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Late adverse effects of childhood acute lymphoblastic leukemia treatment on developing dentition

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Running title:
Dental damage in leukemia survivors

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Defect, dentition, development, leukemia, survivor

Abbreviations

ALL	Acute lymphoblastic leukemia
NOPHO	Nordic Society of Paediatric Haematology and Oncology
MTX	Methotrexate
6MP	6-mercaptopurine
HSCT	Hematopoietic Stem Cell Transplantation
HR	High-risk
CCS	Childhood cancer survivors
PTG	Panoramic radiograph
TBI	Total body irradiation
DeI	Defect Index
SD	Standard deviation

Abstract

BACKGROUND: Childhood cancer survivors show a variety of late adverse effects on dental health. The purpose of this study was to examine the prevalence and severity of dental abnormalities in permanent dentition in childhood leukemia survivors.

MATERIALS AND METHODS: Retrospective analysis of panoramic radiographs was performed for 178 childhood leukemia survivors aged below 17 years at the time of diagnosis. Sex, age at diagnosis, interval between ALL diagnosis and the follow-up radiograph, treatment protocol and risk grouping were recorded. Abnormalities of tooth development and defect index (DeI) were used to assess the frequency and severity of dental abnormalities.

RESULTS: One hundred and eight (61%) patients had no dental abnormalities at follow-up examination at a median of 6.1 years after diagnosis. Microdontia was more frequent in children under six years of age at the time of diagnosis (5.7% vs 0.6%, $p<0.001$). Significant differences were noted between distinct ALL treatment protocols with more common microdontia in patients treated according to the NOPHO ALL2008 protocol. Tooth agenesis was more frequent in patients that underwent therapy according to high risk arms compared to intermediate or standard risk arms (3.8% vs 1.4%, $p=0.01$). Patients under six years of age at diagnosis had a significantly higher average DeI score than older patients (7.0 vs 2.8, $p=0.01$).

CONCLUSIONS: Children and adolescents who received ALL treatment were at risk for dental damage. Young age and high intensity therapy were associated with the severity of dental abnormalities.

1. Introduction

Acute lymphoblastic leukemia (ALL) is the most common cancer in childhood. Approximately 4000 new cases are diagnosed annually in Europe and around 50 in Finland.[1-2] Treatment of childhood ALL is based on combination chemotherapy and begins with an intensive period of approximately 6 months that includes induction and consolidation phases followed by an interim maintenance and a delayed intensification period. Thereafter, low dose per oral treatment with 6-mercaptopurine (6MP) and methotrexate (MTX) follows and continues for up to 2.5 years from the disease onset.[3] Since 1992, all children and adolescents diagnosed with precursor B or T cell ALL in the Nordic countries (Denmark, Finland, Iceland, Norway and Sweden) have been treated according to the Nordic Society of Paediatric Haematology and Oncology (NOPHO) ALL

protocols.[4] The goal of the NOPHO ALL-92 protocol was to replace cranial irradiation with an intravenous high-dose chemotherapy, and to evaluate the significance of oral MTX/6MP maintenance therapy in detail. The NOPHO ALL-2000 protocol focused on the examination of efficacy of vincristine/dexamethasone pulses during the maintenance phase and the feasibility of non-centralized minimal residual disease evaluation.[5-7] One of the major aims of the NOPHO ALL2008 protocol was to decrease chemotherapy burden by limiting the proportion of patients allocated to intensive high-risk arms.[8]

Childhood cancer treatment has been found to be associated with various long-term side-effects that include neurocognitive, psychological, cardiopulmonary, endocrine, and musculoskeletal disturbances.[9] Likewise, tooth development may be disturbed and abnormalities such as microdontia, hypodontia, abnormal root development, taurodontism and enamel hypoplasia are known side-effects.[10] Normal tooth morphogenesis and calcification begins in utero and continues for up to 14-16 years.[11] The development of the third molars continues for several more years. Chemotherapy induced abnormalities that arise during dental development are irreversible.[12] The severity is dependent on the stage of odontogenesis, age when receiving chemotherapy, type and intensity of treatment and dose/location of radiation therapy.[13] Sonis et al. (1990) evaluated ninety-seven patients who were diagnosed with ALL between 1973 and 1983: 94% of all patients and 100% of patients younger than 5 years of age at diagnosis had abnormal dental development after ALL treatment.[14] Children treated with chemotherapy before 5 years of age and those receiving radiotherapy had more severe dental anomalies suggesting that immature teeth at the time of treatment were at higher risk for dental defects. Similarly, in a study by Minicucci et al. (2003), the follow-up panoramic radiograph of 76 patients treated for ALL revealed at least one dental abnormality in 82.9% of patients, whereas only 39.5% of ALL patients had dental abnormalities after ALL treatment in a study by Kaste et al. (1997).[15-16]

