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Review Article

Orthodontic treatment outcomes and safety for secondary dentofacial deformities after childhood cancer therapy: a systematic review and meta-analysis

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Abstract: Aims: To systematically evaluate the treatment outcomes and safety of orthodontic intervention for secondary dentofacial deformities after childhood cancer therapy, with particular emphasis on occlusal outcomes, oral health-related quality of life, treatment-related complications, and dental developmental abnormalities relevant to orthodontic management. Methods: A comprehensive search of PubMed, Embase, Cochrane Library, Web of Science, Scopus, and CINAHL was performed using terms related to cancer, orthodontic treatment, and treatment outcomes. Eligible studies included observational or comparative clinical studies reporting either treatment efficacy outcomes (e.g., w-PAR, ICON, and oral health-related quality of life) or treatment safety/sequelae outcomes (e.g., treatment-related complications and dental developmental abnormalities). Risk of bias was assessed using the Newcastle-Ottawa Scale. For efficacy outcomes, pooled standardized mean differences with 95% confidence intervals were calculated; for safety/sequelae outcomes, pooled risk ratios with 95% confidence intervals were estimated. Random-effects models were applied in Stata, and heterogeneity was assessed using Cochran's Q and the I^2 statistic. Results: Ten studies published between 2001 and 2023 were included. For w-PAR, the pooled effect showed a significant overall change (SMD = -1.12, 95% CI -2.22 to -0.01; I^2 = 98.5%), driven mainly by the immediate post-treatment subgroup. For ICON, the pooled effect was also significant (SMD = 0.68, 95% CI 0.12 to 1.24; I^2 = 97.5%), with the stronger signal observed at follow-up beyond 3 weeks. Oral health-related quality of life, assessed by OHIP-14, showed a small but significant overall improvement (SMD = 0.26, 95% CI 0.03 to 0.49), with moderate heterogeneity (I^2 = 54.3%). In contrast, survivors experienced a significantly higher risk of complications during orthodontic treatment than comparison groups (RR = 2.44, 95% CI 1.07-5.58; I^2 = 36.7%). The pooled relative risk of dental developmental abnormalities relevant to orthodontic planning was not significantly different overall (RR = 1.11, 95% CI 0.40-3.08), although heterogeneity was considerable (I^2 = 90.3%). Conclusion: Orthodontic intervention in survivors of childhood cancer may be associated with improvements in occlusal outcomes and oral health-related quality of life; however, the evidence for treatment efficacy remains uncertain, largely due to substantial between-study heterogeneity. At the same time, survivors appear to have a significantly increased risk of treatment-related complications.

Keywords: Childhood cancer therapy, secondary dentofacial deformities, orthodontic intervention, systematic review, meta analysis

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Introduction

Over the past several decades, major advances in pediatric oncology have transformed many childhood malignancies from fatal diseases into highly survivable conditions, resulting in a rapidly growing population of long-term childhood cancer survivors. However, improved survival has been accompanied by an increasing recognition of treatment-related late effects, among which craniofacial growth disturbances and secondary dentofacial deformities represent particularly complex and clinically challenging sequelae [1]. Children exposed to head and neck irradiation, total body irradiation, intensive chemotherapy, hematopoietic stem cell transplantation, or multimodal oncologic regimens may subsequently develop maxillofacial hypoplasia, occlusal disharmony, dental agenesis, microdontia, root malformations, delayed eruption, and asymmetric craniofacial development [2]. These abnormalities extend far beyond esthetic concerns, potentially impairing mastication, speech, oral health, psychosocial well-being, and overall quality of life, while also complicating long-term oral rehabilitation and orthognathic reconstruction.

Despite increasing awareness of these craniofacial late effects, evidence-based orthodontic management strategies for childhood cancer survivors remain poorly defined. Secondary dentofacial deformities following childhood cancer therapy differ fundamentally from conventional malocclusions encountered in otherwise healthy individuals [3-5]. Their biological basis is shaped by treatment-induced injury to skeletal growth centers, dental follicles, periodontal tissues, and developing tooth roots, frequently occurring within the context of altered craniofacial growth potential and reduced tissue regenerative capacity. Consequently, orthodontic treatment in this population cannot be approached as a simple adaptation of conventional protocols to medically complex patients [6]. Instead, treatment planning requires careful consideration of compromised bone remodeling, root vulnerability, altered growth trajectories, treatment tolerance, relapse risk, and coordination with ongoing oncologic and craniofacial surveillance.

Within this context, the effectiveness and safety of orthodontic intervention have become issues of increasing clinical relevance. Orthodontic therapy in childhood cancer survivors may theoretically provide substantial functional and psychosocial benefits through improvement of occlusal relationships, facial symmetry, and oral rehabilitation potential [7]. Nevertheless, concerns persist regarding treatment-related complications, including root resorption, periodontal compromise, impaired tooth movement, prolonged treatment duration, relapse, and the possibility of exacerbating tissues already damaged by cancer therapy. Furthermore, altered skeletal maturation and unpredictable craniofacial growth patterns may influence both the stability and long-term success of orthodontic correction. As a result, clinicians frequently face uncertainty regarding the feasibility, predictability, and biological safety of orthodontic treatment in this uniquely vulnerable population.

Current evidence on orthodontic outcomes and safety after childhood cancer therapy remains fragmented and methodologically limited. Existing studies are dispersed across the fields of orthodontics, pediatric dentistry, oncology, and craniofacial surgery, with substantial heterogeneity in cancer diagnoses, oncologic treatment exposures, age at treatment, dentofacial phenotypes, orthodontic techniques, and outcome assessment methods. Most available reports consist of retrospective case series or descriptive analyses of late effects rather than rigorous evaluations of orthodontic treatment efficacy and safety. In addition, clinically relevant outcomes - including occlusal correction, cephalometric changes, root resorption, treatment duration, stability, complication rates, and the need for adjunctive orthognathic surgery - are inconsistently reported, limiting meaningful comparisons across studies. This lack of consolidated evidence has important implications for survivorship care. As multidisciplinary long-term follow-up programs increasingly incorporate orthodontic evaluation and craniofacial rehabilitation, clinicians are often required to make treatment decisions in the absence of robust evidence regarding expected outcomes and risks. A clearer understanding of orthodontic treatment performance and safety profiles in childhood cancer survivors is therefore essential to support individualized treatment planning, risk stratification, interdisciplinary communication, and informed

decision-making involving orthodontists, pediatric oncologists, maxillofacial surgeons, restorative dentists, patients, and families.

Accordingly, we conducted a systematic review and meta-analysis to evaluate orthodontic treatment outcomes and safety in patients with secondary dentofacial deformities following childhood cancer therapy. Specifically, we aimed to synthesize the available evidence regarding functional, dentoskeletal, and treatment-related safety outcomes after orthodontic intervention in this population, while also identifying key limitations and gaps within the current evidence base. By consolidating the existing literature, this study seeks to advance evidence-based orthodontic management for childhood cancer survivors and provide a stronger clinical foundation for the rehabilitation of treatment-related dentofacial deformities.

Methods

Search protocol

The extensive and methodical search of the literature was conducted in six electronic databases: PubMed, Embase, Cochrane Library, Web of Science, Scopus, and CINAHL. The search strategy was designed to maximize sensitivity and was based on three core concept domains: malignancy-related terms (which could be neoplasms or cancer), orthodontic terms (orthodontics or orthodontic procedures), and outcome-related terms (treatment outcome, treatment efficacy, or success rate). Controlled vocabulary terms, such as MeSH headings, were used where appropriate, and free-text keywords were added to these keywords, and the syntax was modified to the indexing needs of an individual database. This is a multistep plan intended to achieve extensive retrieval of the studies that assessed the timing of orthodontics interventions and the outcome of these interventions in survivors of childhood cancer having secondary dentofacial deformities (Supplementary Table 1).

