing the most severe discrepancies in the crown-root ratios (Holtta et al., 2005b).

Ko et al. 2013 study focused on the relationship between anticancer therapy and the ectopic eruption of permanent first molars (PFMs) in a cohort of 564 patients. The study, which involved 76 children treated with different anticancer therapies and a control group of 488 children, showed an increased prevalence of ectopic eruptions in the former. Moreover, children who began their therapy before the

age of three years suffered from a higher risk of these dental anomalies (Ko et al., 2013).

Nasman and Dahllof conducted a study comparing dental development in children who received total body irradiation, cyclophosphamide and bone marrow transplantation to children treated with multiagent chemotherapy. The study found that short V-shaped roots were present in 94% of children treated with total body irradiation and cyclophosphamide compared to 19% in the chemotherapy group. Reduced tooth size was more pronounced in the total body irradiation and cyclophosphamide group. The study further revealed that the most severe disturbances were found in children treated at a young age (Nasman et al., 1997).

In 2016, Proc et al. conducted a comparative analysis of panoramic radiographs from 61 cancer survivors and 521 healthy subjects, revealing that dental anomalies, including tooth agenesis and microdontia, were remarkably more pronounced in cancer survivors (Proc et al., 2016). In 2019, another study concluded that while dental caries prevalence was consistent across the study groups, the DMFT was significantly increased in patients who had undergone head and neck radiotherapy (Proc et al., 2019). A later 2022 study revealed that malocclusion patterns differed between cancer survivors and their healthy peers, with the head and neck radiotherapy group showing a higher tendency for crossbites and dental malalignment (Proc et al., 2022).

Rabassa-Blanco et al., in a 2022 study, reported that 85.3% of patients who had undergone early childhood cancer treatment had some dental sequelae, further highlighting the susceptibility of these patients to dental anomalies with microdontia being the most prevalent (Rabassa-Blanco et al., 2022).

A 2021 study by Seremidi et al. noticed a high prevalence of root defects among childhood cancer survivors, particularly those treated with combined protocols, SCT, head and neck irradiation, and chemotherapy (Seremidi et al., 2021).
Lastly, Tanaka et al.'s 2017 research, which included 56 childhood cancer survivors, revealed that almost half the cohort experienced dental anomalies (Tanaka et al., 2017). The tables below summarise each study's outcome based on the treatment modality.

In 2021, Immonen and colleagues retrospectively examined panoramic radiographs of 178 survivors diagnosed with leukaemia under 17. The findings revealed that children treated for acute lymphoblastic leukaemia showed a higher risk of dental anomalies. Mainly, microdontia was prevalent among children who were diagnosed before the age of six years (Immonen et al., 2021).

3.1.3 Summary Tables

Table 3.1 *Summary of the outcomes of chemotherapy studies*

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
(Alpaslan, et al.,1999) Case-control study	30 children (23 male and 7 female), aged 4 to 15 Years.	Cyclophosphamide Oncovine Procarbazine Prednisolone Cyclophosphamide Vincristine Prednisolone Adriamycin L-asparaginase Methotrexate Mercaptopurine Adriamycin Bleomycin Vinblastine Dacarbazine Dexamethasone Prednisolone Vincristine Etoposide Cytosine arabinocide Methotrexate	No significant difference was found between the study and control groups for the gingival index. A higher plaque index was found in the treatment group compared to their controls.	There were no significant differences between the study and control groups.	Root malformations were found in 23 teeth from 9 children out of 30 in the study group. Enamel hypoplasia and Tooth agenesis were significantly higher in the treatment group. Teeth agenesis was found to be statistically significant higher in the study group.	No statistically significant differences were observed between the groups.	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
		Leucovorine Ifosfamide Adriamycin Cyclophosphamide Vindecine sulphate					
(Avsar et al., 2007) Case-control study	96 cancer survivors, 50 boys and 46 girls aged 3 to 13 years.	Not specified	Plaque and gingival index scores were significantly higher in the treated subjects than in the controls. A significantly lower stimulated salivary flow was observed in the study group.	The study group had significantly higher dental caries than the control group.	Enamel disturbances were significantly higher in the study group. Treated subjects showed 52.1% arrested root development with short V-shaped roots and 5.2% with arrested root development and premature apical closure.	**N/A**	**N/A**
(Khojastepour et al., 2014) Case-control study	25 patients including 9 girls and 16 boys. With an age range of 4 to 14 years.	Not specified	**N/A**	**N/A**	There was a statistically significant difference in the incidence of dental anomalies	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					between the case and control groups. Taurodontism was the most commonly found anomaly, with a 16% frequency		
(Krasuska-Slawinska et al., 2016) Cross-sectional study	120 patients with a mean age at treatment of 6 years.	Cyclophosphamide Doxorubicin Etoposide Cisplatin Ifosfamide Actinomycin Dacarbazine Methotrexate Carboplatin Vinblastine Cytarabine Teniposide Fluorouracil Bleomycin Irinotecan	**N/A**	**N/A**	Vincristine, methotrexate, had a positive correlation with enamel hypoplasia. Dental root resorption was positively correlated with age at treatment start, vincristine, cyclophosphamide, ifosfamide, cisplatin, and their doses. Severe root resorption positively correlated with doxorubicin,	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					etoposide, and teniposide. Positive correlation between the absence of tooth buds, certain drugs (vincristine, cyclophosphamide, doxorubicin, ifosfamide, etoposide), and their doses. Vincristine treatment and its doses were related to all observed congenital disorders.		
(Lauritano and Petruzzi, 2012) Case-control study	52 survivors, 27 females, 25 males with a mean age at the treatment of 11.5 years.	Methotrexate Vincristine Daunoblastine Prednisone Desamethasone	**N/A**	The DMFT was significantly higher in leukaemic survivors than in the control group.	Microdontia was more frequent in leukaemic survivors. Upper incisors, canine, and premolars were most affected.	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					Enamel hypoplasia was found in 17% (nine patients) of leukaemic survivors, mainly on the upper lateral incisors and molars. Dental agenesis was observed in 13% (seven patients) of leukaemic survivors, compared to 3.8% (two subjects) in the control group.		
(Marec-Berard et al., 2005) Cross-sectional study	27 patients including 11 males and 16 females with a mean age of 3.6 years	Vincristine Actinomycin Adriamycin Etoposide, Carboplatin Ifosfamide Etoposide	**N/A**	**N/A**	Of the 27 patients treated for nephroblastoma, 19 (70%) displayed dental abnormalities. The specific dental abnormalities found among patients were: Hypodontia in 2 patients (7%), Microdontia in 5	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					patients (18%), Enamel hypoplasia in 6 patients (22%), and Root stunting in 12 patients (44%). The study population and the control group significantly differed regarding the general incidence of dental abnormalities. Microdontia and taurodontia were significantly more common in the study group than in the control group.		
(Nemeth et al., 2014) Case-control study	38 12-year-old children who had received chemotherapy between the ages	Protocols of chemotherapy:	Hyposalivation was detected in 11 out of 38 patients but not in the controls. Stimulated Saliva Flow was significantly lower in the study group	The DMFT was significantly higher in the patient group compared to the controls.	**N/A**	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
	of 31 months and six years.	BFM-95[1] NBL-2 CWS 96 SIOP 93 BFM-98 COSS-96 DAL-HD 90	than in the control group.				
(Nunn et al., 1991) Case-control study	52 cancer survivors (22 males and 30) with an age range of 4.75 to 24.25 years.	Not specified	**N/A**	**N/A**	Significantly more children in the treated group showed radiographic evidence of enamel hypoplasia, Taurodontism Microdontia, Thin roots, and Root constrictions.	**N/A**	**N/A**
(Pedersen et al., 2012) Cross-sectional study	150 children with an age range of 1 to 7 at the treatment	Vincristine Cytarabine Cyclophosphamide Ifosfamide Carboplatin	**N/A**	**N/A**	Microdontia of premolars or permanent molars was found in 19.3% of the 150 children		**N/A**

1 BFM-95=protocol for acute lymphoblastic lymphoma, Berlin-Frankfurt-Munster, NBL-2 = protocol for neuroblastoma, CWS 96 = protocol of Cooperative Soft Tissue Sarcoma Study Group, SIOP 93 = international protocol of the International Society of Paediatric Oncology, BFM-98=protocol for acute lymphoblastic lymphoma, Berlin-Frankfurt-Munster, COSS-96 = protocol of Cooperative Osteosarcoma Study Group, DAL-HD 90 = protocol for Hodgkins's disease.

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
		Cisplatin Etoposide Doxorubicin Dactinomycin Bleomycin Methotrexate Asparaginase			exposed to chemotherapy, while none of the controls had this condition. There was a causal relationship between exposure to chemotherapy and microdontia, supported by an association between microdontia and exposure to chemotherapy before three years of age.	**N/A**	
(Jodłowska and Postek-Stefańska, 2023) Cross-sectional study	40 cancer survivors, aged 5 to 18 years at the treatment.	Vincristine Daunorubicin Asparaginase Methotrexate Cyclophosphamide Cytarabine Mercaptopurine Doxorubicin Thioguanine	**N/A**	**N/A**	No significant statistical correlation was found between the length of intensive treatment, the total duration of treatment, and the occurrence of dental irregularities.	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy medications used	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					No significant correlation was observed between dental abnormalities and the total accumulated doses of chemotherapy.		