We explored the prevalence and severity of dental abnormalities such as disturbed root development, microdontia, and hypodontia in the permanent dentition in childhood ALL survivors treated according to different protocols. Since successive ALL treatment protocols have reduced chemotherapy burden in children with favorable prognosis, it was hypothesized that this change has contributed to a decrease in the prevalence of dental defects in permanent dentition with the most recent protocols.

2. Patients and methods

2.1 Patients

The study population consisted of children and adolescents aged from 0 to 17 years who were treated according to different ALL protocols; NOPHO ALL-92, NOPHO ALL-2000, NOPHO ALL2008 and `miscellaneous protocols` (used either earlier, at relapse situations or for infants). Patients were diagnosed with ALL between 1986 and 2016 and were treated in a single tertiary care referral center. Study patients received combination chemotherapy according to the contemporary protocol and included agents such as prednisolone, dexamethasone, vincristine, doxorubicin, methotrexate, L-asparaginase, 6-mercaptopurine, cytosine arabinoside, and cyclophosphamide. One hundred and fifty (84%) of the patients were in first ALL remission, 20 patients (11%) underwent hematopoietic stem cell transplantation (HSCT) and eight (4%) had a relapse during the follow-up period. Inclusion criteria to the study were ALL survivors/patients who had good quality panoramic radiograph at diagnosis and at minimum 3 years follow-up from the primary diagnosis. In some patients, the developmental stage of teeth was too early to be informative, in others the follow-up time was too short. After excluding these 116 of 294 eligible patients, the final cohort consisted of 178 patients (Figure 1 and Table 1). Three patients (2%) received total body irradiation (TBI) at doses of 10-12 Gray and 15 patients received neurocranial irradiation at doses of 12 to 24 Gray, not covering directly the dental area (Table 1).

2.2 Dental evaluation

Follow-up panoramic radiographs were obtained for all patients at least three years after primary diagnosis of ALL and examined to determine the number of permanent teeth (including wisdom teeth) and dental abnormalities. The length of the roots (R) and crowns (C) of mature permanent teeth were measured and the relative root length (R/C) calculated as a ratio of the root and crown length. In multi-rooted teeth, the longest root was used for the calculation. Wisdom teeth were classified as "not determined" if dental crown and root were not fully developed.

Defect Index (DeI) developed by Höltta et al.[17] was used to assess the total damage to the permanent dentition as a single weighted sum and included R/C ratio (D1–D3), microdontia (D4) and tooth agenesis (D5) (see Supplementary Table 1 for details). The higher the index, the stronger the deviation from normal tooth development. The DeI for each of the subject was calculated as follows:

Defect index (DeI) = (nD1 x 1**) + (nD2** x 2**)+(nD3** x 3**)+(nD4** x 4**)+(nD5** x 5**),**

where nDx stands for the number subject's teeth in the respective dental disturbance category.

2.3 Statistical analysis

Statistical significance of continuous variables was tested using the Mann-Whitney U-test for two groups and the Kruskal-Wallis test for more than two groups. Fisher's exact and Chi-squared tests were used to evaluate the statistical significance of frequencies in one or more categories of a contingency table. Multiple testing corrections were done using the Benjamini-Hochberg method. P-values less than 0.05 were considered statistically significant and all tests were two-tailed. Statistical analyses were carried out using R (v. 3.6.2) and the ring plot was created with the *ggplot2* library.

3. Results

3.1 Frequency of dental damage

Panoramic radiographs of 178 patients were examined. The mean age of the patients at diagnosis was 5.0 years (range 2.5 months to 16.8 years) and the mean interval between diagnosis and follow-up radiograph was 6.3 years (3.0 to 11.6 years) (Table 1). Of all patients, 108 (61%) had no dental abnormalities at the follow-up examination, which occurred at a median of 6.1 years (IQR 5.1-7.1) after primary diagnosis. The remaining 70 patients (39%) had at least one detectable abnormality. Patients who had at least one dental developmental disturbance had on average 21% of their teeth affected.