Review design

The purpose of this review was to determine the efficacy and timeliness of orthodontic treatment in childhood cancer survivors with secondary dentofacial deformities as a result of oncologic treatment with or without radiotherapy. The eligibility criteria were that the patients should have a history of childhood cancer treatment and have reported quantitative orthodontic results following any orthodontic therapy, be it fixed or removable appliances. Comparator groups might be healthy children or teenagers with no history of cancer treatment, or comparisons of various times of orthodontic treatment or methods. Interest outcomes included: occlusal indices, treatment success, relapse, complications, quality of life, and patient satisfaction. We included randomized controlled trials, cohort studies, case-control studies, and prospective observational studies and excluded studies of congenital dentofacial deformities, benign tumors, non-orthodontic interventions, case reports, editorials, letters, reviews, meta-analyses, and studies that lacked suitable controls or outcome data that could be extracted (Supplementary Table 2).

Evaluation of bias

Two reviewers independently determined the risk of bias based on the Newcastle-Ottawa Scale (NOS), as shown in **Table 1**. In non-randomized studies, methodological quality was assessed based on the standard NOS methods of selection, comparability and outcome/exposure measurement, and specifically on how cohort representativeness, control selection adequacy, orthodontic outcome ascertainment and addressing key confounders were handled. Any disagreements in scoring were addressed by discussion and where required, a third reviewer. The NOS was selected as it offers a systematic and generally accepted model of how to evaluate the internal validity of observational studies, which were the most common study designs in the current review. Risk-of-bias judgments were included in the overall evaluation of the confidence and interpretability of pooled results, and was not a purely descriptive exercise in keeping with best practice of meta-epidemiologic interpretation.

PROSPERO registration and methodological transparency

This systematic review and meta-analysis was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO; registration number: CRD42026-1421234), ensuring methodological transparency and adherence to predefined eligibility cri-

Table 1. Risk of bias assessment with the Newcastle-Ottawa Scale (NOS)

Study	Representativeness of the exposed cohort	Study design quality	Selection of the non-exposed cohort	Ascertainment of exposure	Comparability of cohorts	Assessment of outcome	Was follow-up long enough for outcomes to occur?	Adequacy of statistical analysis	Other factors	Overall Risk of Bias
Dahllöf et al. (2001)	+ (Adequate cohort, specific childhood cancer survivors)	+ (Retrospective design, good follow-up)	+ (Appropriate non-exposed cohort)	+ (Clear ascertainment of exposure to orthodontic treatment)	- (Some imbalances in cohort matching)	+ (Outcome assessment was clear and relevant)	+ (Sufficient follow-up time of 20 years)	+ (Statistical analysis was robust)	+ (No other confounding factors identified)	High
Mituś-Kenig et al. (2015)	+ (Well-defined cohort of childhood cancer survivors)	+ (Retrospective study with some cohort matching)	+ (Matching with healthy controls)	+ (Exposure was well-documented for orthodontic treatment)	- (Could have had more precise matching for confounders)	+ (Clear outcome assessment of orthodontic treatment results)	+ (Sufficient follow-up, over 12 months)	+ (Good statistical techniques applied)	+ (No major other bias)	Moderate
Mituś-Kenig et al. (2020)	+ (Cohort of cancer survivors with control group comparison)	+ (Retrospective and prospective elements combined)	+ (Well-matched controls)	+ (Clear assessment of exposure via medical history)	- (Limited matching of confounders, could have adjusted for more variables)	+ (Consistent outcome assessment using QoL tools)	+ (Sufficient follow-up to measure changes)	+ (Proper statistical tests used)	+ (No additional bias found)	Moderate
Mituś-Kenig et al. (2021)	+ (Well-defined cohort and inclusion criteria)	+ (Study had prospective components)	+ (Good control matching for age, sex, and malocclusion)	+ (Exposure to orthodontic treatments well established)	- (Possible imbalance in baseline oral health status)	+ (Follow-up outcome assessment through OHIP-14)	+ (Follow-up adequate to detect outcome differences)	+ (Sound statistical methods used)	+ (No major confounding factors)	Moderate
Neill et al. (2015)	+ (Good representation of orthodontic practices)	+ (Survey design, though not randomized)	+ (Control group from population data)	+ (Exposure well-documented via survey)	- (Possible bias in non-response or treatment group selection)	+ (Outcome assessment via clinical judgment)	+ (Follow-up data in a survey design)	+ (Appropriate analysis for survey data)	+ (No critical bias factors)	High
Proc et al. (2016)	+ (Clear and defined cohort of childhood cancer survivors)	+ (Retrospective cohort analysis)	+ (Control group matched well)	+ (Exposure accurately documented via medical records)	- (Possible issues with matching confounders like age and comorbidities)	+ (Good assessment of treatment outcomes)	+ (Follow-up period appropriate for treatment outcome measurement)	+ (Statistical analysis robust)	+ (No major issues identified)	Moderate
Ritwik et al. (2020)	+ (Study group well-defined, cancer survivors)	+ (Review-based, providing clear assessment of issues)	+ (Relevant control group comparison)	+ (Exposure clearly indicated for oral health issues)	- (Limited data on confounding factors)	+ (Outcomes clearly assessed in QoL measures)	+ (Follow-up adequate for determining long-term oral effects)	+ (Statistical techniques were appropriate)	+ (No unaccounted-for bias)	Not applicable
Stolze et al. (2021)	+ (Cross-sectional survey, with a good cancer survivor cohort)	+ (Good study design but limited by the nature of survey data)	+ (Matched with general population)	+ (Well-assessed exposure through questionnaires)	- (Limited control for other confounders like socioeconomic factors)	+ (Clear outcome measures through survey data)	+ (Follow-up adequately measures long-term outcomes)	+ (Appropriate statistical analyses)	+ (No additional bias factors identified)	Low
Stolze et al. (2023)	+ (DCCSS-LATER study with well-defined cohort)	+ (Cross-sectional with comparison group)	+ (Good control matching)	+ (Clear exposure documentation)	- (Some unaccounted-for confounders in oral health outcomes)	+ (Outcome assessment through OHIP-14)	+ (Follow-up long enough to capture relevant outcomes)	+ (Sound statistical methods)	+ (No other critical bias identified)	Low

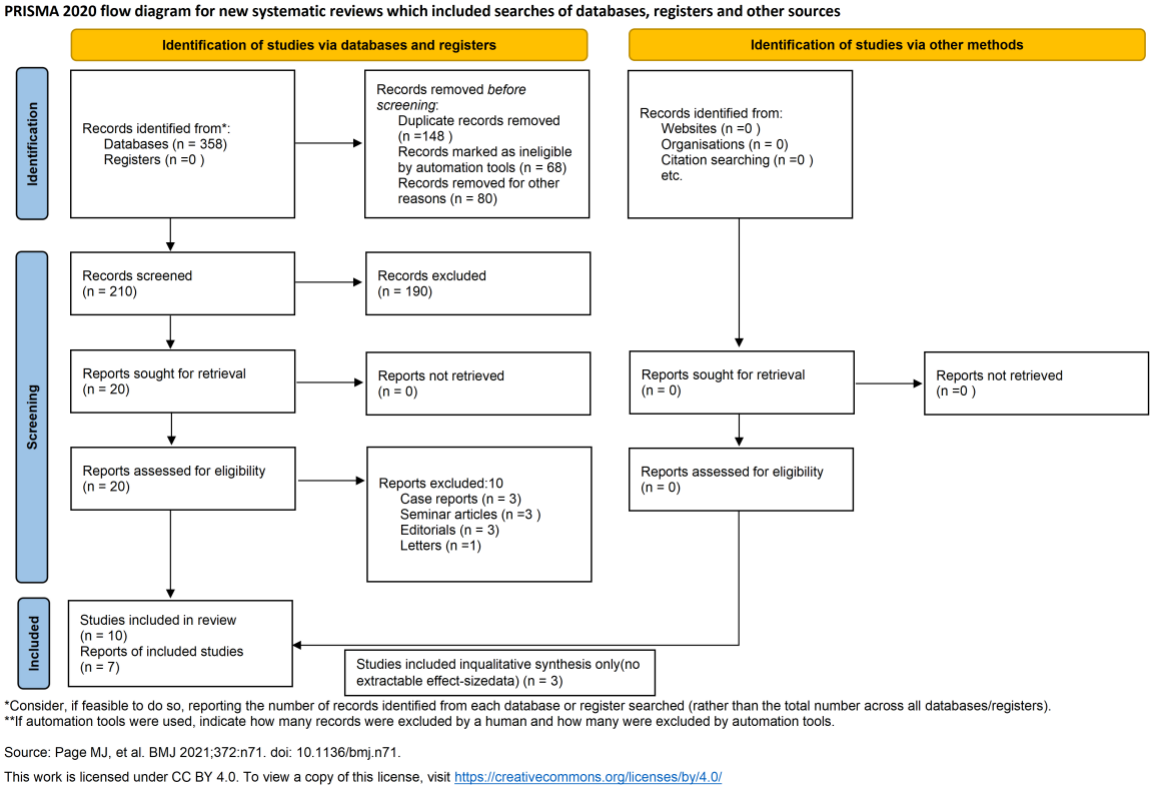

Figure 1. Prisma diagram of the included studies.

