Associations between childhood cancer treatment and tooth agenesis

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ABSTRACT

AIM: The aim of this study was to determine the prevalence of dental developmental disturbances in long-term survivors of childhood malignancies in New Zealand children. This study reports associations with potential risk factors to inform oncologists and dentists of the likelihood of dental abnormalities.

METHODS: The study population was children aged 14–16 years old who were diagnosed with cancer prior to 10 years of age. A total of 156 children were eligible, of which 59 participated in this study. The indices used in this study were Holtta's Defect Index (HDI), and Oral Health Impact Profile-14 (OHIP-14).

RESULTS: The prevalence of agenesis was 15.3%, microdontia 6.8% and root abnormalities 32.2%. Cyclophosphamide equivalent doses above 8,000mg/m^2, stem cell therapy (SCT), and head and neck radiation therapy (HNRT) were associated with a higher mean number of teeth missing due to agenesis. SCT and HNRT were associated with a higher total HDI. A binary logistic regression was carried out to determine the odds of agenesis and found that HNRT was the main contributing factor (OR=7.7, p-value=0.04). The linear regression model found that dactinomycin and agenesis correlated with the largest mean OHIP-14.

CONCLUSION: This study found that childhood cancer survivors in New Zealand had a high prevalence of developmental dental abnormalities and it identified potential risk factors related to their cancer treatment. Inequitable access to oral rehabilitation for this patient group argues for a mechanism for consistent improved access to publicly funded dental care across district health boards in New Zealand.

Globally, approximately 300,000 children are diagnosed with cancer each year,[1] a disease which historically had high mortality rates.[2,3] Recent improvements in oncology treatment and management has led to significant increases in survival rates.[2,3] An important consideration in the management of these patients is the long-term effects of their treatment on their physical and psychosocial health.

The long-term dental effects of childhood oncology treatment are well established, and include tooth agenesis,[4–8] microdontia,[5,7–10] enamel defects[6] and disturbances in root formation.[7,10,11] In addition, oncology treatment can affect the surrounding structures of the oral cavity leading to hyposalivation,[12,13] periodontal disease,[14] dental caries[7,15] and less commonly, trismus and malocclusions.[16] Consequently, these alterations in the oral cavity can negatively affect the patient's oral health-related quality of life.[17]

Chemotherapeutic agents and radiation therapies target neoplastic cells by disrupting the cells' ability to undergo mitosis.[18] However, these therapies lack specificity and thus can affect the developing dentition. Due to the multimodal nature of oncology treatment, including surgery, chemotherapy, radiotherapy and stem cell therapy, it can be difficult to determine causality between specific treatments and the dental effects.

In New Zealand, all children are provided with funded dental treatment, including restorations and preventive treatment up until the age of 18 years. However, the lack of funding for oral rehabilitation including complex restorative, orthodontic treatment and oral surgery, could result in a significant financial burden for long-term

childhood cancer survivors and their families.[19] While medical treatment injuries in New Zealand are covered by the Accident Compensation Corporation (ACC), dental disturbances are considered a well-recognised complication of childhood oncology treatment and therefore ineligible for Government-funded dental rehabilitation. With approximately 150 children being diagnosed with cancer every year in New Zealand,[20] and 10-year survival rates being above 80%,[21] this may lead to significant inequalities. To date, there has been no literature of the late dental effects in childhood cancer survivors on New Zealand's unique and diverse population.

The aim of this study is to determine the prevalence of dental developmental disturbances in long-term survivors of childhood malignancies in New Zealand. Secondarily, this study aims to identify potential specific risk factors such as anti-neoplastic agents, types of treatment and age at diagnosis to help oncologists and dentists understand the likelihood of dental abnormalities.

Methods

Ethics approval for this study was provided by the Northern B Health and Disability Ethics Committee, Health and Disability Ethics Committees, New Zealand.

This cross-sectional study was conducted at multiple sites throughout New Zealand (Auckland, Christchurch, Wellington, Hamilton, Whangarei, Tauranga, New Plymouth, Whanganui, Whakatane, Rotorua, Hastings, Gisborne, Palmerston North, Masterton, Nelson and Dunedin).