Table 3.2 *Summary of the outcomes of combined chemotherapy and radiotherapy studies*

Study and type	**Sample size and age range at treatment**	**Chemotherapy agents used / radiation therapy dose.**	**Soft tissue and periodontal findings**	**Dental caries findings**	**Dental anomalies findings**	**Orthodontic and craniofacial growth findings**	**Other findings**
(Kupferman et al., 2010) Cross-sectional study	61 cancer survivors with an age range of 3.7 to 18.9 years at the treatment	**Chemotherapy:** not specified. **Radiotherapy:** the mean dose of radiation was 58.6 Gy	Permanent facial paresis was noted in 7 patients (12%) and xerostomia in 1 patient (4%).	**N/A**	**N/A**	**N/A**	**N/A**
(Minicucci et al., 2003) Cross-sectional study	76 cancer survivors were treated (43 male and 33 female) with an age range of 1 to 12 years old at the treatment.	**Chemotherapy:** Vincristine Daunorubicin L-asparaginase Methotrexate Cyclophosphamide Cytarabine 6-Mercaptopurine Doxorubicin 6-Thioguanine Dexamethasone **Radiotherapy:** The radiation dose	**N/A**	**N/A**	Out of 76 children treated, 63 (82.9%) had at least one dental abnormality, including late dental development and microdontia. The first and second upper and lower premolars had a higher incidence of abnormalities.	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
		ranged from 18 - 24 Gy.					
(Alberth et al., 2004) Case-control study	45 cancer survivors (25 boys and 20 girls), aged 4 to 25 years.	**Chemotherapy:** not specified. **Radiotherapy:** The radiation dose ranged from 12 - 40 Gy.	**N/A**	DMFT scores were higher in all age groups of patients compared to control groups.	17/45 patients had short V-shaped roots, mainly in the lower incisors. 12/45 patients had enamel hypoplasia in 48 teeth. One patient had microdontia in the lower frontal and premolar regions; another had an extra tooth in each premolar quadrant. Hypodontia was observed in three patients, affecting six teeth, while in the control group, only one child had two	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					lower premolars missing. The differences in the prevalence of these dental anomalies between patients and control groups were highly significant. However, no significant connections were found between these anomalies and potential causes like the type of disease, therapy received, or age when therapy was applied.		
Atif et al., 2022) Cross-sectional study	120 children with a mean age of 5.7 years at the start of cancer treatment	Not specified	**N/A**	**N/A**	Statistically significant differences in the prevalence of microdontia, abnormally shaped	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					teeth and developmental defects of enamel were detected between the sample and the control groups, with Increased risk in the sample group. 40.9% of children who began anticancer therapy before 4 years of age showed microdontia, compared to 15% (4–5 years age group) and 10.3% (>6 years age group). The most common defect in the sample		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					was white enamel opacities (11.7%).		
(Cubukcu et al., 2012) Case-control study	37 Cancer survivors (23 males and 14 females) aged 3 to 9 years at the start of cancer treatment.	**Chemotherapy:** not specified. **Radiotherapy:** the radiation dose was between 25 and 59 Gy.	**N/A**	**N/A**	Altered root development was observed in 86.4% (26 out of 30) of the study group. Only 6.7% of mature permanent teeth remained unaffected in children who underwent both chemotherapy and radiotherapy treatments, compared to 68.2% in the group that received only chemotherapy treatment. There was a significant difference in missing teeth	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					between the study group and the controls. Microdontia was identified in 13.5% of the cancer survivors' group, with five children having 19 microdontic teeth. There was a statistically significant difference in the number of microdontic teeth between the treatment groups and controls.		
(Estilo et al., 2003) Cross-sectional study	10 Cancer survivors (8 males and 2 females) aged 1 to 19 years at the start of cancer treatment.	**Chemotherapy:** not specified. **Radiotherapy:** the radiation dose was	**N/A**	**N/A**	Out of 10 patients studied, 8 exhibited enamel defects and root deformities.	The most common clinical and radiographic findings was bony hypoplasia	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
		between 50 and 61 Gy.				and facial asymmetry.	
(Guagnano et al., 2022) Cross-sectional study	52 (31 males and 21 females) childhood cancer survivors.	Not specified.	**N/A**	**N/A**	Significant differences between childhood cancer survivors and control subjects were noted in root malformations, microdontia, and tooth agenesis. 59.6% of childhood cancer survivors showed alterations in root development vs. 11.5% of controls. There were more frequent root alterations in patients treated with both chemotherapy and radiotherapy	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					compared to those with chemotherapy alone and more in patients treated before five years of age who received SCT. 6.6% of teeth in cancer survivor subjects exhibited microdontia vs. none in controls. Most of these were detected in patients who underwent therapy before age 5. The number of missing teeth was higher in survivors than in controls. Childhood cancer survivors had		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					significantly more enamel defects than controls. The mean dmft (decayed, missing, filled primary teeth) score was significantly higher in the survivors' group compared to the controls. For permanent dentition, subjects had higher DMFT scores than controls.		
(Jodłowska and Postek-Stefańska, 2021) Cross-sectional study	38 childhood cancer survivors with a range of 4 months to 8 years and 6 months at the cancer treatment.	Not specified.	**N/A**	**N/A**	Hypodontia (missing teeth) was observed in 5 out of 38 (13.16%) cancer survivors. All five individuals had undergone chemotherapy, with	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					none receiving head radiotherapy. Among these five individuals, 13 teeth were missing, categorised as two lateral incisors, one first premolar, five second premolars, three second molars, and two third molars. Of the five survivors with hypodontia, 3 had additional dental abnormalities such as microdontia, reduced crown size, and root stunting. One survivor, missing all second premolars, was		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					treated at the early odontogenesis age period and reported a one-year delay in teeth eruption. Three survivors missing a total of 6 teeth received chemotherapeutic medications just before the growth of hard dental tissues. The remaining two patients, missing three teeth, began their therapy before or at the onset of the expected initiation of odontogenesis.		
(Jodlowska and Postek-Stefanska, 2022a)	37 cancer survivors were treated with antineoplastic	**Chemotherapy:** Vincristine Doxorubicin Daunorubicin	**N/A**	**N/A**	There were significant differences in treatment duration	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
Cross-sectional study	therapy before 10 years of age.	Cyclophosphamide Ifosfamide Etoposide Carboplatin Cisplatin Actinomycin-D **Radiotherapy:** not specified.			between affected and non-affected patients for microdontia in the doxorubicin group. Significant positive correlations were identified in the affected group between microdontia in cyclophosphamide recipients.		
(Jodlowska and Postek-Stefanska, 2022b) Cross-sectional study	37 childhood cancer survivors with a range of 0 to 9 years at the cancer treatment.	**Chemotherap**y: Vincristine Doxorubicin Cyclophosphamide Etoposide Carboplatin Actinomycin D **Radiotherapy:** not specified.	**N/A**	**N/A**	Most abnormalities were observed after the administration of the highest drug doses. In most patients who received the least toxic doses, tooth anomalies were either higher or comparable to the	**N/A**	The highest number of abnormalities per person was observed in survivors treated with the highest doses of vincristine, doxorubicin,

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					average for each drug group.		cyclophosphamide, and actinomycin D.
(Karsila-Tenovuo et al., 2001) Case-control study	40 cancer survivors aged between 3 and 7 years at the start of cancer therapy.	**Chemotherapy:** Not specified. **Radiotherapy:**19.5 – 59.6 Gy.	**N/A**	**N/A**	**N/A**	Children treated for intracranial tumours had shorter midface and ramus dimensions and lower anterior-posterior alveolar heights than the controls.	**N/A**
(Kaste et al., 2009) Case-control study	8522 cancer survivors with a median age of 6 years at the start of treatment.	Not specified	Survivors reported a higher likelihood of severe gingivitis. Xerostomia was more prevalent among survivors.	**N/A**	Survivors were more likely to report microdontia, hypodontia, abnormal root development, and enamel hypoplasia than controls.	**N/A**	**N/A**
				Fifteen patients (29%) had	Dental anomalies were identified in 37	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
(Kaste et al., 1998) Cross-sectional study	52 childhood cancer survivors ranging from 0 – 7 years at the start of the cancer therapy.	Not specified.	**N/A**	more than four decayed or filled primary teeth at the beginning or during treatment, with a mean of 7.8 affected teeth.	of the 52 eligible children. Microdontia was observed in twenty patients (38%). Root stunting was present in nine patients (17%). Hypodontia and enamel hypoplasia each occurred in 9 patients (17%). Eighteen patients (35%) exhibited more than one type of dental abnormality.		
			23 patients reported trismus.		**N/A**	**N/A**	Patients exposed to radiotherapy had significantly

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
(Kilinc et al., 2019) Case-control study	93 childhood cancer survivors whose ages at cancer treatment were between 9 months and 7 years.	Not specified.	A significant relationship existed between the years after radiotherapy and complaints of limited mouth opening. Mucositis increased significantly with the rising number of radiotherapy sessions.	**N/A**			reduced width of the mandibular canal, decreased cortex thickness, and limited maximum jaw opening compared to controls.
(Mattos et al., 2019) Cross-sectional study	27 childhood cancer survivors (15 males and 12 females) whose ages at cancer treatment were between 0	**Chemotherapy:** Doxorubicin Ifosfamide Vincristine Actinomycin Cyclophosphamide Etoposide	**N/A**	**N/A**	Root shortening was the most frequent dental abnormality, accounting for 24.2% of abnormalities, followed by partial	A significant proportion, 74.1% of the patients, displayed asymmetric facial features, 70.4%	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
	months and 5 years.	**Radiotherapy:** 41.4 to 5.4 Gy.			and total anodontia, which accounted for 17.7%. When assessing the location of tumours, patients with tumours in the nasopharyngeal, nasal cavity, and paranasal sinus areas showed the highest frequency of dental abnormalities at 45.1%. Patients diagnosed and treated between the ages of 0 and 5 years exhibited the most dental alterations, which was statistically significant.	had a reduced facial depth, and 77.8% showed reduced facial height.	

