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Published in:
Supportive Care in Cancer

DOI:
10.1007/s00520-017-3829-y

Publication date:
2018

Support Care Cancer
DOI 10.1007/s00520-017-3829-y

ORIGINAL ARTICLE

A systematic review of dental disease management in cancer patients

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Received: 26 February 2017 / Accepted: 10 July 2017

Abstract

Introduction This systematic review aims to update on the prevalence of odontogenic-related infections and the efficacy of dental strategies in preventing dental-related complications in cancer patients since the 2010 systematic review.

Review method A literature search was conducted in the databases MEDLINE/PubMed and EMBASE for articles published between 1 January 2009 and 30 June 2016. Each study was assessed by 2 reviewers and the body of evidence for each intervention was assigned an evidence level.

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Published online: 22 July 2017

Results After examination of the abstracts and full-text articles, 59 articles satisfied the inclusion criteria. The weighted prevalence of dental infections and pericoronitis during cancer therapy was 5.4 and 5.3%, respectively. The frequency of dental-related infections during intensive chemotherapy after complete, partial, and minimal pre-cancer dental evaluation/treatment protocols ranged from 0 to 4%. Protocols involving third molars extractions had the highest complications (40%). *Conclusions* In view of the low prevalence of infections and the potential for complications after third molar extractions, it is suggested that partial dental evaluation/treatment protocols prior to intensive chemotherapy; whereby minor caries (within dentin), asymptomatic third molars or asymptomatic teeth without excessive probing depth (<8 mm), mobility (mobility I or II) or with periapical lesions of <5 mm were observed; is a viable option when there is insufficient time for complete dental evaluation/treatment protocols. The use of chlorhexidine, fluoride mouth rinses as well as composite resin, resin-modified glass ionomer cement (GIC), and amalgam restorations over conventional GIC in post head and neck radiation patients who are compliant fluoride users is recommended.

Keywords Dental caries · Periodontal disease · Anti-neoplastic agents · Hematopoietic stem cell transplantation

Introduction

Significant advancement has been made in the field of cancer treatment and the increasingly affordable field of genetic deep sequencing has offered unprecedented insight into the biology of cancers. With the advent of precision medicine, targeted therapy with new chemotherapeutic agents targeting specific biology of cancers is becoming more widely available [1]. Despite these advances, surgical resection, radio-, and chemotherapy remain the main modalities of cancer management. Although effective in treating the cancer, these treatment modalities may cause significant morbidity from direct damage to the head and neck structures and indirect effects from systemic toxicity [2]. Specific to the dental apparatus, the increased risk for development of rampant decay post head and neck radiation is well documented. Additionally, high restoration failure is another problem frequently encountered in this population. Both are direct consequences of the loss of protection from saliva due to salivary gland damage by high dose head and neck radiation. In this review, we seek to update findings from our previous publication in 2010, whereby conventional glass ionomer cement (GIC) restorations was reported to perform poorest compared to other materials (resin modified GIC, composite resin, and amalgam) in patients post head and neck radiation [3]. This recommendation was based on three relatively old studies; and with rapid advancement in material technology; this may no longer be valid.

Another common concern in patients undergoing intensive anti-neoplastic chemotherapy is the risk of infections from odontogenic sources. Even though the prevalence of dental infections during chemotherapy has been reported to be relatively low (5.9%), the consequence from an infection in a severely pancytopenia patient is potentially serious [3–5]. Hence, many cancer centers mandate that all patients undergo a pre-cancer dental evaluation prior to initiation of anti-neoplastic chemotherapy [6, 7]. In 2010, Hong et al. reported that there were only two studies on the various dental evaluation/treatment protocols prior to cancer therapy and no recommendations could be made due to a lack of data from clinical trials to support or refute a specific protocol [3].

Since the 2010 systematic review, new studies have been published on pre-cancer therapy dental evaluation/treatment protocols and restorative strategies in cancer patients. The aims of this review were to update current understanding with regard to the (1) prevalence of infections from odontogenic sources in patients undergoing cancer therapy, (2) efficacy of pre-cancer therapy dental evaluation/treatment protocols in preventing complications, (3) dental disease management strategies, and (4) changes in the dental-related oral microorganisms associated with cancer treatment.

Materials and methods

Literature search

A literature search was conducted with assistance from a research librarian using the electronic databases of PubMed and EMBASE for articles published between 1 January 2009 and 30 June 2016. This is detailed in Fig. 1. As the previous publication by our group had addressed the dental disease and the management strategies in cancer patients [3], this review reports these aspects from relevant articles published since January 2009, namely from the end of the literature search of our previous publication while combining current findings with the previous articles. Electronic database searches were performed using different combinations of Medical Subject Headings (MeSH) terms: "dental caries," "periodontal disease," "cancer," "cancer therapy," "radiotherapy," "anti-neoplastic agents," and "total body irradiation" for the literature search.

Eligibility criteria

Only English language articles were included. The inclusion criteria were (1) studies assessing dental disease in patients undergoing cancer therapy, (2) studies performed in cancer patients of all age groups, (3) studies published in peer