teria, outcomes, and analytical strategies prior to data extraction and synthesis. The review was conducted in accordance with PRISMA guidelines and followed a structured protocol designed to minimize bias in study selection, data extraction, and evidence synthesis. Any deviations from the registered protocol were transparently documented and justified in the final report. This prospective registration enhances the methodological rigor, reproducibility, and credibility of the evidence synthesis, and supports the robustness of the conclusions regarding orthodontic treatment outcomes and safety in childhood cancer survivors with secondary dentofacial deformities.

Statistical protocol

All statistical tests were done by means of the Stata software. To summarize continuous outcomes, such as w-PAR, ICON, and OHIP-14, pooled effect sizes were estimated as standardized mean differences (SMDs) with 95% confidence intervals (CIs), whereas risk ratios (RRs) with 95% confidence intervals (CIs) were used to summarize dichotomous outcomes, such as treatment-related complications and prevalence of dental developmental abnormalities. The Cochran Q test was used to assess statistical heterogeneity, and the I^2 statistic was used to quantify its magnitude. A random-effects model was chosen as the main model of analysis in consideration of the anticipated clinical and methodological heterogeneity among the studies such as the variations in study design, study participants, follow-up periods and definition of outcomes. Prespecified subgroup analyses based on assessment timing (immediate post-treatment versus > 3 weeks follow-up), and study design, where relevant, were performed. Asymmetry of funnel plots was visually examined to assess potential publication bias. The interpretation of pooled estimates was done with caution when heterogeneity was high in order to avoid overinterpretation of summary effects in the occurrence of a marked between-study dispersion.

Results

Study selection

The study selection process is summarized in **Figure 1**. A total of 358 records were identified

through database searching, with no additional records retrieved from registers or other sources. Prior to screening, 228 records were removed, including 148 duplicates and 80 records excluded for other reasons, leaving 210 records for title and abstract screening. Of these, 190 records were excluded as clearly irrelevant, and 20 reports were sought for full-text retrieval. All 20 reports were successfully retrieved and assessed for eligibility. After full-text review, 10 reports were excluded, comprising 3 case reports, 3 seminar articles, 3 editorials, and 1 letter, resulting in the inclusion of 10 studies [8-17] in the systematic review. No additional eligible studies were identified through manual or alternative search strategies. As detailed in **Table 2**, the included studies were published between 2001 and 2023 and represented a range of study designs, predominantly retrospective and cross-sectional investigations, reflecting the limited but clinically relevant body of evidence on orthodontic intervention and treatment outcomes in survivors of childhood cancer with secondary dentofacial deformities.

w-PAR and ICON index

For w-PAR, the pooled effect size showed a modest but statistically significant overall change (SMD = -1.12, 95% CI -2.22 to -0.01; I^2 = 98.5%, P < 0.001). Subgroup analysis suggested that this overall effect was primarily driven by the "After" timepoint, which showed a significant negative pooled estimate (SMD = -2.28, 95% CI -4.01 to -0.56; I^2 = 98.3%, P < 0.001), whereas the effect at more than 3 weeks was small and non-significant (SMD = 0.04, 95% CI -0.39 to 0.47; I^2 = 82.4%, P = 0.001) (**Figure 2**). In contrast, ICON-based analyses yielded a significant positive overall pooled effect (SMD = 0.68, 95% CI 0.12-1.24; I^2 = 97.5%, P < 0.001). This signal was largely attributable to the subgroup assessed beyond 3 weeks, in which a significant pooled effect was observed (SMD = 1.24, 95% CI 0.48-2.00; I^2 = 96.6%, P < 0.001), while the "After" subgroup showed no statistically significant difference (SMD = 0.13, 95% CI -0.47 to 0.74; I^2 = 95.4%, P < 0.001) (**Figure 3**).

Quality of life (OHIP-14)

The pooled analysis demonstrated a small but statistically significant overall improvement following orthodontic intervention (SMD = 0.26, 95% CI 0.03-0.49), with moderate between-study heterogeneity that approached, but did not reach, conventional statistical significance (I^2 = 54.3%, P = 0.053). In the subgroup analysis, the effect estimate at the immediate post-intervention assessment ("After") was larger in magnitude but did not achieve statistical significance (SMD = 0.38, 95% CI -0.07 to 0.83; I^2 = 75.0%, P = 0.018), reflecting substantial heterogeneity across studies. By contrast, outcomes assessed more than 3 weeks after treatment showed a smaller and more consistent effect that was not statistically significant at the subgroup level (SMD = 0.15, 95% CI -0.07 to 0.37; I^2 = 0.0%, P = 0.610). Notably, the study by Dahllöf et al. [9] contributed the largest positive effect estimate in the immediate post-treatment subgroup, whereas the remaining studies showed more modest changes (**Figure 4**).

Complications observed during orthodontic treatment

The pooled effect estimate demonstrated more than twofold increased risk overall (RR = 2.44, 95% CI 1.07-5.58), with low-to-moderate between-study heterogeneity that was not statistically significant (I^2 = 36.7%, P = 0.192), suggesting a reasonably consistent direction of effect across studies. Individually, three studies showed a significant excess of complications in survivors, including Mituś-Kenig et al. [11] (RR = 2.85, 95% CI 1.01-8.05), Mituś-Kenig et al. [12] (RR = 4.35, 95% CI 1.00-19.01), and Stolze et al. [16] (RR = 3.26, 95% CI 1.12-9.50), whereas Dahllöf et al. [9] reported a non-significant estimate in the opposite direction (RR = 0.32, 95% CI 0.04-2.46), likely reflecting limited statistical power and the small sample size of that early cohort (**Figure 5**).

Prevalence of dental developmental abnormalities relevant to orthodontic planning

The pooled analysis of dental developmental abnormalities relevant to orthodontic planning revealed no statistically significant overall difference between childhood cancer survivors and comparison groups (RR = 1.11, 95% CI 0.40-3.08), but this summary estimate was accompanied by very high between-study het-