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					Chemotherapy and radiotherapy dosages did not significantly influence the number of dental abnormalities.		
(Nishimura et al., 2013) Cross-sectional study	46 long-term survivors treated for paediatric cancers aged between 0 to 13 years at the start of the treatment.	**Chemotherapy:** Busulfan Cyclophosphamide Melphalan Thiotepa Ranimustine Ifosfamide **Radiotherapy:** doses given were 12 Gy.	**N/A**	**N/A**	89.1% (41 out of 46) of all cancer survivors exhibited tooth formation anomalies. The occurrence of short-rooted teeth was most pronounced in those with tooth agenesis/microdonts across different treatment types Tooth formation anomaly scores	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					were notably higher in the high dose chemotherapy group than in the conventional chemotherapy group. The overall tooth formation anomaly scores were significantly higher in the high dose chemotherapy group group than in the conventional chemotherapy group. Among subjects treated with high dose chemotherapy, the tooth formation anomaly scores were significantly		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					higher in those who received busulfan than those who received cyclophosphamide.		
(Owosho et al., 2016) Cross-sectional study	13 childhood cancer survivors whose ages at cancer treatment were between 1.5 months and 13 years.	**Chemotherapy:** Not specified. **Radiotherapy:** doses given were between 45 and 50.4 Gy.	Three patients (treated between 5 and 13 years of age) presented with xerostomia. Four patients exhibited trismus, treated between ages 5 and 13 years. Xerostomia was reported in four patients treated between ages 7 to 13 years.	**N/A**	Nine patients (treated between 1.6 and 7 years of age) exhibited effects on dental tissue, including tooth agenesis, root agenesis/stunting, and malformed enamel. These patients received radiation doses of 45-50.4 Gy to the mid-face. Root agenesis/stunting was observed in all nine patients, affecting both jaws	Statistically significant findings of the impacts of the treatment on patients include facial asymmetry and jaw hypoplasia. Seven patients (treated between 1.6 and 7 years of age) presented with facial asymmetry and jaw hypoplasia.	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					and anterior and posterior teeth. Hypodontia involving posterior teeth was identified in seven patients. Enamel hypoplasia was identified in three patients	Jaw hypoplasia was observed in both the maxilla and mandible. The primary tumours in these patients were in the mid-face region and received radiation doses between 25-50.4 Gy to the maxilla.	
(Quispe et al., 2019) Case-control study	97 childhood cancer survivors aged between 0.5 to 15 years at the start of cancer therapy.	**Chemotherapy:** Vincristine Doxorubicin Methotrexate Cyclophosphamide **Radiotherapy:** ranged between 12 to 54 Gy.	**N/A**	**N/A**	More dental anomalies were identified in the panoramic radiographs of childhood cancer survivors compared to the control group. Microdontia, hypodontia and root	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					anomalies were more prevalent in the study group compared to the control group. In the study group, impacted teeth were the only anomalies associated with the type of antineoplastic treatment. Of those with impacted teeth, 75% underwent chemotherapy with radiation Therapy, and 25% underwent only chemotherapy. Microdontia was the only anomaly associated with age at cancer diagnosis. However, the duration of treatment		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					did not show a significant statistical difference in the prevalence of dental anomalies.		
(Sonis et al., 1990) Cross-sectional study	97 childhood cancer survivors Who were younger than 10 years of age when therapy began.	**Chemotherapy:** Methotrexate **Radiotherapy:** doses between 18-24 Gy	**N/A**	**N/A**	Patients more than 5 years at diagnosis who had not received radiation therapy had the lowest disturbance. Most severe dental-developmental disturbances were observed in patients less than 5 years at diagnosis. Patients less than five years at diagnosis had significantly higher dental disturbance	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					scores than older patients.		
(Stolze et al., 2021) Cross-sectional study	154 survivors, aged between 0.3 to 16.1 years at the start of cancer therapy.	**Chemotherapy:** Ifosfamide Busulfan Melphalan Vincristine Vinblastine **Radiotherapy:** Not specified	**N/A**	**N/A**	36.1% of the study group had at least one dental anomaly. The most prevalent dental anomalies were short roots (14.6%), agenesis/hypodontia (14.3%) and microdontia (13.6%). Over 19.9% had dental anomalies in either the lower or upper premolars. Missing teeth were predominantly second premolars, while microdontia predominantly	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					affected first premolars.		
(Tanem et al., 2022) Cross-sectional study	46 survivors (22 females and 24 males) with a range of 0.2 to 19.2 years at the cancer treatment.	**Chemotherapy:** Alkylating agents and vincristine **Radiotherapy:** Ranged between 23.4 and 36 Gy	17.4% of the survivors showed mild oral dryness, and 2.2% had moderate signs. 35% had reduced mouth opening.	There was no significant difference in the DMFT score between survivors treated at age of 5 years and less than 5 years.	30.4% of participants had one or more dental anomalies.	**N/A**	**N/A**
(Defabians et al., 2023) Cross-sectional study	88 survivors with an age range of 2 to 8 years at the start of treatment	Not specified	**N/A**	**N/A**	The most common dental anomaly observed was abnormal root development (72.0%), followed by microdontia and tooth agenesis,	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					occurring in 28.4% of cases. Children treated before age 5 more commonly exhibited tooth agenesis and microdontia, while older children predominantly showed alterations in root development.		
(Stolze et al., 2022) Cross-sectional study	292 participants who were 0 to 17 years old at the diagnosis of cancer.	Not specified	9.4% of survivors reported experiencing xerostomia.	**N/A**	**N/A**	**N/A**	**N/A**
(Stolze et al., 2023) Cross-sectional study	249 participants with a median age of treatment at 5.3 years old.	**Chemotherapy:** Alkylating agents Vinca alkaloids Anthracyclines Epipodophyllotoxins Platinum compounds	The most common self-reported oral health issues were oral blisters or aphthae (25.9%) and halitosis (23.3%). Regarding dental	Dental caries were reported in 34.0% of the participants.	**N/A**	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
		Radiotherapy: mean dose of 36 Gy.	problems, the most frequently mentioned were gum issues (31.6%) and sensitivity in exposed root surfaces (22.1%).				

Table 3.3 *Summary of the outcomes of combined chemotherapy, radiotherapy and stem cell transplantation studies*

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
(Hölttä et al., 2002) Cross-sectional study	18 patients With age range at cancer treatment of 1 to 5.8 years	**Chemotherapy:** Etoposide Cisplatin Cyclophosphamide Dacarbazine Vincristine Doxorubicin **Radiotherapy:** ranged between 6 to 20 Gy.	**N/A**	**N/A**	Disturbances in dental development: In the high-dose chemotherapy and autologous stem cell transplantation with total body irradiation group, only 5.1% of mature permanent teeth were unaffected compared to 64.3% in the non-TBI group. All patients in the TBI group had missing teeth, with a mean of 6.6 missing teeth.	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					In the TBI group, 27.7% of the teeth were missing, compared to 4.8% in the non-TBI group. Microdontia: commonly found but with no difference between the TBI and non-TBI groups. 9.3% of teeth in the TBI group were affected		
(Nasman et al., 1994) Cross-sectional study	19 children (8 boys, 11 girls) with an age range of 1.8 to 8.4 years at the treatment.	**Chemotherapy:** Cyclophosphamide **Radiotherapy:** A range between 7 to 10 Gy.	Children treated with SCT had a significantly lower salivary secretion rate than those treated with chemotherapy and healthy controls.	**N/A**	The chemotherapy group and the SCT group had a significantly higher number of teeth affected by enamel disturbances than the healthy controls.	**N/A**	A significantly higher proportion of children treated with SCT or Chemotherapy had higher streptococci mutant counts than controls.

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
			A higher proportion of children in the Chemotherapy and SCT groups exhibited a low buffer capacity of saliva.		Children treated with SCT had significantly more disturbances in dental development. All types of disturbances were more frequent in children treated with SCT than those treated with chemotherapy. Children treated with SCT exhibited a significantly higher mean number of teeth with disturbances in root development compared to those treated with chemotherapy and the control group.		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					Younger children, particularly those younger than 5.4 years of age at the time of TBI, showed the most extensive and severe dental disturbances.		
(Holtta et al., 2005a) Cross-sectional study	55 patients, including 28 males and 27 females who underwent cancer treatment at ages between 1 and 9.4 years	**Chemotherapy:** Prednisolone Vincristine Doxorubicin Methotrexate L-asparaginase Cyclophosphamide Cytosine arabinoside 6-mercaptopurine Dacarbazine Cisplatin Ifosfamide Etoposide Actinomycin D Bleomycin	**N/A**	**N/A**	Agenesis of permanent teeth occurred in 31% of the SCT recipients. Agenesis was most prevalent in the youngest group. The number of missing teeth in TBI-treated patients was statistically higher than in non-TBI patients.	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
		Radiotherapy: ranged between 6 to 24 Gy.			Microdontia was present in 44% of the analysed patients. Younger SCT recipients had significantly higher rates of microdontia.		
(Holtta et al., 2005b) Cross-sectional study	52 patients, with a range age at the treatment of 1 to 9.4 years.	**Chemotherapy:** Prednisolone Vincristine Doxorubicin Methotrexate L-asparaginase Cyclophosphamide Cytosine arabinoside 6-mercaptopurine Dacarbazine Cisplatin Ifosfamide Etoposide Actinomycin D	**N/A**	**N/A**	All 52 paediatric recipients of SCT showed altered root development. Patients in the TBI group were more severely affected than non-TBI patients.	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
		Bleomycin **Radiotherapy:** ranged between 6 to 24 Gy.					
(Hsieh et al., 2011) Cross-sectional study	106 participants with a range of 1.3 - 8.5 years at the start of cancer treatment.	**Chemotherapy:** Cyclophosphamide Doxorubicin Vincristine Vinblastine Actinomycin-D Methotrexate **Radiotherapy:** Not specified.	In the group that received total body irradiation, 37.5% of children had lower salivary flow rates.	**N/A**	Age at the start of treatment and treatment types, such as total body irradiation (TBI) and head and neck irradiation, were significant predictors of the Holtta's Defect Index (HDI)[2] scores. HDI scores increased with	**N/A**	**N/A**

[2]. Holtta et al. invented the Holtta Defect Index (HDI) in 2002 to assess dental defects in childhood bone marrow transplantation patients (Holtta et al., 2002). The HDI integrates abnormalities in the root-to-crown ratio, microdontia, and tooth agenesis, summarising the overall damage to the permanent dentition into a single figure. A higher HDI indicates greater deviations from normal tooth development, with a normal HDI being 0.

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					greater doses of cyclophosphamide. The proportion of teeth with a below-average crown-root ratio was 21% higher in individuals taking any cyclophosphamide dosage.		
(Immonen et al., 2021) Cross-sectional study	178 participants aged 3 – 6 at the treatment	**Chemotherapy:** Prednisolone Dexamethasone Vincristine Doxorubicin Methotrexate (MTX) L-asparaginase 6-Mercaptopurine (6MP) Cytosine arabinoside Cyclophosphamide **Radiotherapy:** 10 to 24 Gy.	**N/A**	**N/A**	Seventy patients (39%) had at least one detectable dental abnormality. Younger patients (below six years at diagnosis) had significantly more abnormal teeth than those diagnosed between ages 6 and 17. Microdontia was significantly more	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					common in younger patients, with 5.7% of their teeth affected, compared to 0.6% in older patients.		
(Ko et al., 2013) Case-control study	76 cancer survivors	Not specified	**N/A**	**N/A**	There was a significantly higher prevalence of ectopic eruption in the anticancer therapy group, 16%, compared to the control group, 5%. Patients who started anticancer therapy after three years old had a noticeably lower prevalence of ectopic eruption than those who started	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					treatment before three years old.		
(Nasman et al., 1997) Cross-sectional study	68 children treated at the age of 2 to 10 years old.	**Chemotherapy:** Cyclophosphamide Methotrexate Cyclosporin **Radiotherapy:** The range of doses was from 18 to 24 Gy.	**N/A**	**N/A**	Children in the SCT group exhibited disturbances in dental development significantly more often than children treated with chemotherapy alone. Crown size in the SCT group was significantly reduced compared to the control and chemotherapy groups. Severe root development disturbances, especially in the SCT group, mainly	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					accounted for the total tooth size reduction. In the SCT group, crown/root ratios were significantly correlated with age at TBI or initiation of chemotherapy.		
(Proc et al., 2016) Case-control study	61 survivors with a range of 1 month to 16.3 years from the beginning of anticancer therapy.	Not specified	**N/A**	**N/A**	Cancer survivors showed an increased prevalence of tooth agenesis in the central incisors, second premolars, and first and second molars compared to the control group. Microdontic teeth were found more often among first and second	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					premolars and second and third molars in cancer patients compared to the control group. Teeth with short roots were significantly more common among first and second premolars and first and second molars in cancer survivors. The frequency of teeth with short roots was greater in patients with cancer than in control subjects. The number of cancer patients with various dental		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					anomalies was higher than control subjects. Ten cancer patients had more than one dental abnormality (16.39%) versus 1.72% in the control group.		
(Proc et al., 2019) Case-control study	109 childhood cancer survivors, age at the start of cancer treatment ranged from 4 to 18 years.	Not specified	**N/A**	Cancer survivors had significantly more deciduous teeth with active caries. The total DMFT score was higher among	**N/A**	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
				cancer survivors. Patients undergoing additional radiotherapy of the head and neck region had significantly higher scores of deciduous teeth filled and higher scores of DMFT and decay in their permanent teeth.			