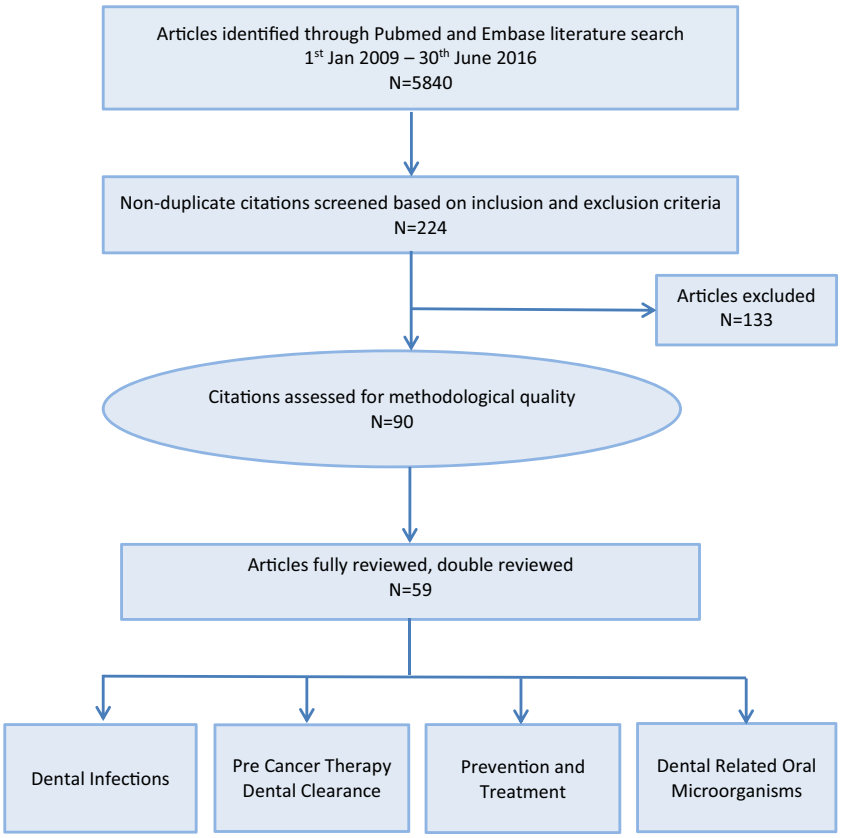

Fig. 1 Prisma diagram

reviewed journals. The exclusion criteria were systematic or narrative reviews, opinion papers, case reports, abstracts, and animal model and/ or in-vitro studies. The studies evaluating dental evaluation/treatment protocols prior to head and neck radiation were also excluded because the considerations for these patients are their life-long risk for osteoradionecrosis; rather than the risk of immunosuppression and life threatening bloodstream infections in those undergoing intensive anti-neoplastic chemotherapy [8, 9].

Review tools, selection of studies, and data extraction

For the purpose of this study, an electronic form was composed which included multiple coded answers and space for free text, covering the following items: (1) reviewer and manuscript details, (2) oral involvement, (3) intervention details, (4) study aim and design, (5) study groups and sites, (6) demographics, (7) cancer type, (8) percentage of individuals or clusters who refused to participate or were lost to follow-up, (9) inclusion criteria, (10) dental disease assessment, (11) confounding factors, (12) outcome measures, (13) pain, (14) quality of life, (15) pre-cancer therapy dental evaluation/treatment protocols, (16) changes in cariogenic and periodontal organisms, (17) main findings, (18) conclusion, (19) flaws, and (20) Level of evidence.

Each study was independently evaluated by two reviewers with a standard electronic collection form customized for reviewing dental disease data. Reviewers were recruited from the membership of the Oral Care Study Group, MASCC/ISOO. The utilization of the electronic form was standardized within the reviewers by a written manual, teleconferences, and a calibration exercise. For the calibration phase, each individual reviewer reviewed one paper [10]. For the review phase, articles were assigned to each pair of reviewers in alphabetic order. Any discrepancy in inclusion of a study was resolved by the section head (CH). Once the electronic forms were completed by the reviewers, the forms were sent to the section head who compared the reviews, assessed discrepancies between the reviewers based on the publication, reviewed the publications to resolve any inter-reviewer inconsistencies and concentrated the data.

Studies were scored for their Level of Evidence based on the Somerfield criteria [11] and flaws were listed according to the Hadorn criteria [12]. A well-designed study was defined as a study with no major flaws per the Hadorn criteria [12]. Tertiary reviews were completed by the section head and a final section head template was devised for the summary of all publications.

Findings from the reviewed studies were integrated into guidelines based on the overall Level of Evidence for each

intervention. Guidelines were classified into three types: recommendation, suggestion, or no guideline possible.

Results

The electronic searches identified over a thousand titles and abstracts. After examination of the abstracts and full-text articles by the review group, 59 articles satisfied the inclusion criteria (Fig. 1).

Infections from odontogenic sources during cancer therapy

Dental related infections/abscess during cancer therapy (largely anti-neoplastic chemotherapy) was reported in six studies [13–18] including those from the 2010 systematic review. The mean weighted prevalence was 5.4% (standard of error 1.16, 95%, confidence interval 3.14–7.7), Exclusion of studies whereby patients were not completely eliminated of all active and chronic foci of infections prior to cancer therapy did not appreciably change the prevalence.

The mean weighted prevalence of pericoronitis during cancer therapy (Baliga et al. [14]: anti-neoplastic chemotherapy; Fayle et al. [15]: cancer therapy not defined) from both studies [14, 15] was 5.3% (standard of error 2.35, 95% confidence interval 0.65–9.85).

Pre-cancer therapy dental evaluation/treatment protocols

There were a total of 11 studies (from 2010 and current review) that evaluated different types of dental evaluation/treatment protocols prior to anti-neoplastic chemotherapy and hematopoietic stem cell transplantations (HSCT) (Table 1). Expectedly, there were no randomized controlled trials due to ethical concerns with assigning patients undergoing cancer therapy to be in the no dental evaluation/treatment group.

The types of pre cancer therapy dental evaluation/treatment protocols was broadly categorized to either (i) complete protocols which involved treatment of all dental pathology prior to initiation of anti-neoplastic chemotherapy and HSCT [19–21], (ii) partial protocols which differed from complete protocols in that (a) *minor* dental caries (Yamagata et al. [25, 26]: not defined, Tsuji et al. [24]: within dentin) were not treated and observed, (b) teeth with apical periodontitis were only managed if symptomatic and if size of the periapical lesion was ≥5 mm, (c) only teeth with severe periodontitis (though the definition of advanced disease varied between studies) were extracted; the threshold for extraction of these teeth was if they had probing depth of ≥8 mm (rather than 6 mm in complete dental evaluation/treatment protocols) and/ or with mobility III, (d) extraction of severely mobile deciduous teeth that were expected to exfoliate within a few weeks (rather than 50% root resorption in complete dental evaluation/treatment protocols), and (e) extraction of partially erupted symptomatic third molars with purulence (versus extraction of partially erupted third molars in complete dental evaluation/treatment protocols), and lastly (iii) minimal protocols included protocols whereby treatment was only administered if the patient was symptomatic or if patient was either not evaluated/treated due to time restraints and/ or did not complete dental treatment. A side by side comparison of the three types of pre-cancer therapy dental evaluation/treatment protocols is detailed in Table 2.