The study population consisted of children aged 14–16 years old (inclusive in June 2015) who had been diagnosed with cancer prior to 10 years of age and who attended the National Child Cancer Network Late Effects Assessment Programme (LEAP). Children who successfully completed their cancer treatment in New Zealand are monitored in LEAP. The LEAP database includes information on the treatment-related effects including organ dysfunction and secondary malignancies, and is regularly updated by regional LEAP clinical nurse specialists. This database was used to identify potential participants, and source demographic data and information concerning diagnosis, oncology treatment and related comorbidities. However, this database does not provide any clinical or radiographic dental data. Participants who resided in the Wellington region were contacted via phone to inform them of the study and invite them to participate. Those residing outside of Wellington were sent a letter and also contacted via telephone. Once the clinic venue and dates were finalised, all participants were contacted via phone to arrange an appointment time. This appointment was emailed to the participants, and the day prior to the appointment, participants were called to remind them of the appointment. Consent was obtained in writing from participants aged 16 years and older, and from parents/guardians and participants if under the age of 16.

Each participant in this study underwent a clinical examination, radiographs and a self-reported oral health-related quality of life (OHRQoL) survey. Results from the clinical examination will be reported in a separate paper.

Radiographic examination

Radiographic analysis required an orthopantomogram radiograph (OPG). These were taken in the dental clinics of the respective hospitals or donated by private dental practices with this facility. If the child reported to have had an OPG taken in the past 18 months then attempts were made to source this.

After the completion of all clinical examinations, seven clinicians came together and analysed the radiographs using Holtta's Defect Index.[4] The OPGs were also used to identify any other commonly occurring dental abnormalities that may not have been previously described in this group.

Holtta's Defect Index (HDI)[4] is an established method of quantifying dental defects using OPG radiographs. It comprises of three components—tooth agenesis, microdontia and root-crown ratios (Figures 1 and 2). This study used the HDI to classify the permanent dentition of participants. A tooth was considered missing due to agenesis if it was not present on the OPG and after cross referencing with the patient's dental records to ensure that the teeth were not extracted.

Figure 1: Holtta's Defect Index.[4]

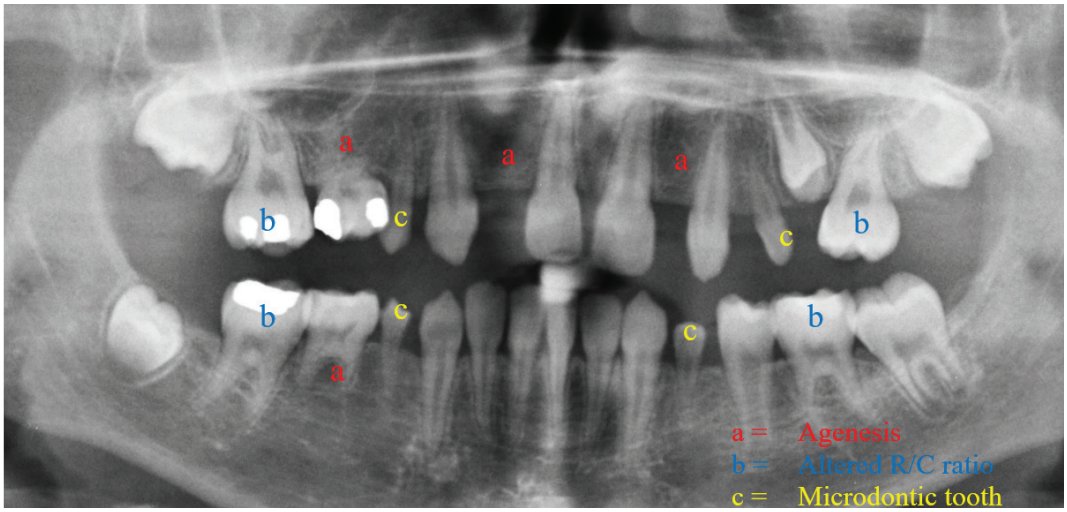
Score	Description
ND	Not determined a. Developing teeth with an unclear final outcome b. Missing teeth not categorised in the aplasia group because of age c. Teeth not reliably seen on radiograph
D0	R/C ratio >1.6; no disturbance
D1	R/C ratio 1.2–1.6; mild disturbance
D2	R/C ratio 0.9–1.1; severe disturbance
D3	R/C ratio <0.9; very severe disturbance or arrested root development
D4	Microdontia; exceptionally small tooth
D5	Aplasia; missing tooth A tooth was not considered missing before the following ages: First premolar <5 years Second premolar <6 years Second molar <6 years Third molar <13 years