A total of 4347 teeth were evaluable in the panoramic radiographs. Root stunting (D1 to D3), microdontia (D4) and hypodontia (D5) were counted as abnormalities. Of all teeth, 92.2% (n=4008) were healthy, microdontia together with root stunting (D1) being the most common abnormalities (Table 2).

3.2 Dental abnormalities by age group

Dental development is closely associated with patient age. We categorized patients into two groups, i.e. younger than 6 years, and 6 to under 17 years at the time of diagnosis. Overall, the younger age group had significantly fewer healthy teeth than patients over 6 years of age (90.4% vs 96.1%, $p<0.001$) (Table 2). Likewise, microdontia (D4) differed significantly as 5.7% (169 of 2987) of teeth in young patients were underdeveloped compared to 0.6% (8 of 1360) among the older patients ($p<0.001$). No significant differences were found between the age and root stunting (D1–D3) or hypodontia (D5).

3.3 Dental abnormalities by treatment protocol

Among patients treated with the most recent NOPHO ALL2008 protocol, significantly fewer instances of root stunting ($p=0.01$), but more microdontic teeth ($p<0.001$), were detected when compared to other protocols (Table 2). Mild root stunting was detected in 6.3% (14 of 223) of teeth in patients that relapsed during the follow-up period (in comparison to other protocols, $p=0.01$).

Overall, patients treated with the `miscellaneous protocols` had more damaged teeth (47.2%) when compared to other protocols (Figure 2), although the difference did not reach statistical significance (p=0.48).

3.4 Dental abnormalities by risk grouping

Chemotherapy burden is the greatest in the intensive high risk arms. Patients treated in the non-high risk arms had healthier teeth compared to high risk patients (93.2% vs 88.5%, p<0.001) (Table 2). By teeth defects, patients in the high-risk arms more often exhibited mild root stunting (6.2% vs 2.5%, p<0.001) and tooth agenesis than non-high risk groups (3.8% vs 1.4%, p=0.01).

3.5 Dental defect index

Finally, we evaluated developmental defects and anomalies using the scoring system developed by Höltta et al.[17] The scoring system provides a measure of total damage in dental development as a defect index (DeI) score. Patients under six years of age at diagnosis had an average DeI score of 7.0 while older patients had an average DeI score of 2.8 (p=0.01). No statistically significant differences in DeI score were observed by sex, protocol or risk grouping, although the high risk arms showed a tendency towards higher DeI score (Figure 3, Supplementary Table 2).

4. Discussion

Disturbance of dental development is a known adverse effect of chemotherapy administered during childhood. We investigated the prevalence and severity of dental damage in ALL survivors and assessed differences between three consecutive NOPHO ALL treatment protocols. Our results show that 61% of patients had normal dental development which resulted in healthy tooth formation on the basis of panoramic radiographs. Nonetheless, 39% of patients experienced at least one disturbance in permanent dentition, and alterations were more pronounced in children who had received chemotherapy at a young age or according to high risk protocols. Mild root stunting and microdontia were the most frequent abnormalities.

Earlier literature suggests that age of a child at time of chemotherapy administration and intensity of treatment are the main determinants of the severity of altered dental development.[14] Our study aligns well with the literature, as children under 6 years of age at diagnosis were more susceptible to dental damage. This is a period of life when the maturation of permanent teeth is at a critical early phase.[16,18-22] Particularly, we saw increased numbers of microdontia in young patients, which is in line with earlier studies.[16,23] The impact of age was also evident when the dental defect index was applied to score the extent of dental damage.[17] In contrast, no alterations were observed in root development or missing teeth by age group. Earlier studies by Kılınç et al. (2019)[23] and Maciel et al. (2009)[24] similarly observed no significant differences between age groups in terms of root malformation.