Melkos et al. and Tsuji et al. evaluated patients who underwent complete or partial pre-cancer therapy dental evaluation/treatment protocols versus those who did not complete or go through dental treatment prior to anti-neoplastic chemotherapy [21, 24]. Melkos et al. found no odontogenic sources of infection in both patients who underwent complete dental evaluation/treatment protocols versus those who did not prior to HSCT [21]. Additionally, the authors found no association between the presence of dental foci of infection and HSCT complications or survival rate [21]. Tsuji et al. reported that patients who completed the partial pre-cancer therapy dental evaluation/treatment protocol had significantly (p <0.05) lower incidence of systemic (15.8 versus 37.4%) and dental complications (2.9 versus 34.0%) when compared to patients who did not complete any pre-cancer therapy dental evaluation/treatment [24]. The dental complications reported by Tsuji et al. included redness, warmth, swelling, pus discharge, and pain in and around the teeth or periodontium [24]. These complications were significantly more frequent in chemotherapy regimens associated with a higher degree of myelosuppression [24]. The dental protocol used in the Tsuji et al. study [24] was modified from earlier studies by Yamagata et al. [25, 26]; who also found no odontogenic infections occurred in both pediatric and adult HSCTs.

There have been two studies on minimal pre-cancer therapy dental evaluation/treatment protocol whereby only acute dental pathologies were treated prior to intensive anti-neoplastic chemotherapy [16, 18]. In Toljanic et al. study, two patients (10%) with severe chronic dental pathology had febrile episodes due to odontogenic sources; while patients classified as having mild or moderate chronic dental pathology did not develop any odontogenic related complications during anti-neoplastic chemotherapy [16]. Similar to the findings in Toljanic's study [16], the prevalence of exacerbation of chronic oral foci during anti-neoplastic chemotherapy in Schuurhuis et al. study [18] was 4% (3% of total sample). In addition, Schuurhuis et al. found no difference between patients with or without chronic oral foci of infection/s and those with treated acute oral foci of infection/s with regards to the duration of neutropenia and fever [18].

(i) Complications from dental evaluation/treatment protocols

Table 1 Dental evaluation/treatment protocols prior to anti-neoplastic chemotherapy and hematopoietic stem cell transplantation

Author/year	Study design	Diagnosis/sample/age	Cancer therapy	Pre and peri cancer therapy dental evaluation/treatment	Findings
Gürgan et al. [19]	Cohort	HE[ß] cancer *N* = 29 Age: 32.5 ± 8.4 years	CT* only	(i) Teeth with periapical lesions needing endodontic therapy and, partially erupted third molars, advanced periodontal destruction (i.e., presence of furcation involvement >degree II, loss of 2/3 of bone support, advanced tooth mobility) were extracted under prophylactic antibiotic administration and thrombocyte transfusion when indicated. (ii) Full mouth non-surgical periodontal treatment with subgingival 0.2% chlorhexidine irrigation. (iii) Restoration of carious lesions. (iv) Corrections of ill-fitting restorations (v) Tooth brushing with soft brushes, rinsing with 0.2% chlorhexidine and fluoride solution, use of interdental brushes and/or dental floss. (vi) Artificial saliva as needed (vii) During ulceration or profound thrombocytopenia, brushing discontinued, and intraoral cleaning performed with sponge brushes or cotton buds moistened in 0.2% chlorhexidine (vi) Oral hygiene instructions given to the caregivers for the maintenance of oral hygiene level during conditioning regimen and post-SCT[#] period.	(i) There were significant improvements in all measures of periodontal status after periodontal treatment ($p < 0.001$). (ii) However, the alterations in periodontal parameters did not influence engraftment period or duration of febrile neutropenia.
Haytac et al. [20]	Cohort	HE[ß] cancer *N* = 124 Age: 7.0 ± 2.3 years	CT* only	(i) Preventive and restorative treatment were performed on caries-free permanent molars and superficial enamel and dentin caries respectively. (ii) Periodontal treatment including oral hygiene instruction, rubber-cup prophylaxis and scaling performed. (iii) Deciduous teeth extracted if there was severe caries, pulpal necrosis and physiological root resorption of 50% of the root length; permanent teeth extracted if there was severe caries, pulpal necrosis, cracked teeth, supernumerary teeth and teeth with apical lesions. Antibiotics cover was given before extractions and periodontal therapy.	(i) Baseline dental status: 62 children with dental decay; 9 with hypodontia, microdontia and enamel hypoplasia requiring restorative treatment. (ii) Episodes of complications post treatment: 12 • Delayed wound healing: 2 • Delay of chemotherapy: 2 • Mucositis: 3 • Teeth staining: 5
Melkos et al. [21]	Cohort	Mixed cancers • No dental foci: *N* = 36 Age: 37.8 years • Dental foci present: *N* = 22 Age: 42.9 years	SCT[#]: Allogeneic: *N* = 56 Autologous: *N* = 2 Details on RT and chemotherapy not stated	(i) Clinical and radiographic examination (ii) Restoration of all active carious lesions (iii) Extraction of all non-restorable teeth and those with advanced periodontal disease (iv) Non vital teeth were treated with root canal therapy (RCT) or extracted; apical lesions were treated with RCT, apicoectomy or extraction	(i) Dental foci, age or gender was not associated with occurrence of post SCT[#] infections. (ii) Dental foci was not significantly related to survival rate. (iii) No correlations were found between decayed, impacted, semi-impacted teeth and infections,

Table 1 (continued)