The total HDI was calculated as follows: (nD1x1)+(nD2x2)+(nD3x3)+(nD4x4)+(nD5x5)
Where n is the number of teeth in the respective disturbance category D1, D2, D3, D4, D5

Oral health-related quality of life

All participants were asked to complete an oral health-related quality of life questionnaire prior to the radiographs. The Oral Health Impact Profile-14 (OHIP-14) is a self-reported, internationally validated measure,[22] whereby a questionnaire is used to assess seven different domains of oral health-related quality of life (OHRQoL). It consists of 14 questions graded on a scale from 0–4. The final score is a sum of the 14 scores, ranging from 0 to 56. The prevalence of one or more OHIP-14 impacts was computed by identification of those who responded 'very often' or 'fairly often' for at least one of the 14 items. A concurrent validity check was used, where the total OHIP-14 value should correlate positively with the global oral health question.

Figure 2: OPG showing dental defects using the Holtta's Defect Index.



NZDep2013

NZDep2013 [23] is an area-based measure of socioeconomic status (SES) in New Zealand using data from the 2013 Census to provide a deprivation score for each meshblock. NZDep was found using the participant's current address. This address was then cross-referenced using Census meshblock data from 2013 to find the participant's deprivation score.

Statistical analysis

Data analysis was carried out using IBM SPSS version 25.0 in conjunction with a biostatistician. Results were considered statistically significant if the p-value was less than 0.05.

Chemotherapeutic drugs where the sample size was less than seven (n<7) were excluded from our analyses (asparaginase, cyclosporin, fludarabine, topotecan, vinblastine, hydrocortisone, lomustine, teniposide). Doses for anthracyclines including doxorubicin, daunorubicin, epirubicin and idarubicin were converted into "Doxorubicin equivalent doses" (mg/m^2) using the COG LTFU guidelines v5.[24] Similarly, doses for alkylating agents (cyclophosphamide, ifosfamide, melphalan, thio-TEPA and busulfan) were converted into "Cyclophosphamide equivalent doses" (mg/m^2) as outlined by Green et al 2014.[25]

A one-way ANOVA was conducted as part of the bivariate analysis, examining mean OHIP-14 score, mean number of teeth missing due to agenesis, and mean total HDI for each independent variable (doxorubicin equivalent dose, cyclophosphamide equivalent dose, dactinomycin, vincristine, cytarabine, methotrexate, etoposide, cisplatin, cyclophosphamide, carboplatin, chemotherapy duration, head and neck radiation therapy, total body irradiation, stem cell therapy, gender, ethnicity, diagnosis, NZDep and age at diagnosis). Outputs that lacked statistical and clinical significance have been omitted from the tables. A binary logistic regression was conducted to determine the likelihood of agenesis (Yes/No). A linear regression was conducted to determine the correlation between oncology treatment and outcome factors on OHIP-14.

Results

As of June 2015, there were 245 patients between the ages of 14 and 16 who were diagnosed with cancer before the age of 10. Twenty patients were not eligible for the study due to being lost to follow up, residing outside of New Zealand, or receiving cancer treatment. Of the remaining 225 patients, 69 are not current LEAP patients—14 are yet to be referred to LEAP, 31 have been discharged from LEAP and 24 did not require any LEAP follow-up. LEAP follow-up is not routinely offered to children with a central nervous system tumour treated with surgery only. Of the 225, 156 children were eligible. Of the 156 eligible children, 68 individuals participated in this study—65 filled out the OHIP-14 questionnaire, and 59 either had OPGs or consented to having OPGs. This gives us a participation rate of 37.8%. The most common reasons for non-participation were lack of interest, unavailability on the day of the clinic or non-response.