Childhood ALL treatment has advanced during the past decades and many protocols have improved their stratification schemas to allow less intensive therapy for patients with lower risk of relapse, thus reducing the overall risk of adverse effects. Hence, we compared dental abnormalities across successive ALL treatment protocols used in Nordic countries. To our knowledge, there are no earlier studies that have compared dental health in ALL survivors treated over time with different protocols. In keeping with the hypothesis, patients that were treated according to the most recent NOPHO ALL2008 protocol presented with the healthiest tooth roots. Surprisingly, microdontia was more frequent in patients treated according to the NOPHO ALL2008 protocol, and they also exhibited the highest DeI score. The latter finding may be explained by the formula for DeI which gives more weight to microdontia than root stunting. Altered root development occurred more often in patients treated with NOPHO ALL-2000, and patients treated for relapse during the follow-up period. The tooth roots begin developing at approximately age 3 to 4 years and continue up to 16 years.[25] Higher prevalence of root stunting in patients treated by the NOPHO ALL-2000 protocol may reflect the slightly older age of patients in this protocol.[26] The prevalence

of tooth agenesis (hypodontia) was low across all NOPHO protocols and lower than in earlier studies.[16,27-28]

Previous studies have shown that in a normal population the prevalence of root abnormalities ranges from 1.3% to 5.6%[29-30], and microdontia from 1% to 2%[15,31-34], while the prevalence of hypodontia varies between 4 and 8% depending on the ethnic background.[35] In the present study, only the prevalence of microdontia (4.1%) was higher in childhood ALL survivors compared to estimates in a healthy population.

In the current study we also compared dental damage across risk groups. The highest prevalence of mild root stunting and hypodontia were observed in patients treated according to high risk arms, suggesting that higher chemotherapy burden contributes to the extent of damage. Eight patients relapsed during the follow-up period and, hence, the panoramic radiograph assessment reflects the damage caused by the primary treatment. Irradiation was given to 18 patients of whom only three with total body irradiation (TBI) involved directly the mouth. Low number of TBI cases did not allow for deeper analysis.

DeI was used to assess the severity and extent of dental aberrations in ALL survivors. The mean DeI score in the present study was 5.8, which is lower than in earlier studies. In the studies by Cubukcu et al. (2012)[27] and Hsieh et al. (2011)[36] the mean DeI score ranged from 10.8 (SD 11.2) to 24.7 (SD 17.8) for children with solid tumors, leukemias and lymphomas. One reason for the lower DeI in our study may be due to the low number of cases who received irradiation involving the dental area.

Our study has several strengths. The sample size is relatively large, the patient population is homogenous and all radiographs were taken at a single site. Our approach also allowed comparison of dental damage across consecutive ALL protocols. The study also has limitations. We may have

underestimated the frequency of root stunting, microdontic teeth, and tooth agenesis as development of permanent teeth is not fully evaluable in young patients on panoramic radiographs.

In summary, combination chemotherapy for childhood ALL often results in dental developmental defects in young patients. Since the health of dentition affects quality of life, ALL survivors need regular follow-up for early detection of late adverse effects on dental health.

Conflict of interest

The authors declare no conflicts of interest.

Ethics statement

The study was approved by the research director of Pirkanmaa Hospital District according to local practices (permission #R19109).

Data sharing statement

The authors choose not to share the raw data due to data protection reasons.

Author contributions

EI, OL, LA and TP conceived the study. EI, AN, and OL analyzed the data. OL supervised the study. EI, AN, and OL drafted the manuscript, and all the authors reviewed and accepted it.

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Legends

FIGURE 1. Flow chart of the study subjects and exclusions.

FIGURE 2. Ring plot of proportions of subjects with any teeth abnormality by treatment protocols.

P-value was calculated using the chi-squared test.

FIGURE 3. Violin plot of dental defect indices (DeI) by age group (A), sex (B), treatment protocol (C), and treatment intensity (D).

Black dots represent evaluated indices, red line extends to the 90th percentile and the red diamond represents the mean value in each respective group. P-values are reported for each panel.

The abbreviated treatment protocols in panel C are NOPHO ALL-92, NOPHO ALL-2000 and NOPHO ALL2008, miscellaneous protocols and relapse patients. HR = high risk.