Table 2. Characteristics of the included studies

Study	Design	Population/comparator	Outcome domain relevant to this review	Follow-up/assessment window	Corrected source-based summary
Dahllöf et al. 2001 [9]	Retrospective clinical study	10 orthodontically treated long-term survivors after pediatric bone marrow transplantation; no formal non-cancer control group reported	Orthodontic treatment outcome; treatment-related complications	Not explicitly reported as a fixed duration; study concerns long-term survivors	In 4/10 patients the treatment result was judged unsatisfactory; 1/10 showed root resorption; no harmful side effects from orthodontic treatment were reported.
Mituś-Kenig et al. 2015 [10]	Descriptive clinical report/case series	40 childhood cancer survivors undergoing orthodontic treatment; no concurrent control group reported in the abstract/source snippet	Treatment completion, normocclusion, interruptions, mucosal complications	Treatment time: 12.5 months	Normocclusion was not reached in 6/40; treatment was stopped in 9 because of recurrence; mucosal inflammation was observed in 11; treatment stopped in 1 because of poor oral hygiene.
Mituś-Kenig et al. 2020 [11]	Prospective case-control study	40 cancer survivors vs healthy orthodontic controls matched for age, sex, and malocclusion	Oral health-related quality of life (OHIP-14); clinical treatment documentation	Before, during, and after orthodontic treatment	No significant between-group differences were found in cast-model, cephalometric, or photographic analyses; QoL worsened during treatment and improved after treatment.
Mituś-Kenig et al. 2021 [12]	Prospective case-control study	52 cancer survivors vs 52 healthy controls matched for age, sex, malocclusion, and treatment time	w-PAR, ICON, treatment stability, satisfaction	Before treatment, after treatment, and 3-year follow-up	Ideal occlusion was achieved in all patients; immediate post-treatment results did not differ significantly between groups, but at 3 years survivors showed significantly worse stability with increased w-PAR and ICON values.
Proc et al. 2016 [14]	Retrospective case-control radiographic study	61 cancer survivors vs healthy controls	Dental developmental abnormalities relevant to orthodontic planning	Mean follow-up after end of cancer therapy: 4.9 years	Dental anomalies were found in 62.29% of survivors and 13.24% in controls; agenesis in 31.14% of survivors and 9.21% of controls; microdontia in 36.06% of survivors and 2.87% of controls; short roots were also more frequent in survivors.
Stolze et al. 2021 [16]	Cross-sectional survivor cohort (dentist survey study)	154 childhood cancer survivors with dentist-reported oral health data; no external healthy control group in the primary study	Prevalence and risk factors for dental developmental disorders (DDDs)	Long-term follow-up > 15 years	36.3% had at least one DDD; the most prevalent were short-root anomaly, agenesis, and microdontia.
Stolze et al. 2023 [17]	Cross-sectional survivor cohort	249 childhood cancer survivors; comparison made with two literature-based comparison groups, not a matched concurrent control group	Self-reported oral health problems and OHRQoL	Long-term follow-up > 15 years since diagnosis	Oral blisters/aphthae and halitosis were more frequent in survivors; overall OHRQoL was relatively good. The authors note they could not include a sex- and age-matched control group.
Choi et al. 2019 [8]	Cross-sectional phenotype study	57 DICER1 carriers vs 55 family controls	Dental abnormalities phenotype	Single dental assessment; no orthodontic treatment follow-up	This study characterized dental anomalies in individuals with pathogenic germline DICER1 variation; it is not a general childhood cancer survivor orthodontic-treatment outcome study.
Neill et al. 2015 [13]	Orthodontist survey	381 orthodontist responses; no patient cohort	Clinician experience, knowledge, and management practices	Not applicable	More experienced orthodontists were more likely to have treated survivors; education on this topic was limited, and few had treated > 10 survivors.
Ritwik et al. 2020 [15]	Narrative review	No original patient cohort or comparator	Overview of oral and dental considerations in pediatric cancers	Not applicable	Review article summarizing oral/dental issues during and after pediatric cancer therapy; no original extractable data.

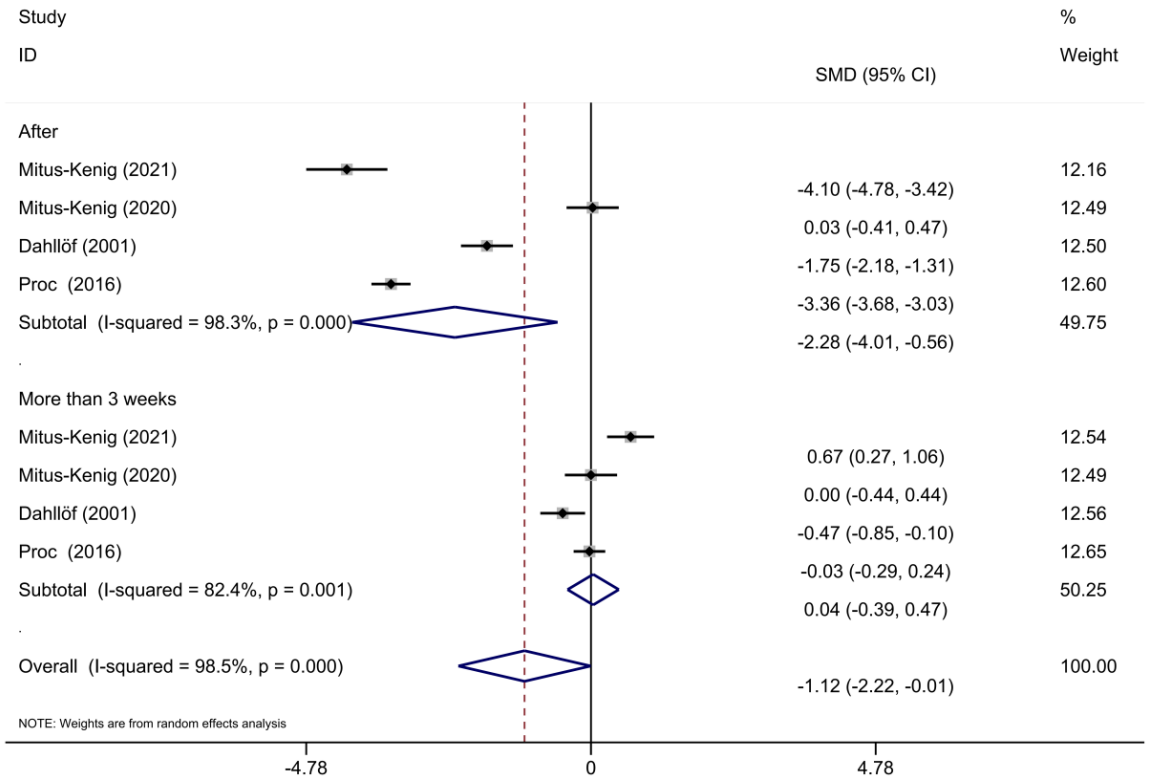

Figure 2. Forest plot of pooled standardized mean differences (SMDs) in weighted Peer Assessment Rating (w-PAR) scores according to assessment timing (immediate post-treatment and follow-up beyond 3 weeks), using a random-effects model with 95% confidence intervals.

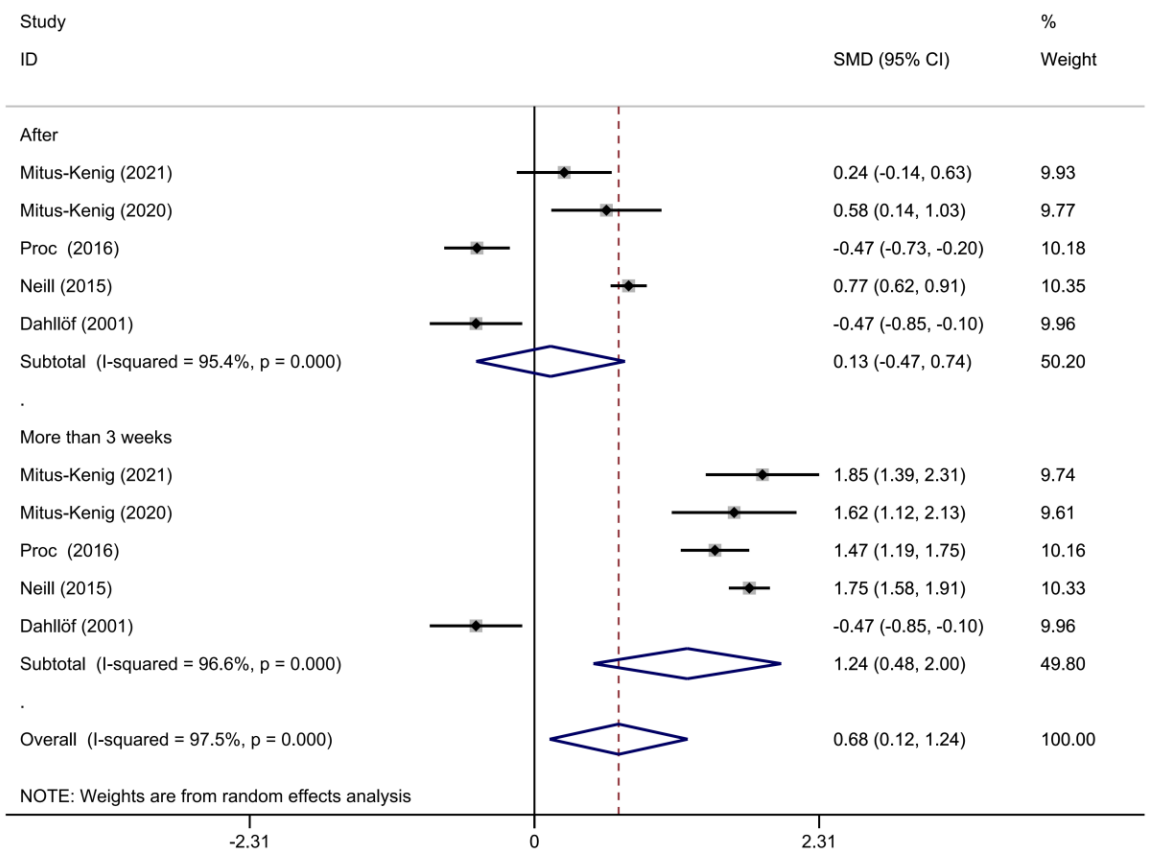

Figure 3. Forest plot of pooled standardized mean differences (SMDs) in ICON scores, stratified by assessment timing (immediate post-treatment vs follow-up beyond 3 weeks), with random-effects estimates and 95% confidence intervals.