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
(Proc et al., 2022) Cross-sectional study	75 survivors between the age of 4 to 18 at the examination.	Not specified	**N/A**	**N/A**	**N/A**	Cancer patients were more likely to demonstrate anterior and posterior crossbites and malalignment of teeth than the control group. Patients who began therapy later in life were more prone to tooth disturbances such as malalignment, crowding, or spacing.	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
(Rabassa-Blanco et al., 2022) Cohort study	109 survivors with a range age of 1.2 to 4.6 years at the start of treatment	Not specified	**N/A**	**N/A**	Microdontia was the most common dental alteration in 52.3% of the patients. Older patients at the start of treatment had fewer dental lesions. Starting therapy before 36 months increased the relative risk for the presence of lesions by 2.19 times. The risk for microdontia was 3.43 times higher, and for taurodontism, it was 6.21 times higher when treatment	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					started before 36 months. Alkylating agents (e.g., cyclophosphamide, cisplatin, carboplatin) were associated with a higher number of dental lesions and, specifically, higher rates of agenesis, root alterations and microdontia. Patients treated with radiotherapy and chemotherapy and those who underwent SCT presented with more dental sequelae.		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					SCT patients had increased tendencies for microdontia, agenesis, and root changes.		
(Seremidi et al., 2021) Cross-sectional study	70 survivors who were treated at ages 0 to 10 years.	**Chemotherapy:** Alkylating agents Cyclophosphamide Antimetabolites Steroids Vincristine **Radiotherapy:** Not specified	**N/A**	**N/A**	Root defects were found in 62% of the participants. Impaired root growth was the most common defect. Arrested root growth was seen in 30%. Microdontia and tapered roots each affected 28% of participants. Among patients with crown defects, 90% had impaired root	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					growth, 49% had arrested root growth, and 42% had microdontia. Younger age at diagnosis was linked to agenesis; older age to taurodontism. Patients undergoing combined treatments presented more impaired root growth and delayed eruptions. Impaired root growth was higher in those irradiated in the head and neck. Antimetabolites, steroids, and		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					vincristine were associated with impaired root growth, taurodontism, agenesis, and delayed eruption. Higher dosages of cyclophosphamide were linked to a higher incidence of arrested root growth. More severe defects were found in older patients at the examination, those who underwent combination treatments, and those with more years since treatment ended.		

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					High doses of cyclophosphamide increased the risk of severe dental defects by eight times; undergoing SCT increased it by nine.		
(Tanaka et al., 2017) Cross-sectional study	56 survivors, aged 0 to 13.7 years at the start of cancer treatment.	**Chemotherapy:** Alkylating agent Vincristine Vinblastine **Radiotherapy:** Not specified	**N/A**	**N/A**	73.2% of patients had oral or maxillofacial abnormalities. 46.4% had dental defects, including hypodontia, 16.1%, abnormal roots, 16.1%, enamel hypoplasia, 10.7%, and microdontia, 21.4%. There was no significant association between	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					DDA incidence and primary disease or treatment.		
(Halperson et al., 2022) Cross-sectional study	121 survivors with Age Range of 0.1–17.7 years at the start of treatment.	**Chemotherapy:** Prednisolone Dexamethasone Vincristine Doxorubicin Methotrexate (MTX) L-asparaginase 6-mercaptopurine (6MP) Cytosine arabinoside Cyclophosphamide **Radiotherapy:** 27–70 Gy.	**N/A**	**N/A**	46% of patients had at least one dental anomaly. Hypomineralisation or hypoplasia of enamel was present in 17% of patients. Microdontic teeth were seen in 17% of patients, altered root development in 21%, and hypodontia in 11%. Patients treated at age six or younger were more likely to have DDA. 56% had malformed teeth.	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
					All types of DDA were more frequent in patients who began anticancer treatment at age six or younger. Patients receiving radiation had a higher DMFT than those with chemotherapy alone. Those who had received any radiation also had more malformed teeth.		
(Latoch et al., 2022) Cross-sectional study	561 children diagnosed with cancer before the age of three years with a range of range 0.03 to 2.99 years.	Not specified	Oral and masticatory dysfunction was found in 26.9%.	**N/A**	**N/A**	**N/A**	**N/A**

Study and type	Sample size and age range at treatment	Chemotherapy agents used / radiation therapy dose.	Soft tissue and periodontal findings	Dental caries findings	Dental anomalies findings	Orthodontic and craniofacial growth findings	Other findings
(Seremidi et al., 2023) Cross-sectional study	70 Childhood cancer survivors diagnosed and treated before the age of 10 years.	**Chemotherapy:** Alkylating agent Cyclophosphamide Antimetabolites Steroids Vincristine **Radiotherapy:** Not specified.	**N/A**	The mean dmft score for primary dentition was 1.26, while the mean DMFT score for permanent dentition was 1.65	Among 58 participants, anomalies were observed, with enamel defects being the most common. Other defects were found in decreasing order of frequency: microdontia in 15%, hypodontia in 8.5%, malformed teeth in 4.3%, and oligodontia in 2.8%. Notably, microdontia occurred significantly more frequently in older patients.	**N/A**	**N/A**

3.2 Service Evaluation of Paediatric Cancer Patient Data at Leeds Dental Institute

3.2.1 Patient Demographics and Cancer Diagnoses

From 2009 to 2023, 806 patients who had received cancer treatment and were seen in either LDI or Leeds General Infirmary during ward visits were identified. Out of this group, only 85 patients were eligible for the study as they had complete and accessible medical and dental records. For excluded patients, their dental records were either unavailable because they were recorded on paper forms during ward visits while under treatment for cancer, or they were stored in an older, inaccessible version of the patients' dental record system (Salud). Some patients' files which were not transferred to the new Salud system were for excluded patients who either passed away, discontinued their follow-up at LDI, or were diagnosed with Thalassemia and did not undergo any form of anticancer therapy. Of the eighty-five patients, 47 (55.3%) were males and 38 (44.7%) females. The mean age at the start of cancer treatment was 5.6 years (SD = 4.2) with a range of 3 months to 16 years of age at the induction of cancer treatment (Table 3.2). Patients' ages at the start of cancer treatment were categorised as follows: 49 (57.65%) were less than 6 years old, 30 (35.29%) were between 6 and 12 years old, and 6 (19.77%) were over 12 years old (Table 3.3). At the final evaluation, the mean patient age was 9.9 years (SD = 3.92) with a mean range between

the treatment start and the first dental assessment of 4.25 years (SD = 2.75) (Table 3.2).

Table 3.4 Descriptive statistics of patients' ages at cancer treatment and dental appointments.

Variable	Min	Max	Mean	Std. Deviation
Age at cancer treatment in years	0.25	16	5.65	4.21
Age at dental appointment in years	3	18	9.90	3.92
Range between treatment start and the first dental assessment	0	14	4.25	2.75

Table 3.5 Ranges of patients' ages included in the research.

Age at cancer treatment	N	%
Less than 6 years	49	57.64
Between 6 and 12 years	30	35.29
More than 12 years	6	7.05
N =	85	100

Cancer diagnoses in this patient population included acute lymphoblastic leukaemia (37.64%), neuroblastoma (8.23%), rhabdomyosarcoma (7.05%), Wilms tumour (7.05%), and others such as Ewing's sarcoma, osteosarcoma, and Hodgkin's lymphoma. Three patients (3.52%) were diagnosed with aplastic anaemia or beta thalassemia major but have received antineoplastic therapy (Table 3.4).

Table 3.6 Patient diagnosis with corresponding numbers and percentages.

Diagnosis	N	%
Acute lymphoblastic leukaemia	32	37.64 %
Acute myeloid leukaemia	4	4.70 %
Aplastic anaemia	1	1.17 %
Beta thalassaemia major	2	2.35 %
Brain stem ganglioglioma	1	1.17 %
Chronic myeloid leukaemia	2	2.35 %
Dysplastic gangliocytoma of the cerebellum	1	1.17 %
Ependymoma	2	2.35 %
Ewings sarcoma	3	3.52 %
Hepatoblastoma	1	1.17 %
Hodgkin's lymphoma	3	3.52 %
Immunoblastic malignant lymphoma	1	1.17 %
Lymphoblastic lymphoma	3	3.52 %
Medulloblastoma	3	3.52 %
Metastatic primitive neuroectodermal tumour	1	1.17 %
Neuroblastoma	7	8.23 %
Osteosarcoma	4	4.70 %
Pineal germinoma	1	1.17 %
Primitive myxoid mesenchymal tumour of Infancy	1	1.17 %
Rhabdomyosarcoma	6	7.05 %
Wilms tumour	6	7.05 %
N =	85	100 %

3.2.2 Cancer Treatment Types and Combinations

Eighty-one patients received chemotherapy, 28 patients received radiotherapy, and 14 of the 85 received SCT (Table 3.5).

Table 3.7 Modalities of treatments provided to patients.

Chemotherapy		**%**
YES	81	95.3 %
NO	4	4.70 %
Radiotherapy		**%**
YES	29	34.12 %
NO	56	65.88 %
SCT		**%**
YES	14	16.47 %
NO	71	83.53 %

Treatment combinations included chemotherapy with radiotherapy in 24 patients, chemotherapy and stem cell transplantation in 7 patients, chemotherapy, radiotherapy and SCT in 5 patients while 45 patients received only chemotherapy and 2 patients received SCT only. Two patients received other types of treatments included surgery and immunosuppressive therapy alone (Table 3.6).

Table 3.8 Combinations of treatment modalities administered to patients.

Type of treatment	**Chemotherapy**	**Radiotherapy**	**SCT**
Chemotherapy	45	24	7
Radiotherapy	24	0	0
SCT	7	0	2
Chemotherapy Radiotherapy and SCT	5		
Other modalities only	2		

3.2.3 Chemotherapy

The average length of chemotherapy treatment was 18 months, with an average number of 18.84 cycles (Table 3.7).

Table 3.9 Descriptive statistics of chemotherapy administered to patients.

Variable	Min	Max	Mean	Std. Deviation
Length of Chemotherapy in months	1	62	18	14.8
Number of chemotherapy cycles	1	67	18.84	13.2

The most commonly used chemotherapeutic agents in the 81 patients who received chemotherapy were vincristine, cyclophosphamide, cytarabine and doxorubicin. Other less commonly used medications included anthracyclines, bleomycin. Additional medications used in a small percentage of patients included anti-GD2 antibody hydrocortisone and granulocyte colony-stimulating factor (Table 3.8).

Table 3.10 Chemotherapy medications used with the corresponding number of patients and percentages.