Participant sociodemographic characteristics are detailed in Table 1. The mean age of participants at follow up was 14.9 years, and 4.1 years at diagnosis. 54.2% of participants were male. A majority of participants were European (76.3%), followed by Māori (11.9%) and Asian (6.8%). The most common cancers were leukaemia (39.0%), followed by CNS tumours (13.6%) and kidney cancers (11.9%). Other cancers included germ cell tumours (n=2) and hepatoblastomas (n=2).

All participants had a combination of surgical, chemo-, radio- and/or stem cell therapies, with a summary of the oncology treatment characteristics being found in Table 2. Nine out of 10 participants received chemotherapy with an average of four drugs. The most commonly administered drugs were cyclophosphamide (66.1%), doxorubicin (64.4%) and vincristine (61.0%). One in four participants had head and neck radiation therapy with a mean dose of 35.2Gy, and three participants had total body irradiation with a mean dose of 13.0Gy. In addition, 12 children (20.3%) had stem cell therapy.

Details of the prevalence of developmental dental anomalies can be found in Table 3. Using Holtta's Index, this study found that

Table 1: Summary of the sociodemographic characteristics.

	Participants N=59 (%)		**Non-participants N=97 (%)**	
Mean age at diagnosis (±sd)	4.1	(±2.9)	4.0	(±2.7)
Mean age at follow up (±sd)	14.9	(±0.8)	15.2	(±0.8)
Sex				
Male	32	(54.2)	53	(54.6)
Female	27	(45.8)	44	(45.4)
Types of cancer				
Leukemia	23	(39.0)	49	(50.5)
Lymphoma	4	(6.8)	8	(8.2)
Kidney	7	(11.9)	8	(8.2)
Retinoblastoma	5	(8.5)	2	(2.6)
Central nervous system	8	(13.6)	17	(17.5)
Rhabdomyosarcoma	3	(5.1)	1	(1.0)
Other sarcoma's	5	(8.5)	6	(6.2)
Other cancers	4	(6.8)	6	(6.2)
Ethnicity				
European	45	(76.3)	60	(61.9)
Māori	7	(11.9)	20	(20.6)
Asian	4	(6.8)	7	(7.2)
Pacific Islander	2	(3.4)	8	(8.2)
Other	1	(1.7)	2	(2.1)
Cancer centre at diagnosis				
Auckland	29	(49.2)	51	(52.6)
Wellington	11	(18.6)	15	(15.5)
Christchurch	14	(23.7)	25	(25.8)
Overseas	5	(0)	6	(6.2)
Mean NZDep (±sd)	4.7	(±2.9)	5.6	(±3.1)

15.3% of participants had at least one tooth missing due to agenesis, 6.8% had at least one tooth affected by microdontia, and 32.2% had a decreased root:crown ratio affecting at least one tooth. An inter-examiner reliability was conducted for the radiographical analysis (κ=0.83).

Table 4 shows the impact of potential late dental effects on OHRQoL. Participants who experienced agenesis (7.9) had a higher mean OHIP-14 than those who did not (3.7) (p-value$\leq$0.05). Those with microdontia (50.0%) were also more likely to report having 1+ OHIP-14 impacts "Fairly Often" and "Very Often" almost three times as frequently than those who did not (18.2%).

Table 5 presents an overview of the bivariate analysis. No statistically significant results at the p=0.05 level were found for Doxorubicin equivalent doses, cytarabine, cisplatin, etoposide, methotrexate, chemotherapy duration, total body irradiation,

Table 2: Oncology treatment characteristics summary.

Chemotherapy	**N (%)**		**Mean dose in mg/m² (±sd)**	
Drug				
Carboplatin	14	(23.7)	3,045.9	(±2,785.4)
Cisplatin	8	(13.6)	380.9	(±87.6)
Cyclophosphamide	39	(66.1)	5,634.6	(±5,600.7)
Cytarabine	13	(22.0)	15,926.5	(±14,769.4)
Dactinomycin	7	(11.9)	4.5	(±5.3)
Daunorubicin	17	(28.8)	122.8	(±69.6)
Doxorubicin	38	(64.4)	170.6	(±104.6)
Etoposide	25	(42.4)	3,068	(±4,841.3)
Ifosfamide	10	(16.9)	38,900	(±21,200)
Methotrexate	13	(22.0)	33,000	(±45,264)
Vincristine	36	(61.0)	22.8	(±22.7)
Doxorubicin equivalent dose	43	(72.9)	181.4	(±96.1)
Cyclophosphamide equivalent dose	44	(74.6)	7,107.9	(±11,034.9)
Number of chemotherapy drugs			4.1 drugs	(±2.2)
Chemotherapy duration			504.1 days	(±402.2)
Radiation therapy			Mean dose in Gy (±sd)	
Head and neck radiation therapy	15	(25.4)	35.2	(±21.0)
Total body irradiation	3	(5.1)	13.0	(±1.3)
Stem cell therapy				
Overall	12	(20.3)		
Bone marrow	5	(8.5)		
Peripheral blood	5	(8.5)		
Cord blood	2	(3.4)		