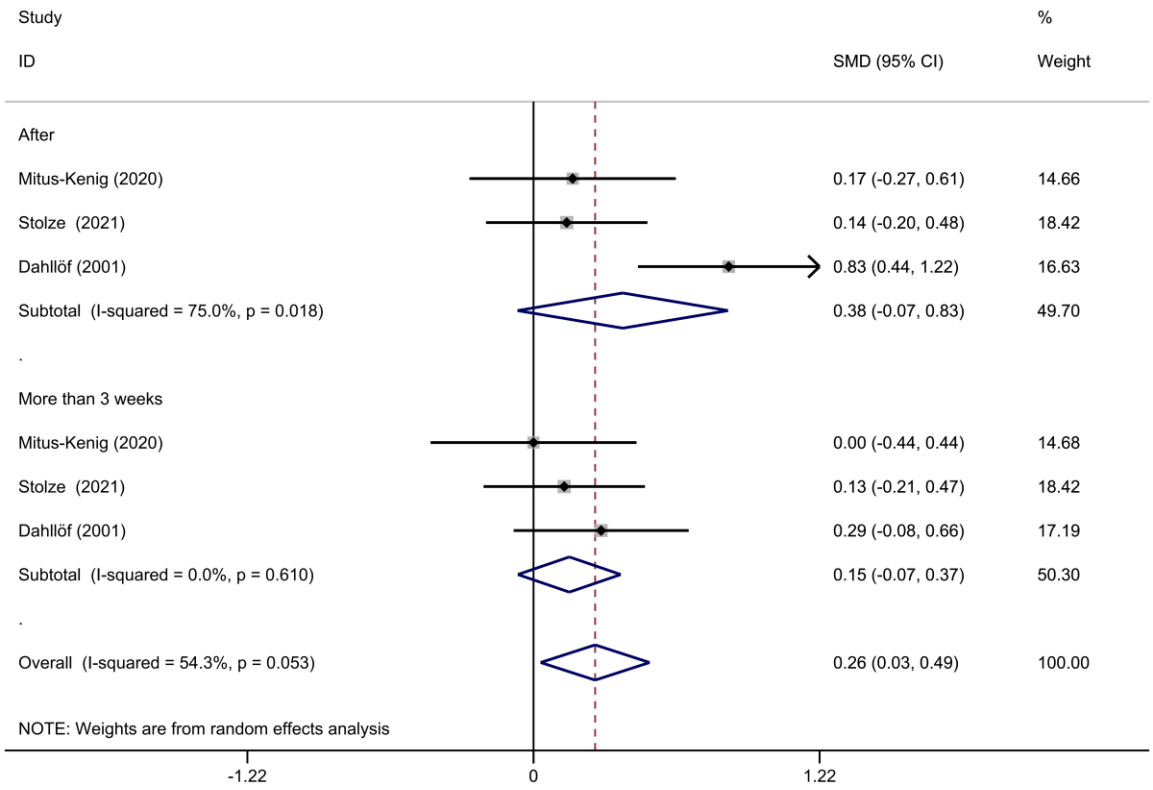

Figure 4. Forest plot for OHIP-14.

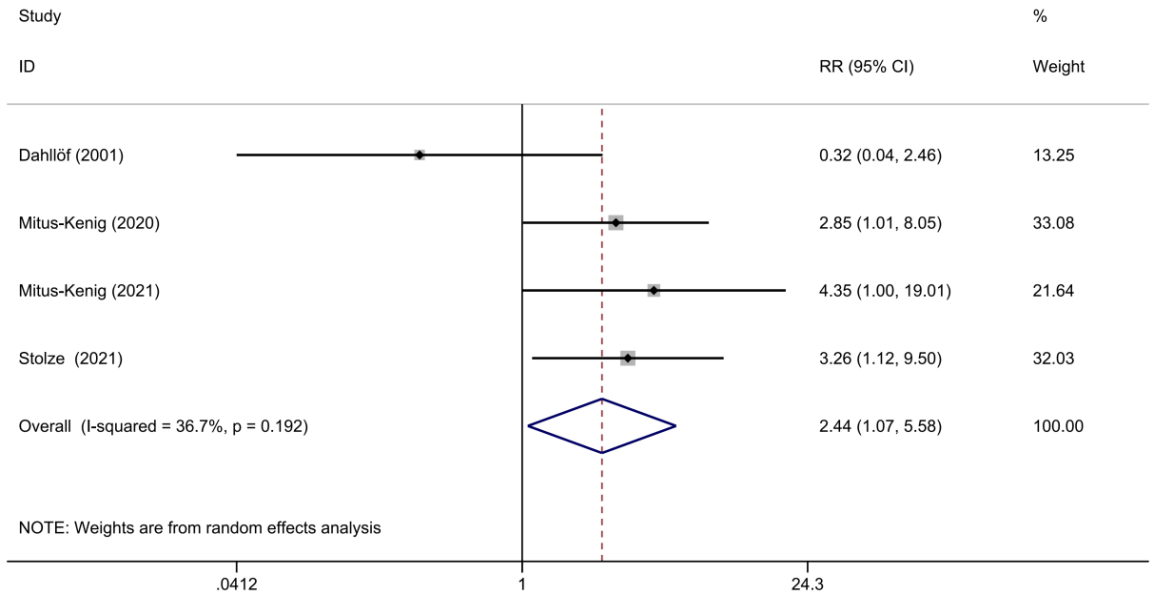

Figure 5. Forest plot for complications observed during orthodontic treatment.

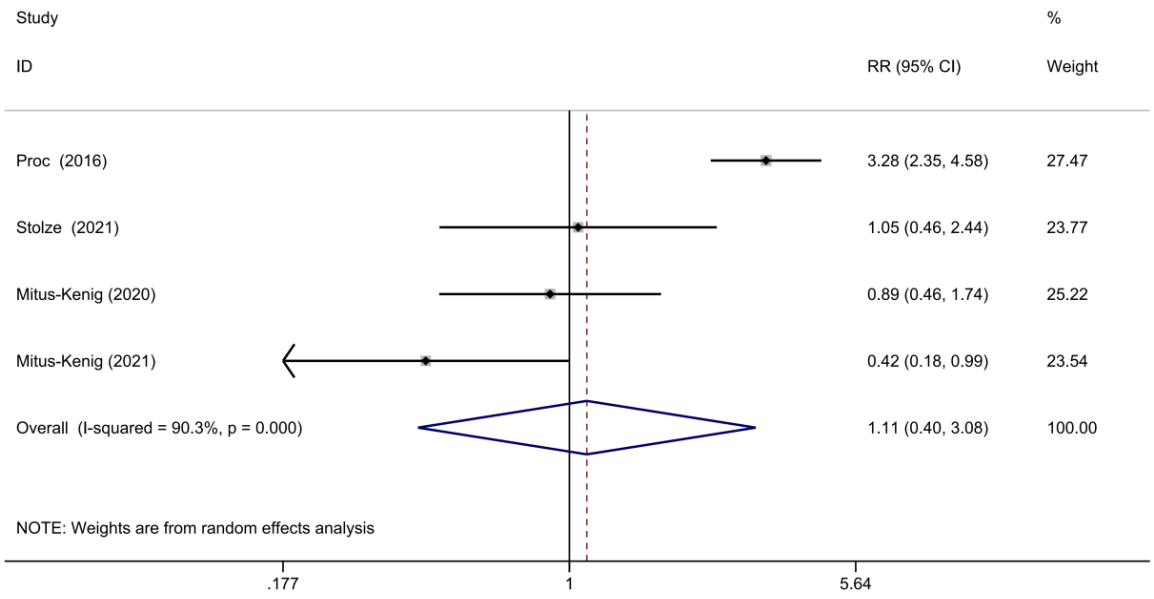

Figure 6. Forest plot for prevalence of dental developmental abnormalities relevant to orthodontic planning.