Author/year	Study design	Diagnosis/sample/age	Cancer therapy	Pre and peri cancer therapy dental evaluation/treatment	Findings
					fever of unknown origin and oral mucositis post SCT#. (iv) Acute Graft Versus Host Disease was significantly associated with dental foci (p = 0.002), impacted teeth (p = 0.005) and periapically infected teeth (p = 0.0034). (v) No relationship between periapical radiolucencies and infections was established in the control group (p = 0.819).
Raut et al. [22]	Cohort	HEß cancer • Extractions: N = 69 Age: 38.1 years • No extractions: N = 319 Age: Not stated	Extraction group: • SCT# with and without total body irradiation: N = 45 • CT* only: N = 23 • No treatment: N = 1	Extractions of teeth with dental abscess, advanced caries and/or periodontal disease prior to SCT#.	(i) Post extraction complication: 13% (N = 9/69 patients, 18 episodes) • Delay in SCT#: N = 3 • Delay in CT*: N = 4 • Extended bleeding requiring platelets: N = 2 • Platelet transfusions required: N = 3 • Hospitalization in the setting of extraction: N = 5 • Pain after extraction: N = 1 • 6 patients had >1 event. (ii) Mean hospital stay • Patients without extraction: 43 days • Patients with extractions/no complications: 47 days • Patients with extractions/ complications: N = 46
Schuurhuis et al. [18]	Cohort	Mixed cancers N = 63 • Leukemia group: 51 ± 12.4 years • Autologous SCT# group: 51 ± 10.1 years	Leukemia group (N = 28) • Intensive CT* Autologous SCT# group (N = 35)	(i) Dental examination (including periodontal examination) and radiographs if indicated ii) Acute oral pathology and/or teeth causing pain or other symptoms were eliminated pre-CT*, whereas chronic oral foci were not eliminated [1]. (iii) Gingival samples were taken at dental screening. (iv) Throat swabs taken at dental screening, on the first day of hospitalization, before the start of CT*, and weekly during hospitalization. (v) All patients were advised to continue normal daily oral care (tooth brushing and/or interdental cleaning) as long as possible. When brushing became too painful, patients were advised to rinse the oral cavity with saline solution 4×/day and to remove their removable prosthesis, if any, during CT*. (vi) If chronic oral foci of infection became acute during or between CT*, antibiotics were given and appropriate dental treatment provided.	(i) Prevalence of chronic oral foci of infection at screening: • Leukemic group: 86% (N = 24/28) • Autologous SCT group: 63% (N = 22/35) (ii) Prevalence of acute oral foci of infection at screening: • Leukemic group: 7% (N = 2/28); both patients had both acute and chronic oral foci of infection • Autologous SCT group: 6% (N = 2/35), 1 patient had both oral acute and chronic foci of infection (iii) The prevalence of periodontal pathogens was not significantly different between leukemia and autologous SCT# groups. iv) Positive blood cultures (p = 0.798), duration of neutropenia (p = 0.066) or fever (p = 0.059) were not significantly different between patients with or without chronic oral foci of infections. (v) Duration of neutropenia and fever were not significantly difference between patients with or without chronic oral foci of infection and those with treated acute oral foci of infection

Table 1 (continued)

Author/year	Study design	Diagnosis/sample/age	Cancer therapy	Pre and peri cancer therapy dental evaluation/treatment	Findings
					(vi) Prevalence of exacerbation of chronic oral foci during cancer treatment: 4% (N = 2) • Leukemia patient with an acute exacerbation of an asymptomatic periapical granuloma present at screening (N = 1) • Autologous SCT patient with an acute exacerbation of pre-existent gingivitis (N = 1) vii) The presence of acute (p = 0.954) or chronic oral foci of infection (p = 0.197), periodontal disease (pockets ≥6 mm; p = 0.437), Periodontal Inflammation Surface Area score (p = 0.474), plaque scores (p = 0.941), bleeding scores (p = 0.456), age (p = 0.127), positive blood cultures (p = 0.453), or a significantly different duration of neutropenia (p = 0.398) and fever (p = 0.278) were not significantly different between patients who developed (N = 15) and those who did not develop oral complications (N = 48) during anti-neoplastic therapy.
Tai et al. [23]	Cohort	Mixed cancers N = 28 Age: 34.9 ± 16.0 years	SCT[#]: 32.1% CT*: 46.4% RT^: 50% Surgery: 10.7% Others: 7.1%	Prophylactic extractions of third molars	(i) Presentation of symptomatic third molar: N = 25/28; 16 had signs and symptoms after initiation of cancer treatment (ii) Treatment: • Extraction: N = 15/28 • Local anesthetic injection for gingival bleeding associated with third molar: N = 1/28 • Operculectomy: N = 1/28 • Antibiotics and analgesics: N = 11/28 (iii) Postoperative complications: N = 6/15
Toljanic et al. [16]	Cohort	Mixed cancers N = 48 Age: 45 years	SCT[#]: N = 12 CT* only: N = 36	(i) Dental examination with radiographs (ii) Study specific minimal intervention pre-intensive CT* dental treatment protocol	(i) Baseline • Chronic odontogenic pathology: 79% (N = 38); 21/38 had severe chronic dental pathology • Acute dental infection and underwent extraction: N = 3 (6%) (ii) During cancer therapy: N = 2 (4% of total sample, 10% of those with chronic dental disease) had febrile episodes due to odontogenic sources. • Previously diagnosed and untreated site of chronic periodontal disease: N = 1 • Acute infection at a site of previously diagnosed chronic caries: N = 1

Table 1 (continued)