Medication	N	%
Actinomycin	20	24.69%
Amsacrine	2	2.47%
Anthracyclines	1	1.23%
Anti GD2 antibody	2	2.47%
Asparaginase	3	3.70%
Alemtuzumab	1	1.23%
Bendamustine	1	1.23%
Bevacizumab	1	1.23%
Bleomycin	1	1.23%
Blinatumomab	1	1.23%
Brentuximab	1	1.23%
Busulphan	5	6.17%
Campath	1	1.23%
Carboplastin	20	24.69%

Medication	N	%
Carmustine	1	1.23%
Cisplatin	15	18.52%
Clofarabine	2	2.47%
Cyclophosphamide	56	69.14%
Cytarabine	38	46.91%
Dacarbazine	2	2.47%
Dasatinib	1	1.23%
Daunorubicin	18	22.22%
Dexamethasone	5	6.17%
Doxorubicin	38	46.91%
Etoposide	34	41.98%
Fludarabine	9	11.11%
GCSF	2	2.47%
Hydrocortisone	11	13.58%
Idarubicin	7	8.64%
Ifosfamide	13	16.05%
Imatinib	1	1.23%
Inotuzumab	1	1.23%
Irinotecan	1	1.23%
Isotretinoin	2	2.47%
Lomustine	4	4.94%
Melphalan	3	3.70%
Mercaptopurine	33	40.74%
MESNA	16	19.75%
Methotrexate	45	55.56%
Mifamurtide	3	3.70%
Mitoxantrone	6	7.41%
Mitozantrone	1	1.23%
Ozogamicin	1	1.23%
Pegaspargase	30	37.04%
Pembrolizumab	1	1.23%
Prednisolone	1	1.23%
Procarbazine	1	1.23%
Retinoic acid	2	2.47%
Rituximab	3	3.70%
Ruxolitinib	1	1.23%
Temozolomide	1	1.23%

Medication	N	%
Thioguanine	1	1.23%
Thyroxine	1	1.23%
Tioguanine	2	2.47%
Topotecan	1	1.23%
Trametinib	1	1.23%
Vincristine	68	83.95%
Vinblastine	1	1.23%
Vinorelbine	2	2.47%

3.2.4 Radiotherapy

Among the patients receiving radiotherapy, 25 (86.21%) received targeted radiation, and 4 (13.79%) received total-body irradiation. The average radiotherapy period was 3 months, with an average of 17.62 fractions and an average dose of 26.72 Gy (Table 3.9).

Table 3.11 Descriptive statistics of radiotherapy administered to patients.

	Minimum	Maximum	Mean	Std. Deviation
Range of radiotherapy in months	0.03	21.8	3	5.37
Number of radiotherapy fractions	1	47	17.62	12.85
Dose of radiotherapy (Gy)	12	56	26.72	12.83

3.3.5 Dental and Oral Health Evaluation During Anticancer Treatment

In this service evaluation, data from 85 patients were analysed. Among them, 16 (18.82%) had a dental assessment/examination during and after cancer treatment, while 70 (82.35%) were assessed after cancer treatment only, as they were referred to LDI on completion of their anticancer therapy. Of the 16 who were assessed during and after their cancer treatment, one patient

(6.25%) presented with a dental anomaly already present during cancer treatment (generalised hypomineralisation of first permanent molars), while the rest (93.75%) had none. Dental caries was present in 8 patients (50%), while the other half of the patients seen during cancer treatment (50%) were caries-free. Gingival hyperplasia was observed in 2 patients (12.5%), while the rest (87.5%) had no periodontal conditions. Moreover, none of the patients exhibited growth anomalies or orthodontic conditions. Mucositis was observed in 2 patients (12.5%), and 14 patients (87.5%) had none. These detected oral conditions were later excluded from the findings after the completion of anticancer therapy to prevent duplicated findings.

3.3.6 Dental and General Medical Conditions After Anticancer Treatment

When the records were examined at a period after treatment had been completed, a more significant number of patients were shown to have dental anomalies (26.7%), including hypodontia, short roots, enamel hypoplasia and root agenesis (figures 3.2-3.4). Dental caries was recorded in 26.7% of patients following treatment; among the affected teeth, the permanent first molars were the most affected, followed by the first primary molars.

Three patients (3.5%) had periodontal conditions, while 18 (20.9%) were assessed as having orthodontic conditions, including dental crowding and impactions, anterior open bite and crossbite. Additionally, seven patients (8.1%) had soft tissue conditions. Eight patients (9.3%) had facial and temporomandibular joint conditions and 18 (20.22%) presented with other medical and general side effects of anticancer treatment including growth hormone deficiency, and epistaxis. Table 3.10 summarises the findings of

dental and general medical conditions after anticancer treatment in the whole sample.

Figure 3.2 A panoramic radiograph of a patient who received vincristine, doxorubicin, dactinomycin, ifosfamide and radiotherapy of 15 Gy at the age of 1 year showing hypodontia of the upper right and left first premolars and lateral incisors, the lower second premolars and the lower right third molars and microdontic upper and lower left third molars.

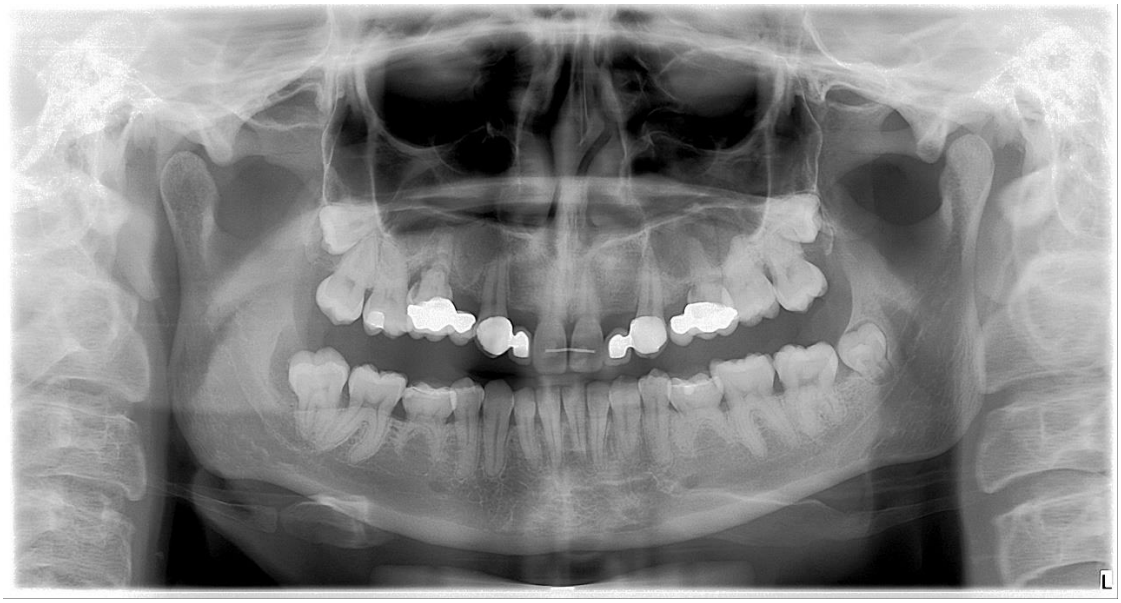


Figure 3.3 A panoramic radiograph of a patient who received dexamethasone, vincristine, daunorubicin, cytarabine, thioguanine, etoposide, asparaginase, methotrexate, hydrocortisone, mercaptopurine, cyclophosphamide, mitoxantrone and radiotherapy of 14.4 Gy at the age of 2.5 years showing short roots of lower first molars and lower anterior teeth.

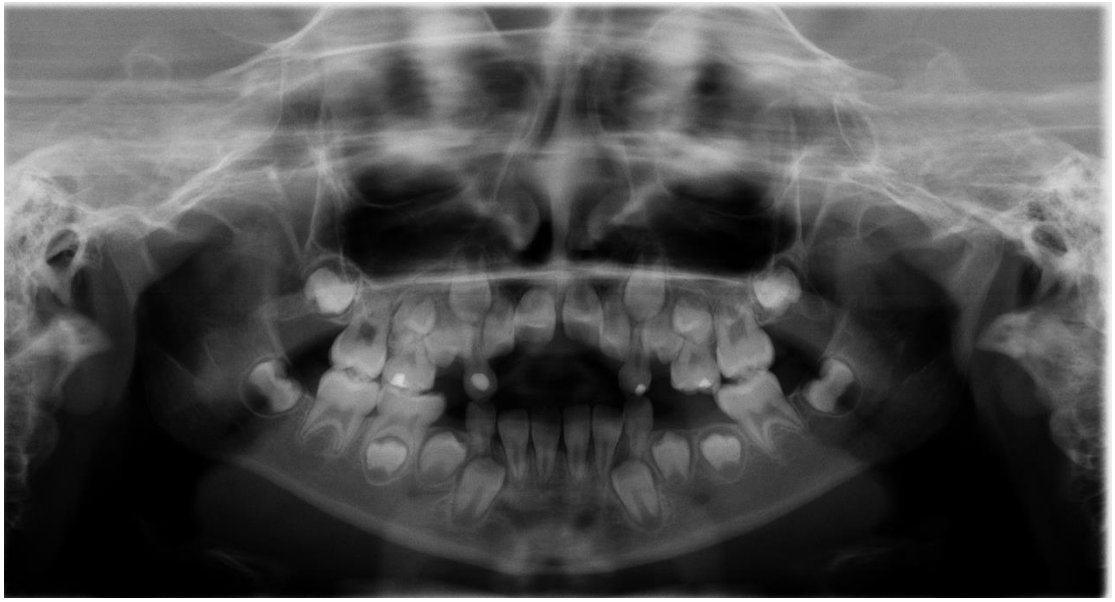


Figure 3.4 A panoramic radiograph of a patient who received vincristine, methotrexate, mercaptopurine, doxorubicin, cyclophosphamide, cytarabine, hydrocortisone, mesna and etoposide at the age of 3 years showing generalised enamel hypoplasia, short roots of first molars and rotation of upper left and lower left premolars and the lower left canine.