Table 3: Prevalence of late dental effects.

	N	**(%)**	**Mean ±sd**	
Tooth defect				
Agenesis	9	(15.3)	5.3 teeth	±2.9
Microdontia	4	(6.8)	3.0 teeth	±1.8
Root abnormalities	19	(32.2)	4.4 teeth	±3.8

Table 4: The impact of potential late dental effects on oral health-related quality of life.

	OHIP-14 Mean ±sd		**1+ OHIP-14 impacts "Fairly Often" and "Very Often" N (%)**	
Overall	4.3	(5.2)	12	(20.3)
Tooth defect				
Agenesis				
Yes	7.9	(5.8)	3	(33.3)
No	3.7	(4.3)#	9	(18.0)
Microdontia				
Yes	4.1	(4.6)	2	(50.0)
No	7.0	(7.5)	10	(18.2)
Root abnormalities				
Yes	4.1	(4.6)	4	(21.1)
No	4.9	(5.1)	8	(20.0)

= p-value<0.05.

gender, ethnicity, NZDep or age at diagnosis. No statistically significant results were found with the individual OHIP-14 domains.

Six of 25 participants (40%) who received head and neck radiation therapy were missing at least one tooth due to agenesis, whereas only 6.8% who did not have head and neck radiation therapy were missing at least one tooth (p-value=0.006). Participants who had up to and including 20Gy of HNRT were missing on average 2.3 teeth, compared to 0.3 teeth in those who did not have HNRT. Participants who had over 20Gy of HNRT were only missing 1.6 teeth on average. HNRT was also associated with higher mean HDI scores, with participants who did not receive HNRT having a mean HDI of 2.5. Those participants who received ≤20Gy and >20Gy of HNRT (p-value=0.003) had HDIs of 17.0 and 16.0 respectively. A binary logistic regression was carried out to determine the odds that a participant was likely to have at least one tooth missing due to agenesis (yes/no) (see Table 5). Variables examined in this analysis included dactinomycin (yes/no), head and neck radiation therapy (0Gy, >0–≤20Gy, >20Gy), stem cell therapy (yes/no) and cyclophosphamide equivalent dose (0mg/m^2, >0–<4,000mg/m^2, 4,000–<8,000mg/m^2, ≥8,000mg/m^2). We found that HNRT was the strongest correlator for agenesis, with participants who received more than 20Gy having an OR=7.7 (p-value=0.04).

One third of participants who received SCT were more likely to have teeth missing due to agenesis while 1 in 10 participants who did not receive SCT had teeth missing due to agenesis. Those who received SCT had a mean HDI score of 15.2, in contrast to an HDI score of 3.7 for those who did not receive SCT (p-value=0.029).

The mean total HDI score was highest for rhabdomyosarcoma (RMS) with a score of 30.7, followed by retinoblastoma (12.8) and other sarcomas (10.2). Conversely, leukaemia had the lowest mean total HDI score of 0.6.

No statistically significant results were found for counts of "Fairly Often" and "Very Often" in OHIP-14. Participants who had missing teeth due to agenesis were almost twice as likely (33.3%) to report having problems "Fairly Often" or "Very Often" with their OHRQoL than those who did not (18.0%). Participants who received dactinomycin (42.9%) or vincristine (27.8%) reported problems more frequently with their OHRQoL than those who did not (17.3% and 8.7% respectively).

Table 5: Results of bivariate analysis between oncology treatment and outcome factors.