Author/year	Study design	Diagnosis/sample/age	Cancer therapy	Pre and peri cancer therapy dental evaluation/treatment	Findings
					• Both patients had been previously scored as having chronic odontogenic pathology. • No pathology arose in those with mild or moderate chronic dental disease or in those without dental disease.
Tsuji et al. [24]	Cohort	HE[ß] cancer *N* = 86 • Group P: 234 observations • Group Q: 106 observations Median age: 60.5 years	Chemotherapy conditioning (Degree of myelosuppression graded from mild [A] to severe requiring 4 weeks for bone marrow recovery [C] and severe with persistent immunodeficiency [D]) and SCT[#]	(i) Dental clearance for all patients (ii) Group P: complete dental clearance (iii) Group Q: incomplete dental clearance	(i) Group P: The incidences of systemic and oral positive findings were 15.8% (37/234 observations) and 2.9% (7/234 observations: A: 0/19, B: 4 /177, C: 2 /18, D: 1/ 20). (ii) Group Q: The incidence of systemic and oral positive findings were 27.4% (29/106 observations) and 34.0% (36/106 observations: A: 0/7, B: 26/77, C: 9/18, D: 1/4). (iii) Total positive systemic findings: 66 observations (iv) Total positive oral findings: 43 observations (iv) There were significant differences between groups P and Q in the incidences of systemic positive findings ($P = 0.01$) and oral positive findings ($P < 0.0001$). (v) Comparing between group P and Q according to chemotherapy grade, there were significant differences in the incidences of oral positive findings for chemotherapy grades B ($P < 0.0001$) and C ($P = 0.011$) and the rate of systemic positive findings for grade B ($P = 0.0193$). (vi) Comparing CT* grade, there was a significant difference between grades A and C ($P = 0.006$), And D ($P = 0.005$), B and C ($P = 0.01$), and B and D ($P = 0.0001$) regarding the incidence of systemic positive findings in treatment P.
Yamagata et al. [25]	Cohort	HE[ß] cancer *N* = 41 Age: 41.3 years	SCT[#] Bone Marrow: *N* = 28 Peripheral Blood: *N* = 13	(i) Baseline exam (ii) Study specific dental clearance protocol implementation completed at least 10 days before SCT[#]. • Caries: Teeth with mild or moderate caries were restored if there was sufficient time, if not left alone and observed. Decayed teeth with pulpitis were treated by pulpectomy and root canal filling. Residual roots were extracted. • Endodontics: Teeth with recently symptomatic apical periodontitis or asymptomatic apical periodontitis and periapical radiolucency of the maximal diameter ≥ 5 mm were treated with RCT if time permits, if not teeth were removed. Asymptomatic apical periodontitis with periapical radiolucency of <5 mm were not treated.	(i) Baseline: *N* = 38/ 41 patients (92.7%) had ≥1 dental disease/s. (ii) Clearance: Using the new clearance protocol, 36 patients received ≥1 dental procedure/s. (iii) During SCT[#]: All patients (*N* = 41) did not have any signs or symptoms associated with odontogenic infection.

Table 1 (continued)

Author/year	Study design	Diagnosis/sample/age	Cancer therapy	Pre and peri cancer therapy dental evaluation/treatment	Findings
				• Periodontics: Marginal periodontitis, teeth with gingival swelling, pain and purulent discharge, probing depth ≥ 8 mm or severe mobility were removed, whereas teeth with marginal periodontitis but without these signs and symptoms were observed and tooth brushing instruction and/or scaling provided. • Third molars: Partially erupted third molars with pericoronitis or purulent drainage were extracted, and asymptomatic third molars were left alone. • All patients were given tooth brushing instructions. (iii) Dental follow up during SCT[#] for approximately 3 weeks and treatment if needed.	
Yamagata et al. [26]	Cohort	HE[ß] cancer • Impacted 3rd molars (ITM): *N* = 35 Age: 32.1 years • Non impacted 3rd molars (NTM): *N* = 50 Age: 47.5 years	SCT[#] • Bone marrow: *N* = 51 • Peripheral blood: *N* = 30 • Umbilical cord: *N* = 3 Conditioning regimen • CT* + Total body irradiation: *N* = 40 • CT*:*N* = 40 • Unknown: *N* = 4	(i) Pre transplant oral evaluation focused on management of ITM: • Symptomatic third teeth with gingival swelling and/or pain and /or purulent drainage were extracted • Asymptomatic third molar were not treated regardless of impacted position (ii) Dental treatment were completed at least 21 days before HSCT	(i) There was no odontogenic infection associated with third molars. (ii) The difference in fever duration was not significantly different in both grou.ps (iii) The median number of days on which the patient's White Blood Cell (WBC) was <1000/μL or in the minimum WBC was not significantly different in both groups. (iv) Sepsis occurred from oral mucositis in 2 patients in the ITM group and 4 in the NTM group, this was not significantly different between groups.
Yamagata et al. [27]	Cohort	HE[ß] cancer *N* = 30 Age: 10.8 years	SCT[#] • Bone marrow: *N* = 25 • Peripheral blood: *N* = 2 • Umbilical cord: *N* = 3	(i) Pre transplant dental examination included clinical and dental radiographic evaluations. (ii) Treatment protocol: • Caries: mild dental caries were restored/ observed with treatment, severe caries: pulpectomy/ pulpotomy. • Endodontics: Teeth with periapical periodontitis treated with RCT or extraction. • Periodontics: Simple gingivitis and gingivitis associated with tooth eruption were treated with toothbrush instruction and scaling. • Mobility: Primary teeth with mild mobility were not treated and observed, those with severe mobility and expected to exfoliate within a few weeks were extracted. • All the children were instructed in tooth brushing as 3×/daily and oral hygiene care.	(i) Baseline: 19 children (63.3%) showed ≥1 dental pathologies; 8 patients had 1 pathology, 10 had 2 pathologies and 1 had 3 pathologies. • Mild caries: *N* = 9 • Pulpitis: *N* = 2 • Periapical periodontitis: *N* = 2 • Loose primary teeth: *N* = 7 • Gingivitis associated with erupting permanent teeth: 6 teeth in 4 patients • Simple gingivitis: *N* = 7 • No dental pathology: *N* = 11 (ii) Treatment: • Caries: *N* = 6 had restorations, *N* = 3 had their cavities observed • Permanent teeth pulpitis: *N* = 2 had pulpectomy • Permanent teeth with periapical periodontitis: *N* = 2 had RCT and restored with temporary

Table 1 (continued)

Author/year	Study design	Diagnosis/sample/age	Cancer therapy	Pre and peri cancer therapy dental evaluation/treatment	Findings
					root canal fillings by calcium hydroxide because of the limited time available. • Loose deciduous teeth: All 8 loose deciduous teeth in 3 children were removed, and mildly mobile primary teeth in 4 children observed. • Simple gingivitis: 7 patients had scaling and oral hygiene care with tooth brushing instruction. (iii) No odontogenic infection occurred in any patients.