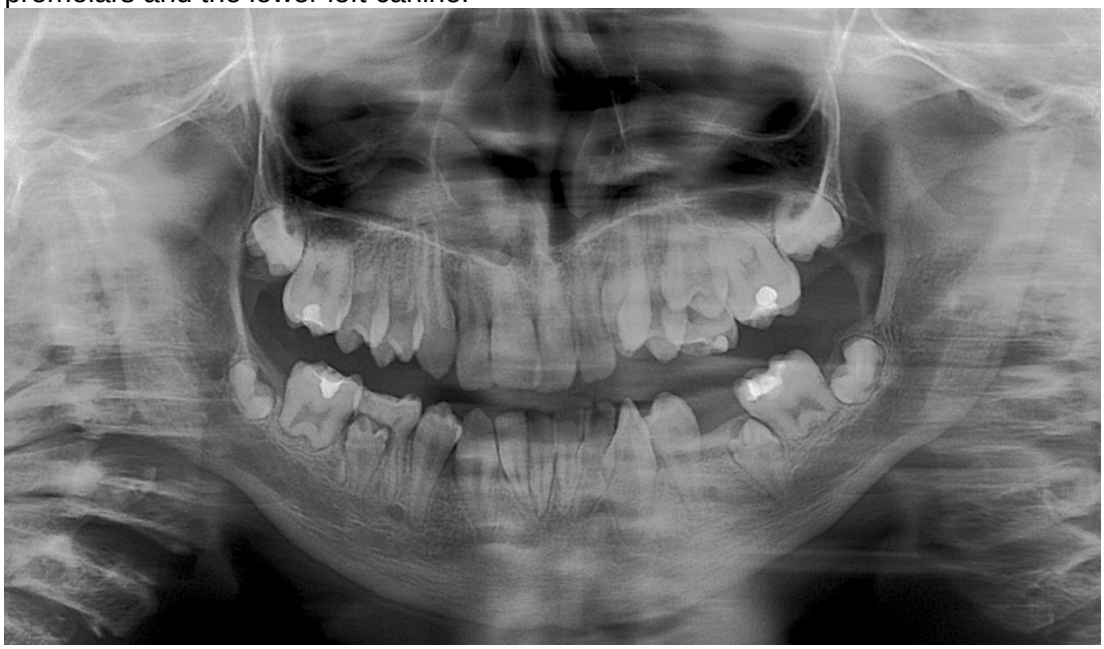


Table 3.12 Dental and general medical findings following anticancer treatment.

Dental Anomalies		
Type	**Number**	**Percentage**
Enamel hypomineralisation in primary teeth	1	1.18 %
Enamel hypomineralisation in permanent teeth	8	9.41 %
Enamel hypoplasia	5	5.88 %
Hypodontia	5	5.88 %
Microdontia	5	5.88 %
Supernumerary teeth	2	2.35 %
Root anomalies	2	2.35 %
Periodontal findings		
Type	**Number**	**Percentage**
Gingival hyperplasia	1	1.18 %

Increased mobility of teeth	1	1.18 %
Generalised gingival recession	1	1.18 %
Orthodontic findings		
Type	**Number**	**Percentage**
Delayed eruption and retained primary teeth	7	8.23 %
Dental crowding and impactions	4	4.70 %
Anterior open bite	1	1.18 %
Increased overjet	2	2.35 %
Increased overbite	4	4.70 %
Decreased over jet	1	1.18 %
Rotated teeth	1	1.18 %
Infra-occluded teeth and ectopic eruptions	4	4.70 %
Crossbites	5	5.88 %
Soft tissues findings		
Type	**Number**	**Percentage**
Xerostomia	2	2.35 %
Hyperkeratotic patches	1	1.18 %
Oral haematoma	1	1.18 %
Oral granuloma	1	1.18 %
Eruption cysts	2	2.35 %
Sloughing of mucosa	1	1.18 %
Facial and Temporomandibular Joint (TMJ) findings		
Type	**Number**	**Percentage**
Trismus	5	5.88 %
Facial pain	2	2.35 %
Facial palsy	2	2.35 %

Facial asymmetry	1	1.18 %
Mandibular hypoplasia	1	1.18 %
TMJ disorder	1	1.18 %
Other medical findings		
Type	**Number**	**Percentage**
Epistaxis secondary to radiotherapy	2	2.35 %
Ataxia	1	1.18 %
Hemiplegia and bulbar palsy	1	1.18 %
Cardiac dysfunction secondary to chemotherapy	1	1.18 %
Nasolacrimal duct blockage	1	1.18 %
Thrombocytopenia secondary to chemotherapy	1	1.18 %
Liver toxicity secondary to chemotherapy	1	1.18 %
Growth hormone deficiency	4	4.70 %
Recurrent urinary tract infections	1	1.18 %
Anxiety and learning difficulties	1	1.18 %
Sleep apnoea	2	2.35 %
Hypothyroidism	1	1.18 %
Joint pain	1	1.18 %
Gastroesophageal reflux	1	1.18 %

3.3.6.1 Findings according to age at cancer treatment

Subgroup 1 – Less than 6 years at start of cancer treatment:

Forty nine of the eighty-five included patients were less than six years old when they started their cancer therapy. 23 (46.7%) were female, and 26 (53.3%)

were male. The mean age at initiation of cancer therapy was 2.5 years (SD = 1.34), with a mean age at the first dental visit of 7.7 years (SD = 3.07) and a mean range between treatment and the first dental visit of 5.18 years (SD = 2.8). Of those patients, 46 (93.88%) had received chemotherapy, 19 patients (38.77%) had received radiotherapy, and SCT was received by nine patients (18.36%).

Soft tissue and periodontal findings included gingival hyperplasia in 1 patient, and increased mobility of the upper incisors in 1 patient (2.04%). Hyperkeratotic patches on the tongue and buccal mucosa were noticed in 1 patient (2.04%), xerostomia in 1 patient (2.04%), haematoma in the anterior midline on alveolar ridge in 1 patient (2.04%) and granuloma in the upper right region in 1 patient (2.04%).

Dental caries were found in 20 of 49 patients (40.81%). Fourteen of this group (28.57%) were diagnosed with dental anomalies, including hypodontia in two patients (4.08%), which was mainly noted in the upper and lower second premolars, with generalised short root defects in 2 patients (4.08%), and microdontia in 5 patients (10.2%) mainly affecting premolars and permanent molars. Enamel defects were noted in 9 patients (64.28%), including generalised enamel hypoplasia and hypomineralisation of permanent incisors and molars.

Orthodontic findings included dental crowding (6.12%), increased overjet and overbite (4.08 %), impacted canines (2.04%), anterior open bite (2.04%) and anterior/posterior crossbites (2.04%). Other facial and TMJ findings included

trismus (2.04%), myofacial pain (2.04%), limited mouth opening (2.04%), mandibular hypoplasia (2.04%), restricted mouth opening (2.04%) and unilateral facial palsy (2.04%).

Subgroup 2: From 6 to 12 years at start of cancer treatment:

Thirty patients were between 6 and 12 years old when they started their cancer therapy. Eleven of the 30 (36.67 %) were female, and nineteen (63.33%) were male. The mean age at the start of cancer therapy was 9.13 years (SD = 2.09), with a mean age at the first dental assessment of 12.4 years (SD = 2.76) and a mean time between treatment and dental assessment of 3.33 years (SD = 2.17). Thirty patients in this subgroup (100%) received chemotherapy, 10 patients (33.33%) received radiotherapy, and SCT was received by three patients (10%).

Soft tissue and periodontal findings included gingival hyperplasia, generalised gingival recession in 1 patient, and xerostomia in another (3.33%). Dental caries was diagnosed in 12 of these patients (40%).

Dental anomalies were observed in 7 patients (23.33%). One patient, (3.33%) exhibited hypodontia that specifically affected the second premolars. Another patient had a generalised short root defect. Additionally, enamel defects were noted in five patients (16.66%). These enamel issues were characterized by generalised enamel hypoplasia and hypomineralisation, predominantly affecting the permanent incisors and molars.

Orthodontic findings included increased overjet and overbite in two patients (6.66%), anterior crossbites in two patients (6.66%), rotated permanent second molars (3.33%) and severe infra-occluded primary molars (3.33%).

Other facial and TMJ findings included facial palsy (2.04%), facial asymmetry (2.04%), limited mouth opening (3.33%), facial and TMJ pain (3.33%), and restricted mouth opening (6.66%).

Subgroup 3: over 12 years of age at the start of treatment:

Six patients were older than 12 years when they started cancer treatment, with a mean age of 14 years (SD = 1.26). The mean age at the dental appointment was 15.3 years old (SD = 1.03), and the mean range between the treatment and the first dental assessment was 1.3 years (SD = 1.03).

One patient had sloughing of dental mucosa, two had dental caries, and one had hypodontia affecting all premolars except the lower right first premolar. Orthodontic findings included increased overbite and bilateral posterior crossbite.

3.3.6.2 Findings according to modalities of treatment

Chemotherapy group:

Forty-five patients received chemotherapy only; of these, 26 were male (57.78%) and 19 were female (42.22%) (Table 3.11).

Table 3.13 Descriptive statistics of patients who received chemotherapy only.

	Minimum	Maximum	Mean	Std. Deviation
Age at cancer treatment in years	1	16	5.7111	4.33601
Age at the dental visit in years	3	18	9.31	4.100
Range between treatment and the dental visit	0	9	3.60	2.016
Length of chemotherapy in months	2	62	23.51	15.997
Number of chemotherapy cycles	2	67	22.24	15.354

Four patients had soft tissue findings (8.88%), including granuloma in the upper anterior region, haematoma in the anterior midline on the alveolar ridge, sloughing of the mucosa and hyperkeratotic patches on the tongue and buccal mucosa.

Three patients had dental anomalies, including microdontia and root anomalies affecting the second permanent molars, mainly affecting the first and second premolars. Enamel defects were noted in 8 patients (17.78 %), including generalised enamel hypoplasia and hypomineralisation of permanent incisors and molars, and 17 patients had dental caries.

Ten patients presented with orthodontic findings, including rotated permanent second molars, increased overjet, anterior and posterior crossbite, crowding, delayed eruption of central incisors and severely infra-occluded primary molars.

One patient who was treated for ALL at 11 years of age suffered from limited mouth opening, TMJ and facial pain. Another who was treated for ependymoma at the age of 1 year old had facial palsy 5 years following cancer treatment.

Chemotherapy and radiotherapy group:

The total of patients who received a combination of chemotherapy and radiotherapy was 24. Of those, 14 were male (58.33%) and 10 were female (41.67%) (Table 3.12).

Soft tissue and periodontal findings included increased mobility of upper anterior teeth in one patient (treated for rhabdomyosarcoma at the age of 4) and generalised gingival recession in another (treated for medulloblastoma at the age of 8). Three patients presented with dental anomalies (12.5%), including hypodontia mainly affecting premolars, microdontia of premolars and second permanent molars and short roots of first permanent molars. Enamel defects were noted in 5 patients (4.16%), including generalised enamel hypoplasia and hypomineralisation of permanent incisors and molars.

Orthodontic findings were reported in four patients (16.66%), including dental crowding, increased overbite and reduced overjet and anterior crossbite.

Five patients had TMJ and facial findings (20.83%), including trismus, myofascial pain, limited mouth opening, mandibular hypoplasia, restricted mouth opening, facial palsy, facial asymmetry and limited mouth opening. Four of these patients were treated for rhabdomyosarcoma at the

ages of 3, 4 and 5 years. The fifth patient was treated at the age of eight years for medulloblastoma.

Table 3.14 Descriptive statistics of patients who received chemotherapy and radiotherapy.