	Number of missing teeth due to agenesis Mean ± sd (N)	Total HDI Mean ± sd (N)	OHIP-14 Mean ± sd (N)	1+ OHIP-14 impacts "Fairly Often" and "Very Often" N (%)
Cyclophosphamide equivalent dose				
0mg/m^2	0.2±0.8 (15)	1.4±3.9 (15)	4.9±6.1 (15)	4 (26.7)
>0–<4,000mg/m^2	0.2±0.9 (25)	2.0±5.6 (25)	2.8±4.5 (25)	2 (8.0)
4,000–<8,000mg/m^2	0.9±1.6 (7)	9.9±14.7 (7)	6.0±6.4 (7)	2 (28.6)
≥8,000mg/m^2	2.1±3.6 (12)[a]	17.9±20.8 (12)[b]	5.6±4.6 (12)	4 (33.3)
Doxorubicin equivalent dose				
0mg/m^2	1.6±2.8 (16)	11.8±18.6 (16)	2.4±4.3 (16)	2 (12.5)
>0–<250mg/m^2	0.3±1.4 (32)	2.8±7.9 (32)	5.2±5.8 (32)	8 (25.0)
>250mg/m^2	0.5±1.2 (11)	7.0±12.3 (11)	4.3±4.3 (11)	2 (18.2)
Cyclophosphamide				
0mg/m^2	0.4±1.1 (20)	3.0±6.8 (20)	4.2±5.6 (20)	4 (20.0)
0–6,000mg/m^2	0.5±1.6 (26)	3.3±8.3 (26)	3.4±4.7 (26)	3 (11.5)
>6,000mg/m^2	1.6±1.9 (13)	16.2±2.8 (13)[c]	6.2±5.6 (13)	5 (38.5)
Dactinomycin				
No	0.6±1.8 (52)	5.2±10.7 (52)	3.5±4.5 (52)	9 (17.3)
Yes	1.3±3.0 (7)	12.3±23.7 (7)	10.3±6.9 (7)[#]	3 (42.9)
Daunorubicin				
No	1.0±2.2 (42)	8.2±14.6 (42)	4.8±5.7 (42)	9 (21.4)
Yes	0.0±0.0 (17)	0.7±1.9 (17)[#]	3.0±3.4 (17)	3 (17.6)
Vincristine				
No	0.4±1.1 (23)	2.7±6.3 (23)	2.2±2.9 (23)	2 (8.7)
Yes	0.9±2.3 (36)	8.2±15.3 (36)	5.6±5.9 (36)[#]	10 (27.8)
SCT				
No	0.4±1.4 (47)	3.7±1.7 (47)	4.1±5.3 (47)	9 (19.1)
Yes	1.8±3.1 (12)[#]	15.3±16.4 (12)[#]	5.2±4.9 (12)	3 (25.0)
HNRT				
0	0.3±1.4 (44)	2.5±7.4 (44)	4.4±5.2 (44)	9 (20.5)
>0–<20Gy	2.3±3.9 (4)	17.0±17.0 (4)	3.3±3.2 (4)	0 (0.0)
>20 Gy	1.6±2.6 (11)	16.0±20.5 (11)[d]	4.2±6.3 (11)	3 (27.3)
Diagnosis				
RMS	4.0±4.0 (3)[#]	30.7±32.3 (3)[#]	7.0±7.5 (3)	1 (33.3)
Non-RMS	0.5±1.6 (56)	4.7±10.0 (56)	4.1±5.2 (56)	11 (19.6)

=p-value<0.05.
The following variables have been omitted due to lack of statistical and clinical significance:
Vincristine, carboplatin, total body irradiation, methotrexate, etoposide, ethnicity, diagnosis, cisplatin, cytarabine, NZdep, age at diagnosis, mean GI.
a = p-value statistically different from 0–4,000.
b = p value statistically different from 0–4,000 and 0.
c = stat sig dif from 0 and >0–<6,000.
d = stat sig dif from 0 and >0–<20.

Table 6: Binary logistic regression model for the association between oncology treatment factors and agenesis (Yes/No).