CT*: Chemotherapy
H&N$^{\alpha}$: Head and neck cancer
HE$^{\beta}$: Hematological
RT^: Head and neck radiation
SCT$^{\#}$: Stem cell transplant (including bone marrow transplant)

Three studies reported the frequency of complications after dental treatment in cancer patients [20, 22, 23]. In a retrospective cohort study of patients with hematological cancers, 9 (13%) patients developed complications post extractions performed during pre-cancer dental evaluation/treatment resulting in delays in initiation of chemotherapy and the need for platelet transfusion due to post extraction bleeding [22]. Haytac et al. reported two (3%) patients with hematological cancers whereby anti-neoplastic chemotherapy initiation was postponed due to delayed wound healing after extractions [20]. In Tai et al. study, a high proportion of patients (40%) who had third molar (symptomatic) extractions developed post-operative complications (e.g., bleeding, trismus, infections etc.). However, the timing of extractions in relation to the patients' timing of cancer therapy (before or during) and the type of cancer therapy was not specified in this study [23].

(ii) Management of third molars

In the studies by Yamagata et al. and Melkos et al., no odontogenic infections were associated with the asymptomatic or semi-impacted third molars during HSCT [21, 27]. However, Tai et al. found that 16 (64%) patients with symptomatic third molars only became symptomatic during cancer therapy (cancer modality not specified) [23].

(iii) Periodontal therapy

The initiation of periodontal therapy before, during and after head and neck radiation and anti-neoplastic chemotherapy resulted in improvements in periodontal health in cancer patients [8, 19]. However, Gürgan et al. reported that the improvement in periodontal parameters did not influence medical outcomes in patients with hematologic malignancies undergoing anti-neoplastic chemotherapy (e.g., engraftment period, duration of febrile neutropenia) [19]. Additionally, if the initial therapy at the time of pre-cancer therapy dental evaluation/treatment was not followed with periodontal maintenance, periodontal disease continued to progress in post head and neck radiation patients [9].

Summary and recommendation

1. Suggest that partial dental evaluation/treatment protocols whereby minor caries, asymptomatic third molars, asymptomatic teeth with periapical periodontitis with lesion <5 mm, periodontally involved teeth <8 mm probing depth, mobility I and II and without severe inflammation, exfoliating primary teeth without severe mobility (not expected to exfoliate in a few weeks) are observed and monitored during anti-neoplastic chemotherapy and HSCTs, may be appropriate when there is insufficient time for

Table 2 Descriptions of complete, partial and minimal dental evaluation/treatment protocols by dental pathology

Protocol Type Dental Pathology	Complete [19–21]	Partial [24–27]	Minimal/incomplete dental evaluation and/ or treatment protocols/not cleared [16, 18]
Caries	Restore all teeth	Mild/ moderate caries were restored if time permitted; otherwise these lesions were left alone and observed.	Intervention only if symptomatic
Severe Caries/ Pulp involvement/Dental abscess	Root canal treatment OR Extract		
Apical periodontitis	• Retreat • Apicoectomy • Extract	• Symptomatic lesions and lesions ≥5 mm were treated • Asymptomatic lesions and lesions <5 mm were observed	
Advanced periodontal disease	Extract teeth with • probing depth ≥ 6 mm • furcation I, II, III	Extract teeth with • probing depth ≥ 8 mm • mobility III • severe inflammation	
Mobile primary teeth	Extract teeth with >50% root resorption	Extract teeth with severe mobility and expected to exfoliate within a few weeks.	
Partially erupted third molars	Extract	• Asymptomatic teeth were observed • Partially erupted third molars with purulence of pericoronitis were extracted.	

complete dental evaluation/treatment protocols [23–26]. (*Level of evidence: III, Grade of Recommendation: B.*)

2. Suggest periodontal therapy prior to and maintenance after cancer therapy (both head and neck radiation and anti-neoplastic chemotherapy) for general good oral health. (*Level of evidence: III, Grade of Recommendation: B)* No guideline is possible with respect to its benefit in relation to oral complications encountered during head and neck radiation and/ or anti-neoplastic chemotherapy.

Approaches in managing dental disease in cancer survivors

(i) Fluoride therapy compliance

Two cohort studies were retrieved in the current literature search examining the compliance of patients to fluoride therapy post radiotherapy. They found that the compliance rate decreased significantly with time; Dhalom et al. [28] found a 54% compliance at 15 months for 5% sodium fluoride varnish and Thariat et al. [29] found only a 12% compliance for fluoride gel (concentration not stated) delivered in a custom tray at 24 months.

(ii) Chlorhexidine

Two new studies were included in this review [30, 31]. A randomized controlled trial compared the effects of once daily regimens (started 3–4 weeks prior to head and neck radiation) of 0.12% chlorhexidine, 0.5% sodium fluoride, 2% sodium iodine and no intervention; and found significant reduction in plaque index ($p = 0.0026$) at 6 months in all the intervention groups (i.e. chlorhexidine, sodium fluoride and sodium iodine) [30]. The chlorhexidine group resulted in the greatest significant decrease in salivary Streptococcus mutans (SM) count compared to sodium fluoride ($p = 0.03$) and sodium iodine ($p = 0.001$) [30]. The other study found that the use of 0.2% chlorhexidine mouth rinse twice daily started 1 week prior to and for 1 month following HSCT resulted in significant improvement of gingival index ($p < 0.05$) from baseline [31]. However, this did not correlate with changes in periodontal pathogens.

(iii) Dental restorations

Only one new study was retrieved in this review. DeMoor et al. compared the clinical performance of conventional GIC, resin modified GIC and composite resin in Class V cavities in post head and neck radiation patients [32]. The authors found that Class V restorations with composite resins had significantly less ($p < 0.05$) failures compared to both resin reinforced and conventional GIC restorations at 24 months. In addition, composite resin restorations had significantly less failures ($p < 0.05$) due to marginal adaptation and anatomical form compared to GIC restorations. At earlier time points (12 and 18 months), the number of failures of composite resin restorations were not significantly different from resin modified GIC. However, in patients who were non-compliant with their fluoride regime, composite resin restorations had