Description	Minimum	Maximum	Mean	Std. Deviation
Age at cancer treatment in years	1	12	5.4583	3.74142
Age at the dental visit in years	4	16	10.38	3.549
Range between treatment and the dental visit	1	11	4.92	3.049
Length of chemotherapy in months	2	36	9.63	7.070
Number of chemotherapy cycles	4	31	14.83	7.562
Length of radiotherapy in days	1	654	99.50	173.587
Number of radiotherapy fractions	1	47	19.63	13.041
Dose of radiotherapy (Gy)	13	56	29.21	12.667

Chemotherapy and SCT group:

Seven patients received a combination of chemotherapy and SCT (Table 3.13). Of those, three were male and four were female. Four patients presented with dental caries. The others were caries-free; no other findings were noted during their dental assessment. Table 3.13 summarises the descriptive statistics of those patients.

Table 3.15 Descriptive statistics of patients who received chemotherapy and stem cell transplants.

Description	Minimum	Maximum	Mean	Std. Deviation
Age at cancer treatment in years	2	14	8.7143	4.34796
Age at the dental visit in years	6	16	11.57	3.505

Description	Minimum	Maximum	Mean	Std. Deviation
Range between treatment and the dental visit	1	4	2.86	1.215
Length of chemotherapy in months	1	31	8.57	10.406
Number of chemotherapy cycles	1	19	8.29	5.964

Chemotherapy, radiotherapy and SCT group:

Five patients received chemotherapy, radiotherapy, and SCT (Table 3.14). Two were male and 3 were female. Four patients received total body irradiation, and one received targeted radiation.

Two patients presented with dental anomalies, including generalised severe short roots in both patients, and microdontia affecting second premolars and a supernumerary tooth in one patient.

One patient presented with dental caries, and two patients presented with orthodontic findings, including increased overjet and overbite, crowding, impacted canines and retained primary teeth.

Table 3.16 Descriptive statistics of patients who received chemotherapy, radiotherapy, and stem cell transplant.

Description	Minimum	Maximum	Mean	Std. Deviation
Age at cancer treatment in years	0.25	5	2.45	2
Age at the dental visit in years	7	15	10	3.16
Range between treatment and the dental visit	3.00	10.75	7.55	3.144
Length of chemotherapy in months	4	37	21.20	12.71
Number of chemotherapy cycles	10	32	22.20	8.70
Length of radiotherapy in days	1	175	45.60	73.23
Number of radiotherapy fractions	1	14	8	6.12
Dose of radiotherapy (Gy)	12	21	14.76	3.68

Other treatment modalities group:

Two patients received SCT only, one received surgery only, and another received immunosuppressive therapy.

Gingival hyperplasia was detected in one patient who received immunosuppressive therapy only for chronic myeloid leukaemia at the age of two years. Dental caries was noted in one patient who received SCT treatment only at the age of three.

Hypodontia was reported in one patient, affecting all premolars; this patient received surgical treatment only for dysplastic gangliocytoma of the cerebellum at the age of 13 years.

4. Chapter 4: Discussion

Cancer, while a life-threatening disease, also possesses the potential to impact the overall quality of life of patients, particularly in children, even post-treatment. Among the numerous areas of concern, the effect of cancer treatments on oral and facial structures is particularly significant. The invasive nature of these treatments often leads to complications that can disrupt the normal growth and development of facial and oral structures in children. Such outcomes can have further implications, not only on the physical aspect but also on the child's psychosocial well-being. In this research, the primary focus was to investigate the prolonged effects of cancer therapy on various aspects of oral health and development in epidemiological studies in the literature and to investigate the long-term effects of cancer treatments on developing dental and orofacial structures in children at LDI from available records.

4.1 Critical Appraisal of the Included Literature

Most of the research included in this review were cross-sectional studies. Cross-sectional studies have a significant advantage as they are relatively quick and inexpensive to conduct. They provide an effective means of determining the prevalence and examining multiple associations of exposures and outcomes. However, when conducting cross-sectional studies, researchers typically have to choose a smaller group of participants from a larger and varied population which can lead to sampling bias (Wang and Cheng, 2020). Some of the cross-sectional

studies included in this research did not justify their sample size. This includes but is not limited to:

- Holtta et al., 2005a.
- Holtta et al., 2005b.
- Hsieh et al., 2011.
- Jodłowska and Postek-Stefańska, 2021.
- Halperson et al., 2022.

This was also noted in other case-control studies (Alberth et al., 2004) which can be attributed to the fact that childhood cancer is relatively rare, and any available data could be of importance when studying rare diseases.

The study conducted in 2022 by Halperson et al. failed to measure inter-examiner reliability, which may have resulted in bias. The examiners' consistency and agreement in assessing caries and dental anomalies in patients were not evaluated (Halperson et al., 2022).

Holtta et al's. (2005a) study aimed to examine the prevalence of teeth anomalies among children who underwent stem cell transplantation and concluded that stem cell transplantation was a stronger risk factor for impacting dental development than total body irradiation (Holtta et al., 2005a). However, the study did not consider the chemotherapy and the diversity of chemotherapeutic agents used during treatment before stem cell transplantation. It was also noted that the same study group and the

exact method of data collection, including age, the centre where the data was collected, and the types of treatment studied, were used in a different publication to report disturbances in root development following stem cell transplantation (Holtta et al., 2005b) which might have led to distortion of the findings (Abraham, 2000). This practice was also noted in other publications, including (Jodłowska and Postek-Stefańska, 2021), (Jodlowska and Postek-Stefanska, 2022a), and (Jodlowska and Postek-Stefanska, 2022b).

Case-control studies are useful for examining various risk factors linked to rare diseases or conditions. However, they have some limitations, such as an unclear target population, potential for bias in participant selection, and difficulty in determining cause-and-effect due to confounding factors (Tenny et al., 2023). The included case-control studies mainly used data from childhood cancer survivors who received treatment at local hospitals (single-centre) with varying treatment methods and ages at treatment. As a result, the conclusions drawn from these studies cannot be generalised to the entire population. The authors of the 2004 study by Alberth et al. failed to consider the odds ratio in their analysis of the correlation between DMFT and cancer treatment compared to the control group (Alberth et al., 2004).

In 2009, Kaste et al. used questionnaires to gather information from both cancer survivors and their siblings who were used as controls (Kaste et al., 2009). However, they did not provide specifics on how the controls

were selected. The use of questionnaires as a method of data collection can result in recall bias which may result in less reliable findings.

Many of the analysed studies did not provide information about the limitations of their research. Some also ignored confounding factors such as the familial and dental trauma history of dental anomalies, dietary habits and other related factors when correlating the dental abnormalities in childhood cancer survivors. This could be attributed to the fact that most of the data were retrospectively collected.

The current study discovered that a large proportion of LDI childhood cancer survivors were diagnosed with Acute Lymphoblastic Leukaemia (ALL). As per Cancer Research UK (CRUK), ALL is the most prevalent type of cancer diagnosed in children in the UK followed by brain and spinal tumours (CRUK, 2021a).

4.2 Periodontal and Soft Tissue Conditions

Among the patients in our study, it was observed that three patients (3.5%) exhibited periodontal conditions, which included gingival hyperplasia, increased mobility of teeth, and generalised gingival recession. These patients had received chemotherapy in addition to targeted radiation therapy. While these conditions may not be primarily caused by cancer therapy, previous research by Alpaslan et al. (1999) and Avsar et al. (2007) has indicated that cancer survivors tend to have higher plaque index scores compared to their controls. Furthermore,

survivors have reported a higher likelihood of severe gingivitis, as mentioned in the study conducted by Kaste et al. (2009). Additionally, seven patients (8.1%) presented with soft tissue conditions, including xerostomia, sloughing of mucosa, hyperkeratotic patches, oral haematoma, oral granuloma and eruption cysts. Several studies have reported findings related to salivary flow and related oral health issues. Avsar et al. (2007) noted a significantly lower stimulated salivary flow in their study group. Similarly, Nemeth et al. (2014) found that hyposalivation was detected in 11 out of 38 patients in their study group but not in the controls, with the stimulated saliva flow being significantly lower in the study group. Kupferman et al. (2010) observed permanent facial paresis in 7 patients (12%) and xerostomia in 1 patient (4%). Kaste et al. (2009) reported a higher likelihood of severe gingivitis among survivors and a higher prevalence of xerostomia. Kilinc et al. (2019) found that 23 patients reported trismus, and there was a significant relationship between the years after radiotherapy and complaints of limited mouth opening. Owosho et al. (2016) documented four patients with trismus, treated between ages 5 and 13 years, as well as xerostomia in four patients treated between ages 7 to 13 years. In Tanem et al.'s (2022) study, 17.4% of the survivors showed mild oral dryness. Nasman et al. (1994) reported that children treated with SCT had a significantly lower salivary secretion rates than those treated with chemotherapy or healthy control children. They also found a higher proportion of children in the chemotherapy and SCT groups exhibited a low salivary buffering

capacity. Finally, Hsieh et al. (2011) noted that in the group that received total body irradiation, 37.5% of children had lower salivary flow rates.

4.3 Dental Caries

In our study, dental caries was recorded in 26.7% of patients following treatment. Comparing our findings with the existing literature, Alpaslan et al. (1999) noted no significant differences between the study and control groups in their investigation. In contrast, Avsar et al. (2007) found that their study group had significantly higher dental caries prevalence compared to the control group. Moreover, Lauritano and Petruzzi (2012) reported a significantly higher DMFT score in leukaemia survivors when compared to the control group. Nemeth et al. (2014) supported this by reporting a significantly higher DMFT score in the patient group in comparison to their controls. Alberth et al. (2004) also observed elevated DMFT scores across all age groups of patients when compared to control groups. Kaste et al. (1998) highlighted the severity of the issue by reporting that 29% of their patients had more than four decayed or filled primary teeth at the onset or during treatment, with an average of 7.8 affected teeth. More recently, Stolze et al. (2023) reported dental caries in 34.0% of their study participants. Additionally, Proc et al. (2019) reported that cancer survivors exhibited significantly more deciduous teeth with active caries and a higher total DMFT score compared to the controls. Notably, patients undergoing additional radiotherapy of the head and neck region displayed significantly higher scores of filled primary teeth and increased DMFT scores in their permanent teeth.

According to an oral health survey of 5-year-old children in the UK in 2022 by the National Dental Epidemiology Programme (NDEP), the national prevalence of children with enamel and/or dentinal decay was recorded at 29.3% (NDEP, 2022). This percentage was higher than what was found in our sample.