erogeneity (I^2 = 90.3%, P < 0.001), indicating substantial inconsistency across the included datasets. At the individual-study level, Proc et al. [14] demonstrated a markedly increased prevalence of abnormalities in survivors (RR = 3.28, 95% CI 2.35-4.58), whereas Stolze (2021) showed no significant difference (RR = 1.05, 95% CI 0.46-2.44). In contrast, both Mituś-Kenig studies suggested lower relative frequencies, reaching statistical significance in Mituś-Kenig et al. [12] (RR = 0.42, 95% CI 0.18-0.99), while Mituś-Kenig et al. [11] remained non-significant (RR = 0.89, 95% CI 0.46-1.74) (**Figure 6**).

Subgroup analysis

Subgroup analysis stratified by study design showed that the overall pooled association remained non-significant and was accompanied by substantial between-study heterogeneity (overall RR = 0.90, 95% CI 0.55-1.47; I^2 = 92.7%, P < 0.001). Among retrospective studies, the pooled estimate was close to the null (RR = 0.96, 95% CI 0.38-2.48), but heterogeneity was extremely high (I^2 = 95.5%, P < 0.001), indicating considerable inconsistency across cohorts. This variability was largely driven by disparate study-level effects, with most retrospective studies suggesting either no clear association or a modest reduction in risk, whereas the study by Proc et al. [14] showed a markedly elevated effect estimate (RR = 3.28, 95% CI 2.35-4.58). In contrast, case-control studies yielded a highly consistent pattern with no evidence of heterogeneity (I^2 = 0.0%, P = 0.787), and the pooled effect again indicated no significant difference between groups (RR = 0.98, 95% CI 0.75-1.29). The cross-sectional subgroup, represented by a single study, suggested a significantly lower relative risk (RR = 0.48, 95% CI 0.38-0.60), although this estimate should be interpreted cautiously given the absence of replication (**Figure 7**).

Publication bias

Visual inspection of the funnel plot suggested a degree of asymmetry, with several studies clustering around the pooled effect estimate and one study [8] showing a markedly larger effect size on the right side of the plot. Although most studies were distributed within the pseudo 95% confidence limits, the overall pattern was not entirely symmetrical, raising the possibility of small-study effects or publication bias. In particular, the presence of an outlying study with a substantially elevated relative risk may have contributed to the observed asymmetry and to the between-study heterogeneity identified in the primary analysis. Nevertheless, given the relatively small number of included studies, the interpretability of funnel plot asymmetry is inherently limited, and any inference regarding publication bias should therefore be made with caution (**Figure 8**).

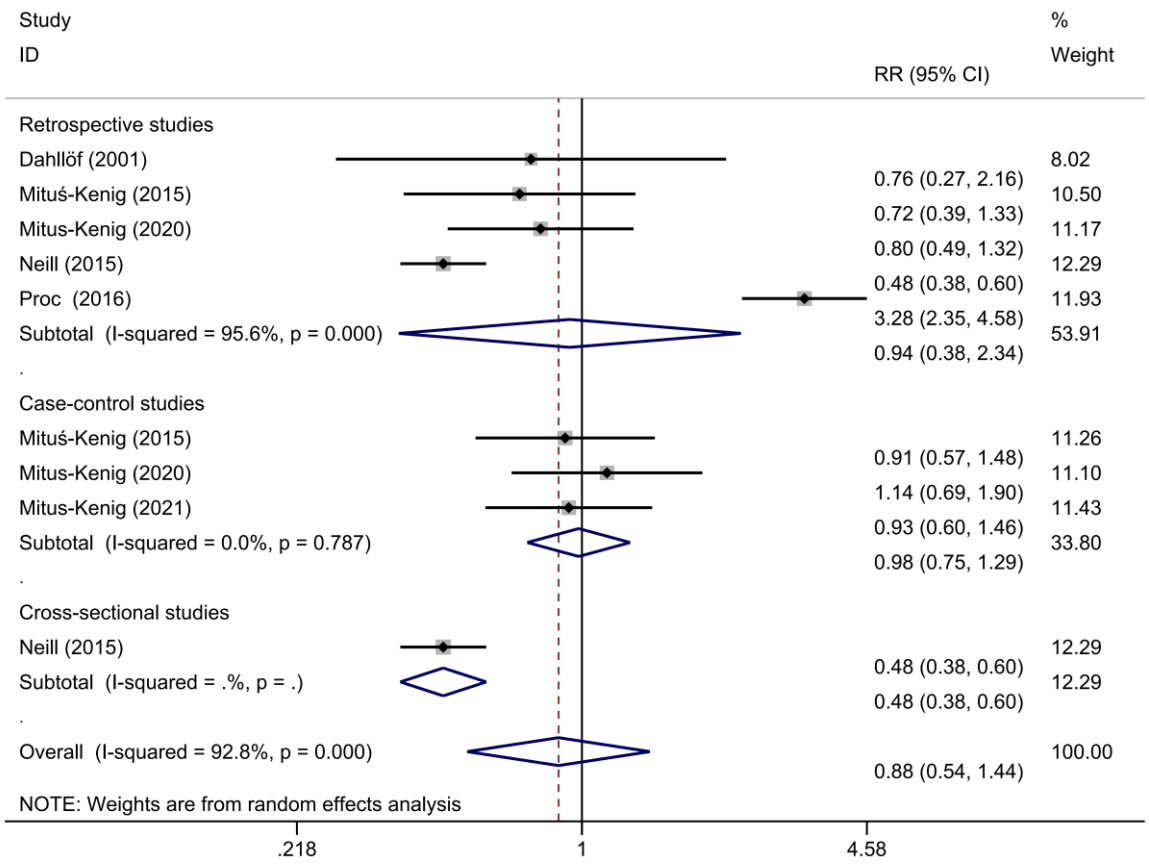

Figure 7. Subgroup analysis.

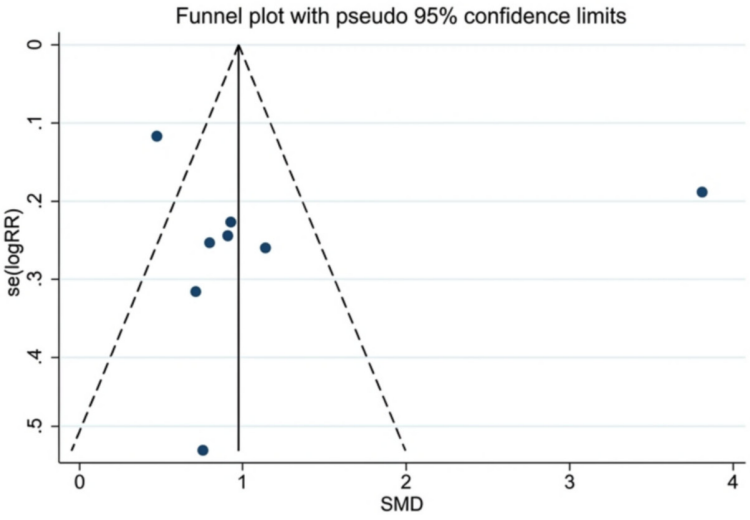

Figure 8. Funnel plot for assessment of publication bias for the outcome of dental developmental abnormalities.