Table 3 Changes in dental related oral microorganisms in cancer survivors

Author/year	Type of study	Patient detail/n/age	Cancer therapy	Intervention	Findings
			Head and neck cancers		
Al-Nawas and Grotz [35]	Cohort	H&N$^{\alpha}$ cancer *N* = 22 Age: 47.9 years	RT^ mean dose: 52.9 ± 15.8 Gy	(i) Pre RT^: All patients underwent dental clearance, oral hygiene instructions, professional plaque removal, and dental treatment if needed. ii) During RT^: 5% dexpanthenol rinse 3×/day, nystatin 4×/day, 1 g sulcralfat 3×/day, 1.25% sodium fluoride 2×/day and 1% chlorhexidine gel 2×/day with carrying trays (iii) Microbial sampling performed at baseline, 3 months, 6 months and 1 year	(i) Caries: DMFS significantly increased from baseline (80.7) to 1 year (88.5). (significance not stated) (ii) Cariogenic bacteria • Mean LB counts indicated an increase from 575 cfu/ml at baseline to 910 cfu/ml at 12 months. • Mean SM counts of 680 cfu/ml at baseline increased to 920 cfu/ml at 3 months and later reached the upper detection limit of 1000 cfu/ml. • From baseline to 3 months: There were no significant changes in intra-individual LB and SM counts. • From baseline to 6 months: There was an increase in mean intra-individual bacterial counts; changes were close to significance for SM (p = 0.102) but not significant for LB (p = 0.257). • From baseline to 12 months: There was increase in mean intra-individual bacterial counts; changes were borderline significant for both SM and LB (p = 0.059 and 0.102). (iii) Periodontal disease • Plaque Index: No significant intra-individual change was noted throughout study period. (iv) Periodontal flora • At baseline, common periodontopathogenic floras were B. forsythus followed by T. denticola and P. gingivalis. • At subsequent review, reduction of the incidence of A. actinomcycetemcomitans, P. gingivalis, B. forsythus and T. denticola and a relative increase of *P. intermedia* without statistical significance was found. • At baseline, 50% of the patients were positive for ≥1 periodontal pathogen. This increased to 80% at 3 months, 71% at 6 months and 64% at 1 year. This difference between the time points was not significant.
Almstahl et al. [36]	Cross-sectional	H&N$^{\alpha}$ cancer *N* = 13 Age: 53 ± 8 years	(1) External RT^ dose: 64.6–76.6 Gy (*N* = 13)	(i) All patients underwent pre-RT^ examination and treatment (ii) Sodium fluoride gel in custom trays for 2 min/day for 2 months recommended	(i) Dorsum of tongue • The mean total microbial count (p = 0.002) and the number of streptococci (p = 0.01), S. salivarius (p = 0.02) and F. nucleatum

Table 3 (continued)

Author/year	Type of study	Patient detail/n/age	Cancer therapy	Intervention	Findings
		Control group: age/ gender/ teeth matched *N* = 13	2) Brachytherapy dose: 6–30 Gy (*N* = 12/13)	• 9 patients used fluoride rinse or gel daily, 1 used every other day, 1 used sodium fluoride spray. (iii) Teeth cleaning and mucositis treatment 1–2 times, (iv) Microbial sampling done 6–8 months after RT^.	(p = 0.003) were significantly lower in the RT^ group than in the control group. • The proportion of streptococci of the total count was slightly higher in the RT^ group than in the control group (mean: 45 ± 34% and median: 34% compared with 35 ± 31% and 21%). • The proportion of F. nucleatum was significantly lower in the RT^ group than in the control group ($p < 0.05$), while the number and proportion of P. intermedia/ *P. nigrescens* were similar in the two groups. (ii) Buccal mucosal The number of S. sanguis/ S. oralis and the proportion of S. sanguis/ S. oralis of the total number of streptococci tended to be higher in the RT^ group (p = 0.06 and 0.07). (iii) Vestibulum • The total bacterial count tended to be higher in the RT^ group (p = 0.06). • The mean proportion of streptococci of the total count tended to be lower in the RT^ group (42 ± 32%) than in the controls (61 ± 30%). (iv) Supragingival plaque • The number of LB spp. were significantly higher (p = 0.0001) and the number of SM tended to be higher in the RT^ group than in the control. • The mean proportion of SM of the total number of streptococci tended to be higher in the RT^ group (6.2 ± 5.9%) than in the control (3.6 ± 11%). (v) Gingival crevicular region The total count was significantly higher (p = 0.02) and the number of P. intermedia/P. nigrescens significantly less (p = 0.03) in the RT^ group than in the control.
Beer et al. [37]	Cohort	H&N$^{\alpha}$ cancer *N* = 21 Median age: 57 years, range: 26–73	RT^ • Unilateral (*N* = 7): 66 Gy (24–70), *N* = 1 had simultaneous CT* • Bilateral (*N* = 13): 74.4 Gy (56–79.2); *N* = 2 had simultaneous CT*	Microbial sampling done before RT^, during RT^ and 6 weeks after RT^.	Streptococcus colonization of >10^5 CFU • Unilateral RT^ group: 40% before RT^, 60% during treatment, 0% 6 weeks after RT • Bilateral RT^ group: 43% before RT^, 75% during RT^, 0% 6 weeks after RT^
Cankar et al. [10]	Cohort	H&N$^{\alpha}$ cancer *N* = 16 Age: 56.3 ± 1.9 years	RT^ dose: 58–70 Gy	(i) Hyperbaric oxygenation (HBO) • 100% oxygen • 2.5 atmospheric pressure	A significant reduction in colony density of SM (p = 0.0003) and LB (p = 0.0014) was observed post hyperbaric oxygen therapy.