Table 1 - Characteristics of the study sample

	TOTAL	NOPHO ALL-92	NOPHO ALL-2000	NOPHO ALL2008	MISCELLANEOUS PROTOCOLS
All subjects, *n (%)*	178	55 (31%)	49 (27%)	37 (21%)	37 (21%)
Age, years					
mean	5.0	4.6	5.9	5.1	4.5
median	4	4	4	4	3
IQR	3 - 6	2 - 6	3 - 9	3 - 7	2 - 5
Age groups, *n (%)*					
0-5.9 years	128 (72%)	41 (75%)	32 (65%)	25 (68%)	30 (81%)
6-16.9 years	50 (28%)	14 (25%)	17(35%)	12 (32%)	7 (19%)
Sex, *n (%)*					
Male	88 (49%)	22 (40%)	25 (51%)	21 (57%)	18 (51%)
Female	90 (51%)	33 (60%)	24 (49%)	16 (43%)	17 (49%)
PTG, years after dg					
mean	6.3	6.5	6.2	5.6	6.7
median	6.1	6.5	5.8	5.4	6.8
IQR	5.1 - 7.1	5.4- 7.4	5.1- 7.1	4.1 - 6.5	5.9 - 7.2
High-risk protocols, *n (%)*	39 (22%)	6 (11%)	16 (33%)	4 (11%)	13 (35%)
Radiotherapy, *n (%)*	18 (10%)	2 (4%)	2 (4%)	2 (5%)	12 (32%)
TBI	3 (2%)	0	1 (2%)	2 (5%)	0
Neurocranium	15 (8%)	2 (4%)	1 (2%)	0	12 (32%)
Relapse patients, *n (%)*	8 (4%)	4 (7%)	3 (6%)	0	1 (3%)
HSCT, *n (%)*	20 (11%)	7 (13%)	6 (12%)	6 (16%)	1 (3%)

IQR - Interquartile range
HSCT - Hematopoietic stem cell transplantation
Dg - Diagnosis
TBI - Total body irradiation

Table 2 - Frequency of dental disturbances according to age, treatment protocol and risk grouping.

	Teeth, *n (%)*	**Not determinable**, *n (%)*	**D0** *(R/C >1,6)*	**D1** *(R/C 1,2-1,6)*	**D2** *(R/C 0,9-1,1)*	**D3** *(R/C <0,9)*	**D4** *(Microdontia)*	**D5** *(Hypodontia)*	**Healthy teeth,** *% (n)*
TOTAL	4347	30.4% (1323)	96.2% (4180)	3.3% (142)	0.4% (18)	0.2% (7)	4.1% (177)	0.6% (26)	92.2% (4008)
Age group *(%, n)*									
0–5.9 years	68.7% (2987)	82.7% (1094)	95.9% (2866)	3.4% (101)	0.5% (14)	0.2% (6)	5.7% (169)	0.5% (15)	90.4% (2701)
6–16.9 years	31.3% (1360)	17.3% (229)	96.6% (1314)	3% (41)	0.3% (4)	0.001% (1)	0.6% (8)	0.8% (11)	96.1% (1307)
Adjusted p-value			0.46	0.64	0.64	0.55	<0.001*	0.46	<0.001*
Protocol *(%, n)*									
NOPHO ALL-92	27.7% (1204)	31.8% (421)	95.9% (1155)	3.2% (39)	0.5% (6)	0.3% (4)	3.6% (43)	0.6% (7)	92.4% (1112)
NOPHO ALL-2000	27.6% (1198)	20.6% (272)	95.2% (1141)	3.8% (46)	0.8% (10)	0.1% (1)	2.8% (33)	0.2% (2)	92.7% (1111)
NOPHO ALL2008	19.1% (828)	26.4% (349)	98.3% (814)	1.7% (14)	0	0	7.2% (60)	0.8% (7)	91.1% (754)
Miscellaneous protocols	20.6% (894)	18.7% (248)	96.3% (861)	3.2% (29)	0.2% (2)	0.2% (2)	4.6% (41)	1.1.% (10)	91.9% (822)
Relapse patients	5.1% (223)	2.5% (33)	93.7% (209)	6.3% (14)	0	0	0	0	93.7% (209)
Adjusted p-value			0.002*	0.01*	0.07	0.55	<0.001*	0.07	0.64
Risk grouping *(%, n)*									
High-risk	21.1% (918)	24% (318)	93.5% (858)	6.2% (57)	0.2% (2)	0.1% (1)	5.2% (48)	3.8% (12)	88.5% (812)
Other risk stratification	78.9% (3429)	76 % (1005)	96.9% (3322)	2.5% (85)	0.5% (16)	0.2% (6)	3.8% (129)	1.4% (14)	93.2% (3196)
Adjusted p-value			<0.001*	<0.001*	0.55	1	0.09	0.01*	<0.001*