Sensitivity analysis

Sensitivity analyses were performed to examine the influence of methodological heterogeneity across the included studies [8-16]. In leave-one-out analyses, sequential omission of individual studies did not materially alter the overall direction of the pooled estimates for the main outcomes, although the magnitude of the effect sizes and the degree of heterogeneity varied across iterations. Additional analyses restricted to studies with directly extractable comparative clinical data yielded results that were broadly consistent with the primary analyses. For outcomes with very high between-study heterogeneity, particularly w-PAR, ICON, and dental developmental abnormalities, exclusion of studies with extreme effect estimates reduced heterogeneity to some extent but did not change the overall interpretation. These findings indicate that the main con-

clusions of the review are reasonably robust, while also confirming that the pooled estimates for highly heterogeneous outcomes should be interpreted with caution.

Discussion

The purpose of this systematic review and meta-analysis was to evaluate the outcomes and safety of orthodontic treatment for secondary dentofacial deformities in survivors of childhood cancer. The results show a small but significant change in the orthodontic results with statistically significant differences in the w-PAR and ICON indices, especially at the immediate post-treatment. Although there is some heterogeneity among studies, the orthodontic interventions appear to yield clinical benefits in the context of dentofacial deformity correction. It is the first extensive literature review of this question that brings different study designs together giving a subtle insight into the potential positive effect of orthodontic care on childhood cancer survivors, as well as a high level of variability in treatment effects is also considered.

Significant occlusal gains can be achieved in orthodontic intervention in childhood cancer survivors, but the time course of response varies depending on the index applied. The pooled w-PAR analysis suggested a greater short-term impact, but the ICON analysis depicted a greater signal at the later follow-up. This is generally observed to be in agreement with the prospective case-control studies by Mituś-Kenig et al. [11, 12] which indicated that end-of-treatment occlusal results could be attained by the survivors, at least in well selected cohorts as compared to healthy controls. Meanwhile, Dahllöf et al. [9] found that not all long-term survivors were able to achieve ideal outcomes following pediatric bone marrow transplantation, indicating that orthodontic response might not be predictable in all groups of survivors. A likely reason is that w-PAR and ICON measure different, yet related aspects of change in treatment: the former is more sensitive to instantaneous occlusal correction, and the latter might be more indicative of overall treatment complexity and long-term retention of finishing. Clinically, this implies that an initial post-treatment response must not be regarded as positive indication of the long-term success especially in patients who have previously been exposed to intensive oncologic therapy.

The quality-of-life advantage of orthodontic care seems to be tangible, although small and time-delicate. In the pooled OHIP-14 estimate, the overall improvement was small though subgroup analysis revealed a post-intervention assessment in the early stage of the intervention to be more varied and did not always show statistical significance. This trend corresponds to the prospective study of Mituś-Kenig et al. [10, 11], where oral health-related quality of life deteriorated during the first active treatment period and subsequently, only improved after the end of the treatment. Stolze et al. [16, 17] also provide longer-term survivor data that indicate that overall OHRQoL in adult survivors might be acceptable at the cohort level, but is nonetheless tightly associated with the burden of self-reported oral and dental problems [18-20]. Mechanistically, this is probably indicative of the duality of orthodontic treatment in survivors: that orthodontic appliances may initially lead to increased physical discomfort, oral disability, and psychosocial consciousness of dentofacial disparity, but subsequent gains in alignment and aesthetics can be functionally and psychosocially rewarding [21, 22]. The clinical implication is that clinicians need to advise survivors and families on the fact that immediate decline in perceived oral health is not unusual, and patient-reported outcomes needs to be followed over time and not based on occlusal indices [23].

The combined relative risk was more than twice and the direction of effect was reasonably similar across the studies. The findings are in line with previous reports that indicated higher mucositis, imaging-based and root-related alterations among other treatment-related burdens in post-oncologic patients. Specifically, the prospective study by Mituś-Kenig et al. [10, 11] reported the increased signs of oral mucositis and root resorption in survivors compared to controls, and Dahllof et al. [9] indicated that lighter orthodontic forces were required in some medically complex patients. A probable biological cause of this susceptibility is disturbed root development, impaired periodontal support, previous cytotoxic damage of odontogenic tissues, impaired tissue remodeling, and decreased tolerance of the oral mucosa following cancer treatment. These considerations are not contra-indicative of orthodontic therapy per se, but are a good case of argument in favor of individualized biomechanics, conservative for-

ce systems, extra radiographic attention where necessary, and close coordination with the rest of the medical history of the patient. Clinically, the data also support that orthodontic care in survivors is to be considered as higher-risk care, as opposed to routine management.

An overall effect of dental developmental aberrations pertinent to orthodontic planning was not significant, although this null finding should be viewed with caution due to the extreme heterogeneity. In fact, the direction and magnitude of the effects across individual studies varied greatly: the study of Proc et al. [14] showed significantly higher prevalence of the anomaly in the survivor group, while Stolze et al. [16, 17] reported a significantly greater burden of dental developmental disorders in the long-term group, and the Mituś-Kenig et al. reported lower or non-significant relative frequencies in Probably. This difference is not contradictory, but rather represents significant variations in the population of the studies, age of cancer treatment, oncologic exposure, referral bias, and outcome definition. Coalitions treated in orthodontics are selective in nature and might not capture the most severely affected survivors but broadened surveys of survivors and dental radiographic literature capture the entire range of the sequelae of development [23]. On a biological level, microdontia, agenesis, short roots, and other related disturbances are well proved to be driven by age at treatment and exposure to cytotoxic agents in active odontogenesis [24]. The clinical practice warning is that therefore, a null pooled estimate does not imply that the developmental abnormalities are not important but it indicates that they are distributed unequally and very context-sensitive.

Subgroup analysis by study design further underscored the methodological heterogeneity of the current evidence base and confirmed that study structure materially influences the observed estimates. Retrospective studies showed extremely high heterogeneity and appeared particularly vulnerable to selection bias, inconsistent outcome definitions, variable follow-up intervals, incomplete control of confounding, and the influence of outlying effects, whereas case-control studies were methodologically more consistent and generally yielded estimates closer to the null. These differences likely reflect variation in patient selection, baseline comparability, measurement rigor, oncologic exposure profiles, and duration and timing of follow-up. Clinically, these findings suggest that orthodontic treatment in childhood cancer survivors should not be approached as routine care, but rather as individualized, risk-adapted care based on comprehensive pretreatment assessment, including previous cancer diagnosis, age at oncologic therapy, radiation field and dose, chemotherapy exposure, dental developmental disturbances, root morphology, periodontal condition, and expected craniofacial growth potential. From a research perspective, future prospective studies should move beyond broad comparisons and adopt standardized core data collection. At minimum, such studies should report: survivor characteristics (cancer type, age at diagnosis, age at orthodontic treatment, time since completion of cancer therapy); treatment exposure variables (chemotherapy regimen, radiotherapy site and dose, hematopoietic stem cell transplantation, and other relevant medical interventions); baseline dentofacial characteristics (malocclusion severity, craniofacial pattern, tooth agenesis, microdontia, short roots, and other developmental abnormalities); orthodontic treatment details (appliance type, biomechanics, force application, treatment duration, adjunctive procedures, and retention protocol); and standardized outcome measures covering both effectiveness and safety, including occlusal indices, treatment stability, patient-reported oral health-related quality of life, root resorption, mucosal and periodontal complications, and treatment interruption or relapse. Standardized follow-up time points should also be prespecified to distinguish short-term treatment response from long-term stability. Such an approach would substantially improve comparability across studies, help identify which survivor subgroups are most likely to benefit from orthodontic intervention, and provide a stronger evidence base for safer and more predictable clinical decision-making.

Several limitations of this review should be acknowledged. The first is that the overall number of eligible studies was minimal and many pooled analyses were founded on the small evidence base. Second, the heterogeneity was significant on several outcomes, especially on occlusal indices and developmental abnor-

malities, which lowers confidence in the precision of the pooled estimates. Third, the studies included differed significantly in terms of study design, survivor characteristics, oncologic exposures, follow-up period and definition of both outcomes and complications. Fourth, most of the studies utilized relatively selected populations of survivors, which might not be generalizable to patients with more severe craniofacial or dental late effects. Fifth, other analyses had to use clinically different endpoints or timepoints due to the relative scarcity of available data. Lastly, the visual inspection of publication bias was naturally weak due to the limited number of studies and thus one cannot rule out the small-study effects.