4.4 Dental Developmental Anomalies

Antineoplastic therapy can cause disturbances in tooth eruption and development. The exact molecular mechanisms of cancer therapy that result in dental anomalies remain unknown (Carrillo et al., 2014). In the current study, our research findings indicate that 26.7% of the study population exhibited a range of dental anomalies, including hypodontia, shortened roots, enamel hypoplasia, and/or enamel hypomineralization in primary and permanent teeth, as well as microdontia, root malformations, and supernumerary teeth. A study by Alpaslan et al. in 1999 observed root malformations in 9 out of 30 children within their study group. Furthermore, they identified a significant prevalence of enamel hypoplasia and hypodontia in the cancer group compared to the control group. Additionally, Avsar et al. (2007) reported higher levels of enamel disturbances, including enamel hypomineralisation. Moreover, microdontia was found to be more frequently observed in survivors of leukaemia, as reported by Lauritano and Petruzzi in 2012. These findings align with previous research, supported by studies conducted by Minicucci, Lopes and Crocci 2003; Alberth et al., 2004 ; Marec-Berard et al., 2005 ; Kaste et al., 2009 ; Cubukcu, Sevinir and Ercan , 2012 ;

Pedersen et al., 2012, Owosho et al., 2016 ; Mattos et al., 2019 ; Quispe et al., 2019 ; Atif et al., 2022 , and Guagnano et al. 2022.

4.5 Orthodontic Conditions

In our study, 18 patients (20.9%) were assessed as having orthodontic conditions, including dental crowding, impactions, anterior open bite, and crossbite. Proc et al. (2022) also found that cancer patients were more likely to demonstrate anterior and posterior crossbites, as well as malalignment of teeth, when compared to the control group. It is worth mentioning that according to Tausche et al., 2004, around 8% of European children have a crossbite in the developing dentition (around 56,000 children in England and Wales per year) (Tausche et al., 2004).

4.6 Facial and TMJ Conditions

Our study found that eight patients (9.3%) had facial and temporomandibular joint conditions and 18 (20.22%) reported trismus, facial pain, facial palsy, facial asymmetry, mandibular hypoplasia and/or TMJ disorder.

Several studies have shed light on the various facial and oral manifestations observed in patients who have undergone treatment for intracranial tumors. Estilo et al. (2003) noted that bony hypoplasia and facial asymmetry were the most common clinical and radiographic findings. Karsila-Tenovuo et al. (2001) discovered that children treated

for intracranial tumours exhibited reduced midface dimensions, shorter ramus lengths, and lower anterior-posterior heights of the alveolar bone in the mandible. Mattos et al. (2019) reported that a significant proportion of patients exhibited asymmetric facial features, reduced facial depth, and reduced facial height, with 74.1%, 70.4%, and 77.8% showing these characteristics, respectively. Owosho et al. (2016) highlighted statistically significant impacts of treatment, including facial asymmetry and jaw hypoplasia, with seven patients presenting with these conditions. Jaw hypoplasia was observed in both the maxilla and mandible, particularly in patients whose primary tumors were located in the mid-face region and received radiation doses between 25-50.4 Gy to the maxilla.

In addition to facial and jaw-related issues, temporomandibular joint (TMJ) problems were also evident in these patients. Latoch et al. (2022) reported that 26.9% of the patients experienced oral and masticatory dysfunction. Tanem et al. (2022) found that 35% of the patients had reduced mouth opening, while Kilinc et al. (2019) noted that 23 patients reported trismus, with a significant relationship between the years after radiotherapy and complaints of limited mouth opening. Furthermore, Kupferman et al. (2010) documented permanent facial paresis in 12% of the patients, highlighting the challenges faced by individuals undergoing treatment for intracranial tumors, encompassing both facial and oral health concerns. In our sample 2 patients presented with facial paresis, one of them had received targeted radiotherapy to an intracranial tumor while the other did not receive any.

4.7 Findings Related to Age at Treatment

In this study, we examined the dental and oral health outcomes in paediatric cancer patients, stratifying them into three subgroups based on their age at the initiation of cancer treatment.

Krasuska-Slawinska et al. (2016) reported a positive correlation between age at treatment initiation and dental root resorption. This observation aligns with our findings in Subgroups 1 and 2, where younger patients, particularly those less than six years old at the initiation of cancer therapy, later exhibited a higher prevalence of dental anomalies, including hypodontia and enamel defects. This suggests that younger patients may be at an increased risk of experiencing more severe dental complications following cancer therapy, highlighting the need for early and ongoing dental care in this age group.

Tanem et al. (2022) found no significant difference in the DMFT scores between survivors treated at or before the age of 5 years and those treated after. This discrepancy with our results in Subgroup 1, which showed a substantial proportion of patients with dental caries, underscores the complexity of dental health outcomes in paediatric cancer patients. A higher incidence of microdontia was observed in children who had undergone cancer therapy before the age of 4 years, as also reported by Atif et al. in 2022. Additionally, survivors treated when they were older than 5 years of age exhibited elevated mean DMFT

scores, as highlighted by Guagnano et al. in their 2022 study. It suggests that while younger patients may be more prone to oral developmental complications, the overall dental health may vary depending on factors more than just age at treatment initiation, such as treatment type, diet and self dental care practices.

4.8 Findings Related to Type of Treatment

In our research, we examined the oral and dental health records of paediatric cancer patients undergoing various treatment modalities. Among the sample analysed, those who received chemotherapy only were the majority of patients. This group had an average age of 5.71 years at cancer treatment and 9.31 years at their dental visit. Notably, some patients experienced soft tissue findings, dental anomalies, enamel defects, and/or orthodontic issues. Additionally, long-term complications such as limited mouth opening, TMJ, and facial pain were observed in some cases, years after treatment. Krasuska-Slawinska et al. (2016) highlighted some significant correlations between specific drugs and dental outcomes in paediatric cancer patients. They found a positive correlation between drugs like vincristine, methotrexate, and enamel hypoplasia. Furthermore, the absence of tooth buds was found to be positively correlated with certain drugs like vincristine, cyclophosphamide, doxorubicin, ifosfamide, etoposide, and the doses used.

We found that 28 patients received radiotherapy. According to the literature, patients who undergo radiotherapy are at an elevated risk to develop multiple dental conditions including dental caries likely due to increased numbers of Streptococcus mutans and Lactobacillus because of xerostomia. Guagnano's 2022 research reported statistically significant higher numbers and frequencies of root alterations in patients who underwent both chemotherapy and radiotherapy compared to those who received chemotherapy alone.

4.9 Strengths and Limitations

Our study is of relevance for paediatric dentists who may encounter children who are undergoing or have undergone cancer treatment. As paediatric dentists play an essential role in the oral health and overall well-being of paediatric cancer patients, the findings of this research provide them with insights to anticipate dental health issues associated with cancer therapies. A significant strength of this research is that these patients' data have not been thoroughly explored or published previously. The data collection method was carried out using the available records; however, it is important to acknowledge that a retrospective data collection method was used and to acknowledge that this approach has limitations, including availability of data, potential inaccuracies in the data, limited control and the possibility of bias. These limitations should be taken into consideration when interpreting the study's findings. It is also important to acknowledge the exclusion of a significant number of patients. This was primarily due to the inaccessibility of dental records,

which were either recorded on paper forms during ward visits while the patients were under cancer treatment or were stored in older, inaccessible versions of the electronic dental record system. Some patients' data were not transferred to the new record system due to patients being deceased.

Childhood cancer is widely recognised as a rare type of cancer, and the treatment regimens can vary depending on the type of cancer and age. As a result, comparisons between the diverse treatments and age groups may not be accurate. In our research, a variety of treatment types were used in different ages. Furthermore, it is important to note that factors beyond cancer therapy, such as genetic and environmental influences on facial and oral development, may have impacted the outcomes. Therefore, while our study offers valuable insights, it is essential to consider these limitations when interpreting the results.

4.10 Recommendations and Future Research

The research team recommends enhancing records and data collection methodologies in LDI by implementing standardised data collection processes, providing comprehensive training to staff, and conducting regular data quality audits.

Moreover, there is a need to integrate education about the risks to dental development in children undergoing cancer treatment into undergraduate dental program curricula. This educational initiative can enhance

practising dentists' knowledge and skills when encountering childhood cancer survivors.

To enhance our understanding of patients' experiences during and after cancer therapy, dental practitioners who provide care to patients undergoing cancer therapy should routinely assess the treatment consequences, utilszing both clinician and patient-reported outcomes. Additionally, we recommend that consideration be given to standardisation of data collection across centres in the UK to ensure homogeneity and allow a larger population to be studied. This standardised approach could facilitate further research studies based on homogeneous data, with a more robust foundation for future investigations in this field.

5. Chapter 5: Conclusions

The literature review indicates that childhood cancer survivors frequently encounter significant long-term dental complications as a result of their treatments. This was clearly observed in the patient sample studied at LDI, highlighting the diversity and severity of these dental issues. Such findings emphasise the necessity for a deeper understanding of the effects of cancer therapy on the developing orofacial structures, focused attention, and enhanced support from healthcare providers, including dental practitioners. Moreover, these insights underscore the critical need for developing follow-up care plans and interventions to meet the dental health needs of childhood cancer survivors.

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Appendices

Appendix 1: Search strategy for the databases search

1. Neoplasms/
2. (Neoplas* or Cancer* or Malignan* or Carcin* or Oncolog* or Tumo?r* or metasta*).ti,ab.
3. 1 or 2
4. Chemotherapy/
5. Chemotherap* or Antineoplastic* or Anticancer or Antitumo?r or Chemoradiotherap* or Radiochemotherap* or Radioimmunotherap*).ti,ab.
6. Radiotherapy/
7. (Beam therap* or low-dose radiotherap* or radioimmunotherap* or radiotherap* dosage or short-course radiotherap* or whole body radiation).ti,ab.
8. Stem cell transplant.ti,ab.
9. or/4-8
10. 3 and 9
11. Tooth development/
12. tooth malformation/
13. mouth malformation/
14. Maxillofacial Development/
15. Orofacial development$.ti,ab.
16. Dental abnormalit$.ti,ab.
17. Dental development$.ti,ab.
18. Dental disturbance$.ti,ab.
19. Dental defect$.ti,ab.
20. Craniofacial defects$.ti,ab.
21. Trismus/ or xerostomia/ or osteoradionecrosis/ or anodontia/
22. Enamel hypoplasia/ or hypoplasia/
23. (Xerostomia or Osteoradionecrosis or hypoplasia$ or anodontia$ or 24.Microdontia).ti,ab.
25. (Tooth agenesis or Impaired root growth or Arrested root growth).ti,ab
26. Face asymmetry/
27. Facial asymmetry$.ti,ab.
28. Temporomandibular joint disorder/
29. Temporomandibular joint disorder$.ti,ab.
30. salivation/ or sputum/
31. (Saliva flow or sputum).ti,ab.
32. or/11-31 [dental terms]
33. Child/
34. child$ or schoolchild$ or "school age" or "school aged" or preschool$ or toddler$ or kid? or kindergar$ or boy? or girl? or minor$).ti,ab.
35. Adolescent/
36. (adolescen$ or teen$ or youth$ or young or juvenile? or minors or highschool$).ti,ab.
37. Pediatrics/

38. p?ediatric$.ti,ab.
39. Infant$.ti,ab.
40. or/33-39 [children]
41. 10 and 32 and 40