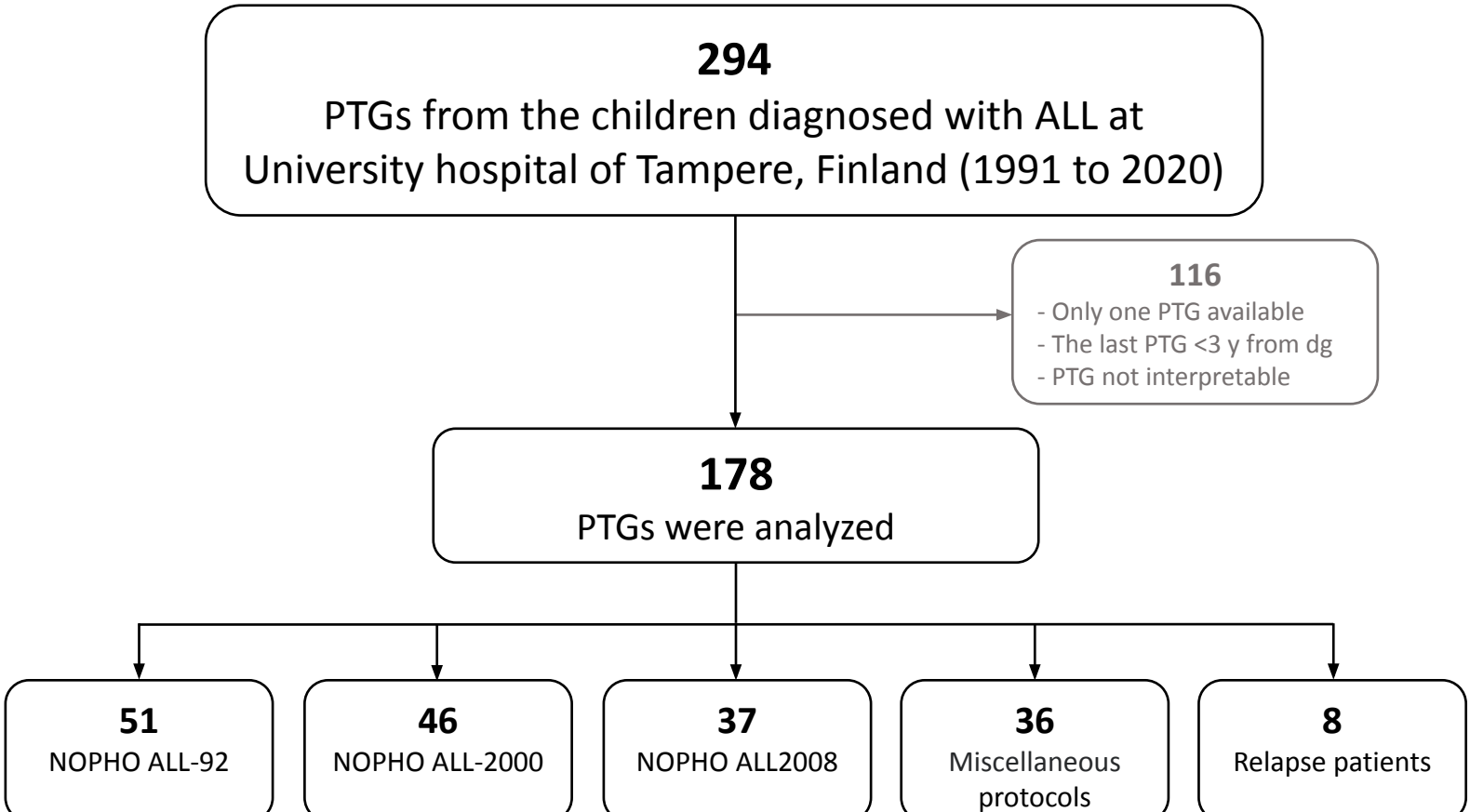
Fisher's exact test was used to test for statistical significance. The p-values were adjusted for multiple testing using the Benjamini-Hochberg method. Statistically significant p-values (<0.05) are marked with an asterisk (*).
R/C - root/crown ratio