In conclusion, this meta-analysis and systematic review reveals that orthodontic care in childhood cancer survivors with secondary dentofacial deformities is practicable and can be used to produce quantifiable changes in the outcomes of occlusions and oral health-related quality of life. These advantages however come with a much greater burden of complications, a great deal of inter-study heterogeneity, and findings that response to treatment can differ dependent upon when and on which dimension outcome is assessed. The findings justify the supporting model of care where orthodontic treatment is neither avoided nor treated as the routine practice, but rather planned in a risk-adapted model that takes into consideration the previous cancer treatment, developmental dental sequelae, biological predisposition, and the necessity of the long-term follow-up. Additional prospective, high quality research in the future is required to establish the best timing of intervention, the survivors to whom the intervention is most likely to be beneficial, and to provide evidence based guidelines on safer and more sustainable orthodontic therapy in this expanding population.

Disclosure of conflict of interest

None.

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Supplementary Table 1. Search strategy

Database	Search Strategy
PubMed	((“Neoplasms”[Mesh] OR cancer*[tiab] OR neoplasm*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR leukemia[tiab] OR lymphoma[tiab]) AND (“Child”[Mesh] OR “Adolescent”[Mesh] OR child*[tiab] OR pediatric*[tiab] OR paediatric*[tiab] OR adolescen*[tiab] OR survivor*[tiab] OR “childhood cancer survivor*”[tiab] OR “cancer survivor*”[tiab]) AND (“Orthodontics”[Mesh] OR “Orthodontic Appliances”[Mesh] OR orthodontic*[tiab] OR orthodontics[tiab] OR malocclusion*[tiab] OR occlus*[tiab] OR “dentofacial deformit*”[tiab] OR “secondary dentofacial deformit*”[tiab] OR craniofacial[tiab] OR maxillofacial[tiab] OR “dental developmental abnormalit*”[tiab] OR “dental anomal*”[tiab] OR microdontia[tiab] OR agenesis[tiab] OR “short root”[tiab] OR “root malformation*”[tiab]))
Embase	(‘neoplasm’/exp OR cancer*:ti,ab,kw OR neoplasm*:ti,ab,kw OR malignan*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR leukemia:ti,ab,kw OR lymphoma:ti,ab,kw) AND (‘child’/exp OR ‘adolescent’/exp OR child*:ti,ab,kw OR pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw OR adolescen*:ti,ab,kw OR survivor*:ti,ab,kw OR ‘childhood cancer survivor*’:ti,ab,kw OR ‘cancer survivor*’:ti,ab,kw) AND (‘orthodontics’/exp OR ‘orthodontic appliance’/exp OR orthodontic*:ti,ab,kw OR orthodontics:ti,ab,kw OR malocclusion*:ti,ab,kw OR occlus*:ti,ab,kw OR ‘dentofacial deformit*’:ti,ab,kw OR ‘secondary dentofacial deformit*’:ti,ab,kw OR craniofacial:ti,ab,kw OR maxillofacial:ti,ab,kw OR ‘dental developmental abnormalit*’:ti,ab,kw OR ‘dental anomal*’:ti,ab,kw OR microdontia:ti,ab,kw OR agenesis:ti,ab,kw OR ‘short root’:ti,ab,kw OR ‘root malformation*’:ti,ab,kw))
Cochrane Library	((MeSH descriptor: [Neoplasms] explode all trees OR cancer*:ti,ab,kw OR neoplasm*:ti,ab,kw OR malignan*:ti,ab,kw OR tumor*:ti,ab,kw OR tumour*:ti,ab,kw OR leukemia:ti,ab,kw OR lymphoma:ti,ab,kw) AND (MeSH descriptor: [Child] explode all trees OR MeSH descriptor: [Adolescent] explode all trees OR child*:ti,ab,kw OR pediatric*:ti,ab,kw OR paediatric*:ti,ab,kw OR adolescen*:ti,ab,kw OR survivor*:ti,ab,kw OR “childhood cancer survivor*”:ti,ab,kw OR “cancer survivor*”:ti,ab,kw) AND (MeSH descriptor: [Orthodontics] explode all trees OR MeSH descriptor: [Orthodontic Appliances] explode all trees OR orthodontic*:ti,ab,kw OR orthodontics:ti,ab,kw OR malocclusion*:ti,ab,kw OR occlus*:ti,ab,kw OR “dentofacial deformit*”:ti,ab,kw OR “secondary dentofacial deformit*”:ti,ab,kw OR craniofacial:ti,ab,kw OR maxillofacial:ti,ab,kw OR “dental developmental abnormalit*”:ti,ab,kw OR “dental anomal*”:ti,ab,kw OR microdontia:ti,ab,kw OR agenesis:ti,ab,kw OR “short root”:ti,ab,kw OR “root malformation*”:ti,ab,kw))
Web of Science	TS=((cancer* OR neoplasm* OR malignan* OR tumor* OR tumour* OR leukemia OR lymphoma) AND (child* OR pediatric* OR paediatric* OR adolescen* OR survivor* OR “childhood cancer survivor*” OR “cancer survivor*”) AND (orthodontic* OR orthodontics OR malocclusion* OR occlus* OR “dentofacial deformit*” OR “secondary dentofacial deformit*” OR craniofacial OR maxillofacial OR “dental developmental abnormalit*” OR “dental anomal*” OR microdontia OR agenesis OR “short root” OR “root malformation*”))
Scopus	TITLE-ABS-KEY((cancer* OR neoplasm* OR malignan* OR tumor* OR tumour* OR leukemia OR lymphoma) AND (child* OR pediatric* OR paediatric* OR adolescen* OR survivor* OR “childhood cancer survivor*” OR “cancer survivor*”) AND (orthodontic* OR orthodontics OR malocclusion* OR occlus* OR “dentofacial deformit*” OR “secondary dentofacial deformit*” OR craniofacial OR maxillofacial OR “dental developmental abnormalit*” OR “dental anomal*” OR microdontia OR agenesis OR “short root” OR “root malformation*”))
CINAHL	((MH “Neoplasms+”) OR cancer* OR neoplasm* OR malignan* OR tumor* OR tumour* OR leukemia OR lymphoma) AND ((MH “Child+”) OR (MH “Adolescence+”) OR child* OR pediatric* OR paediatric* OR adolescen* OR survivor* OR “childhood cancer survivor*” OR “cancer survivor*”) AND ((MH “Orthodontics+”) OR (MH “Orthodontic Appliances+”) OR orthodontic* OR orthodontics OR malocclusion* OR occlus* OR “dentofacial deformit*” OR “secondary dentofacial deformit*” OR craniofacial OR maxillofacial OR “dental developmental abnormalit*” OR “dental anomal*” OR microdontia OR agenesis OR “short root” OR “root malformation*”)

Supplementary Table 2. Eligibility criteria

Domain	Inclusion Criteria	Exclusion Criteria
Participants	Survivors of childhood cancer with secondary dentofacial deformities; History of childhood cancer therapy with or without radiation exposure.	Individuals with congenital dentofacial deformities; Survivors of benign tumors; Individuals without a history of childhood cancer therapy.
Interventions	Any orthodontic intervention to treat secondary dentofacial deformities, including fixed or removable appliances.	No orthodontic intervention; Non-orthodontic interventions for dentofacial deformities (e.g., surgery, prosthetic treatments).
Comparisons	Control group of healthy children or adolescents with no history of cancer therapy; Comparisons between different orthodontic intervention timings or approaches.	No control group; Comparisons of non-orthodontic treatments; Studies without a clear orthodontic intervention comparison.
Outcomes	Quantitative data on treatment outcomes, including occlusal indices, orthodontic success, relapse rates, complications, quality of life, and patient satisfaction.	No quantitative data on outcomes; Data not related to treatment success or outcomes (e.g., focus solely on psychological effects without dental evaluation).
Study Design	Randomized controlled trials (RCTs), cohort studies, case-control studies, and prospective observational studies with data on orthodontic treatment outcomes.	Animal studies; Case reports, editorial letters, or studies with fewer than 10 participants; Systematic reviews or meta-analyses; Studies without appropriate control groups.