Treatment factors	Odds ratio	95% CI	p-value
Dactinomycin			
No	Reference		
Yes	2.4	0.2–26.8	0.48
Head and neck radiation therapy			
0	Reference		
>0–<20Gy	6.3	0.5–81.5	0.16
>20 Gy	7.7	1.1–54.4	0.04
Stem cell therapy			
No	Reference		
Yes	2.0	0.2–21.5	0.57
Cyclophosphamide equivalent dose			
0mg/m^2	Reference		
>0–<4,000mg/m^2	1.8	0.1–25.2	0.67
4000–<8,000mg/m^2	2.4	0.1–53.9	0.58
≥8,000mg/m^2	3.3	0.2–59.4	0.42

Table 7: Linear regression model for the association between oncology treatment factors and mean OHIP-14 scores.

Treatment factors	Parameter estimate	95% CI	p-value
Dactinomycin			
No	Reference		
Yes	5.8	1.7–9.8	0.01
Gender			
Female	Reference		
Male	-2.3	-4.7–0.1	0.06
Agenesis			
No	Reference		
Yes	3.3	-0.22–6.8	0.06
Vincristine			
No	Reference		
Yes	2.3	-0.2–4.8	0.07
Ethnicity			
European	Reference		
Non-European	4.1	-5.5–13.7	0.39

Table 7 outlines the linear regression model used to establish the relationship between variables and OHIP-14 scores. Variables examined included dactinomycin (yes/no), gender (male/female), agenesis (yes/no), vincristine (yes/no) and ethnicity (European/non-European). The use of dactinomycin, with all other factors held equal in the model, correlated with a higher mean OHIP-14 score by 5.8 points (p-value=0.006). There was also a positive association between the presence of missing teeth due to agenesis and mean OHIP-14 score (3.3-point higher), although this finding did not meet the statistically significant threshold (p-value=0.064).

Discussion

This cross-sectional study of the late dental effects of oncology treatment in childhood cancers in New Zealand found a high prevalence of dental agenesis and microdontia among our sample. This study also identified potential risk factors for agenesis including head and neck radiation therapy, stem cell therapy, cyclophosphamide equivalent doses over 8,000mg/m^2, and dactinomycin.

While this study provides useful insights into the late dental effects of childhood oncology treatment, there are some weaknesses. The study had a nonideal participation rate of 37.8%. This may be attributed to the long interval between cancer treatment and the study (on average over 11 years), with the majority of non-participants declining to participate due to lack of interest. In addition to this, participation may have been inconvenient for those who had to travel long distances. The geographical spread of the participants also made the logistical organisation of this study difficult. Furthermore, Pasifika had a proportionally lower participation rate of 20% compared to other ethnicities. This is likely to be a reflection of the inequality in access to healthcare for these individuals.

There are a number of possible implications of the low participation rate. It may be that those with more dental problems had more incentive to participate in this study. Three-quarters of patients who were treated for rhabdomyosarcoma participated in this study and they had the highest mean total HDI score of 30.7, over six times greater than non-RMS diagnoses (4.7). However, only one of the three RMS originated in the head and neck region. This may have biased the results towards more severe dental problems than what is true in the population of interest.

The NZDep, and derived SES, was based on the current address and not the address at time of diagnosis. In addition, the NZDep is based on census data which uses meshblocks of, on average, 81 people.[23] It is therefore not based solely on an individual's SES, but includes the SES of others in that meshblock. While SES was not found to be a risk factor for the late dental effects in this study, this could be attributed to our small sample size.

This retrospective study looked at chronological ages of participants at diagnosis. The current literature shows that late dental effects are correlated with a patients age at treatment.[8,27,28] While this study did not find any significant associations with age at diagnosis, it should be acknowledged that chronological age does not always correlate with dental age. This is an especially important consideration in this study as it has been shown that Māori and Pasifika children tend to have an accelerated dental development.[29]

Another consideration is that children with higher body mass index (BMI) values have also been found to have an accelerated dental development.[30–32] High BMI values could also have been a confounding factor in this study as children with high BMI values may have received higher doses of chemotherapy, which is often calculated by body surface area.

Despite these considerations, this study provides useful and insightful information. This is the first study of its kind in New Zealand, and showed strong correlations of clinical importance between specific oncology treatment factors and their effects on the developing dentition. It involved an interprofessional collaboration between paediatric oncologists, nurses and dentists from all over New Zealand. Moreover, this study showed a respectable degree of rigour with seven dentists and dental specialists reviewing the information and arriving at a consensus. Furthermore, the participants in this study had comparable sociodemographic characteristics to the non-participants for age, sex and most

ethnicities, allowing us to make some generalisations to our population of interest.