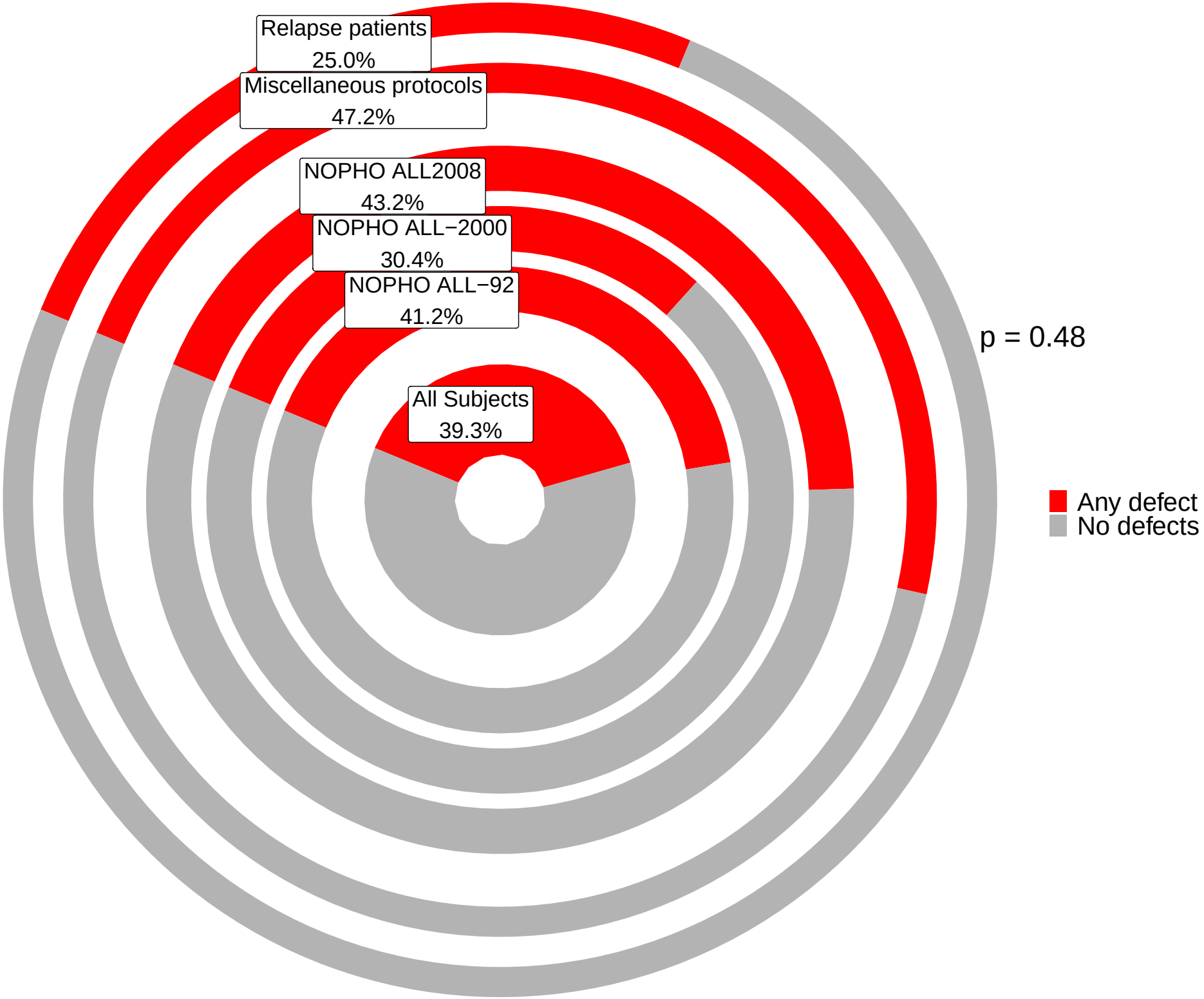
Table 3 - Dental defect indices by sex, age, protocol and risk grouping.