The results of the present study are consistent with the international literature, which shows that agenesis and microdontia are found more commonly among childhood cancer survivors. While this study is cross sectional, we can compare our prevalence data to the general population. This study found the prevalence of agenesis was high at 15.3%, compared with 2.5% to 6.9% in a recent meta-analysis of the general population.[33] A previous study conducted in New Zealand found that 0.35% of five-year old children had missing teeth.[32] The aetiology of agenesis is thought to involve both genetic and environmental factors.[34,35] Another environmental factor to consider is maternal smoking, which has been linked to tooth agenesis and possibly childhood cancers. A study by Al-Ani et al found maternal consumption of 10 or more cigarettes per day during pregnancy was associated with four times the odds of having a child with hypodontia; as maternal smoking was not measured in the present study, this association was not able to be investigated.[34,36] A similar comparison was found for microdontia (prevalence = 6.8%), with studies on the general population finding a prevalence of up to 3%.[37] However, classification of microdontia can be quite subjective depending on which index is used and inter-observer variability.

Hsieh et al 2011 found a positive correlation between cyclophosphamide doses and total HDI.[13] Although not statistically significant because of the small sample size, our study paper consolidates this finding. Our study also showed a dose-response relationship between total cyclophosphamide equivalent dose and number of teeth missing due to agenesis, and total HDI. This dose-response relationship between cyclophosphamide equivalent doses and the likelihood of agenesis persisted with multivariate analysis. While not statistically significant, it suggests that this finding is unlikely due to chance or any external factors.

Our findings corroborated the findings of Das et al,[16] which found that head and neck radiation therapy was twice as likely to result in agenesis, and were missing five times as many teeth due to agenesis, than those who did not receive HNRT. In the present study this association persisted using the binary logistic regression model, and showed that HNRT greater than 20Gy increased the odds of agenesis seven-fold (OR=7.7) compared with those who did not have HNRT (p-value=0.04).

The association between specific treatment factors and agenesis can be attributed to the non-specificity of oncology treatments which potentially risk all cells undergoing division. It is thought that this disrupts ectomesenchymal cells involved in tooth formation resulting in agenesis.

Contrary to expectations, the mean OHIP-14 score of 4.3 was quite low in comparison with adolescents in the general population.[38] The OHIP-14 has been validated in use for adolescents 15 years and older;[39] with the mean age of this study's participants being 14.9 years a child-specific OHRQoL measure such as the Child Perceptions Questionnaire (CPQ11–14) may have been found to be more responsive.[40] The New Zealand Oral Health Survey (NZOHS) 2009 used a global question, similar to the one we used. In the present sample, children reported their OHRQoL to be better, compared with the 2009 NZOHS.[26] While a linear regression model was carried out to ascertain correlations with mean OHIP-14 scores, we should acknowledge that by including sociodemographic, treatment factors and outcome variables, there is likely to be some level of confounding. Nevertheless, this model found that dactinomycin and agenesis correlated with a higher OHIP-14 score.

Ideally, the late dental effects of oncology treatment would best be studied longitudinally, thereby reducing bias and optimising participation rates. In addition, the role of dactinomycin should be further investigated for its potential effects on the developing dentition.

Conclusion

Although all children with childhood cancer need regular dental follow ups, particular attention should be paid to children who have had HNRT, SCT and/or cyclophosphamide equivalent doses greater than 8,000mg/m^2. Particular attention should be paid to dental caries, agenesis and enamel defects, which have been shown to negatively impact OHRQoL. In addition to this, patients treated for rhabdomyosarcomas have the potential to have severe deleterious effects on their oral health. These are important considerations for paediatric oncologists, as patients who have missing teeth are likely to require complex and costly orthodontic and/or rehabilitative treatments.

This study shows that New Zealand survivors of childhood cancer treatment have a significant prevalence of complex dental anomalies. This justifies a review of primary and tertiary dental services to ensure they and their families have consistent publicly funded access to the orthodontic and advanced oral rehabilitative services which they require.

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