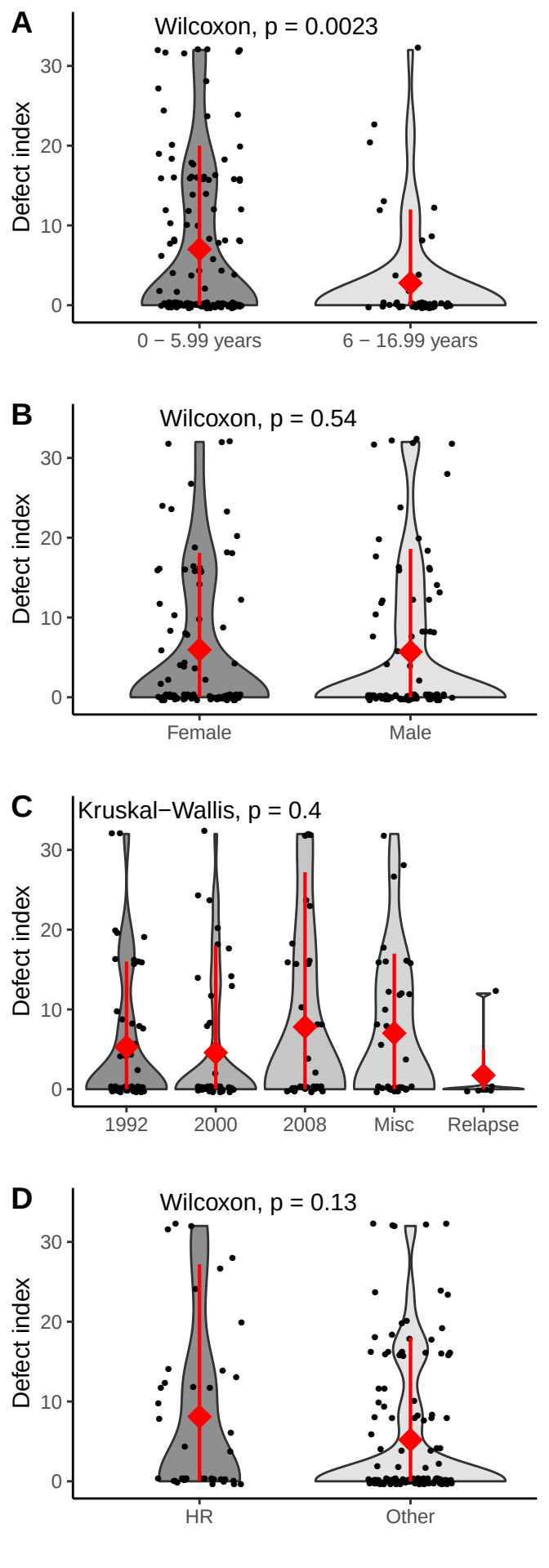
	n *(%)*	**Mean**	**Median**	**p75**	**p90**	**Max**	**p**
TOTAL	178	5.8	0	10	18.3	32	
Sex							0.59
Male	88 (49%)	5.7	0	8.5	18.6	32	
Female	90 (51%)	6	0	11.5	18.1	32	
Age groups							0.01*
0–5.9 years	128 (72%)	7	0	14.5	20	32	
6–16.9 years	50 (28%)	2.8	0	0	12	32	
Protocols							0.53
NOPHO ALL-92	51 (29%)	5.3	0	8	16	32	
NOPHO ALL-2000	46 (26%)	4.6	0	7	18	32	
NOPHO ALL2008	37 (21%)	7.8	0	16	27.2	32	
Miscellaneous protocols	36 (20%)	7.0	0	12	17	32	
Relapse patients	8 (4%)	1.8	0	0.5	5	12	
Risk groups							0.18
High risk	39 (22%)	8.1	0	12.5	27.2	32	
Other risk stratification	139 (78%)	5.2	0	8	18	32	

The p-values were calculated using the Mann-Whitney U-test for groups of two (sex, age and risk group) and Kruskal-Wallis test for three or more groups (protocols). No corrections for multiple testing were used. Statistically significant p-values (<0.05) are marked with an asterisk (*).

p75 - 75th percentile
p90 - 90th percentile


294
PTGs from the children diagnosed with ALL at University hospital of Tampere, Finland (1991 to 2020)
116
- Only one PTG available
- The last PTG <3 y from dg
- PTG not interpretable
178
PTGs were analyzed
51
NOPHO ALL-92
46
NOPHO ALL-2000
37
NOPHO ALL2008
36
Miscellaneous protocols
8
Relapse patients


Relapse patients
25.0%
Miscellaneous protocols
47.2%
NOPHO ALL2008
43.2%
NOPHO ALL−2000
30.4%
NOPHO ALL−92
41.2%
All Subjects
39.3%
p = 0.48
Any defect
No defects


A
Wilcoxon, p = 0.0023
Defect index
30
20
10
0
0 − 5.99 years
6 − 16.99 years
B
Wilcoxon, p = 0.54
Defect index
30
20
10
0
Female
Male
C
Kruskal−Wallis, p = 0.4
Defect index
30
20
10
0
1992
2000
2008
Misc
Relapse
D
Wilcoxon, p = 0.13
Defect index
30
20
10
0
HR
Other