Table 3 (continued)

Author/year	Type of study	Patient detail/n/age	Cancer therapy	Intervention	Findings
				• 90 min • 20 dives ii) Microbial sampling done before HBO therapy and after 20 dives of HBO therapy	
Leung et al. [38]	Case Series	Nasopharyngeal cancer *N* = 18 (15 had microbiology samples taken) Age: 36–68 years	RT^ dose: 55–75 Gy 20–24 days 5–6 weeks	Microbial sampling done 3.3 years after RT^.	(i) The predominant cultivable microflora from all patients comprised of several species of facultative and obligate anaerobic bacteria: Gemella, Peptostreptococcus, Staphylococus, Stomalococcus, Streptococcus, Actinomyces, Eubacterium, Lactobacillus, Propionibacterium, Neisseria, Veillonella, Bacteroides, Campylobacter, Capnocytophaga, Fusobacterium, Kingella, Porphyromonas and Prevotella species. ii) Patients who had bleeding on probing had significantly higher ($p = 0.027$) proportion of Kingella dentrificans than patients who had no bleeding.
Meca et al. [30]	Randomized Controlled Trial	H&N$^{\alpha}$ cancer *N* = 60 (15 per group) Age: Not stated	RT^ dose: 50.4–70.2 Gy	(i) Microbial sampling done prior to RT^, immediate after RT^, 30, 60, 90 days and 6 months after RT^. ii) Treatment protocol • Group 1: chlorhexidine gluconate 0.12% once daily and oral hygiene instructions (OHI) • Group 2: sodium fluoride 0,5% aqueous solution once daily and OHI • Group 3: sodium iodine 2% in hydrogen peroxide once daily and OHI • Group 4: Nothing	SM: • No statistical difference between values in each group was observed before RT^. • At 30 days after RT^, a significant reduction of SM in group 1 (chlorhexidine) was observed in comparison with group 2 ($p = 0.03$), group 3 ($p = 0.001$) or group 4 ($p < 0.001$). • After the beginning of RT^, group 4 had significantly higher counts of cariogenic cocci in relation to the other groups ($p < 0.001$). Comparison between groups 2 and 3 showed no significant difference.
Meng et al. [39]	Case Series	H&N$^{\alpha}$ cancer *N* = 10 Age: 41 years	RT^ dose • 68 Gy: *N* = 2 • 70 Gy: *N* = 5 • 72 Gy: *N* = 2 • 76 Gy: *N* = 1	Microbial sampling done prior to, immediately after, 3 and 6 months after RT^.	Mean SM CFU: • Baseline: 6.41 ± 0.81 • Immediate post RT^: 6.76 ± 0.62 • 3 months post RT^: 7.75 ± 0.58 • 6 months post RT^: 7.68 ± 0.70 • SM levels increase significantly ($p < 0.01$) at 3 and 6 months post RT^ compared to baseline.
Srithavaj and Thaweboon [40]	Cross-sectional	Retinoblastoma *N* = 19 Age: 6.5 ± 3.5 years Healthy Control: *N* = 20 Age: 6.8 ± 3.4 years	RT^ dose: 42.5 ± 2.5 Gy	Microbial sampling done once; unclear time frame to cancer treatment	(i) The isolation frequency for LB was significantly higher ($p < 0.01$) in study group than controls. (ii) The isolation frequency of SM was not significant different between groups. (ii) The numbers/abundance of SM ($p < 0.05$) and LB ($p < 0.01$) detected in saliva were significantly greater in the children with retinoblastoma compared to healthy controls.

Table 3 (continued)

Author/year	Type of study	Patient detail/n/age	Cancer therapy	Intervention	Findings
			Hematological cancers		
Dens et al. [41]	Cohort	Mixed cancers $N = 42$ Age: 34 years	SCT# • Autologous: $N = 22$ • Allogeneic with total body irradiation (8 Gy): $N = 20$ • Conditioning regimen and graft versus host disease prophylaxis details given in article.	Microbial sampling done before and after SCT#: Mean: 71 days post SCT#	(i) In the pre-SCT# period, all patients had $>10^5$ CFU/ml SM and 10^3 CFU/ml LB. (ii) The shift toward a higher concentration of SM in the saliva samples after SCT# was not statistically significant. (iii) In contrast, the increased post SCT# levels of LB reached a significant difference ($p < 0.05$) with pre SCT#.
Jensen et al. [42]	Cohort	Breast cancer • CT*: $N = 45$ Age: 45 years • No CT*: $N = 31$ Age: 54 years	(1) CT* group: • Surgery: 100% • RT^: 87% • Adjuvant CT*: 100% • Anti-hormone therapy: 82% 2) Control group: • Surgery: 100% • RT^: 52% • Anti-hormone therapy: 3%	Microbial sampling done before and 1 year post cancer therapy.	(i) The number of patients harboring SM in their saliva did not change noticeably in response to CT*; and baseline levels and levels at 1 year after CT* were similar to those in the control group. (ii) The CT*group had lower baseline LB counts compared to the control group ($p < 0.05$), but the groups were comparable at the 1 year mark.
Kang et al. [43]	Cross-sectional	HEß cancer $N = 30$ Age: 49.3 ± 15.7 years Solid tumor (SO) $N = 41$ Age: 57.2 ± 5.7 years Control $N = 40$ Age: 53.2 ± 11.1 years	Not stated	Microbial sampling done once, unclear time frame to cancer treatment	(i) Percentage of salivary samples with bacteria detected in • Cancer group: - SM: HE-40%, SO-78% - S.sobrinus: HE 3.3%, SO-22.0% - L.salivarius: HE-70%, SO-85.4% - L.acidophilus: HE-40.0%, SO-48.8% • Control: - SM: 60% - S.sobrinus: 7.5% - L.salivarius: 70% - L.acidophilus 37.5% (ii) The frequencies of all four cariogenic bacteria were highest in the SO group. (iii) SM and L. salivarius were the most commonly detected in all three groups. (iv) SM • Mean number of SM in cancer patients were not significantly higher than controls. • Mean number of SM in the SO group was significantly higher ($p < 0.05$) than in the HE group. (v) Mean number of S. subrings in the SO group was significantly higher ($p < 0.05$) than in both HE group and the control. (iv) Mean number of L. salivarius was significantly higher ($p < 0.05$) in the SO group than in the control.

Table 3 (continued)

Author/year	Type of study	Patient detail/n/age	Cancer therapy	Intervention	Findings
					(vi) Proportions of cariogenic bacteria • Proportions of SM, S. subrings, and L. salivarius were significantly higher ($p < 0.05$) in the SO group than in the control. • Proportions of SM and S. subrings were significantly higher ($p < 0.05$) in the SO group than in the HE group.
Merman et al. [44]	Cohort	HE[@] cancer $N = 56$ Age: surviving: 49.0 years; deceased: 51. 9 years	CT* only	Microbial sampling done prior to anti-cancer therapy, during active treatment phase (2 and 4 months), 1 year and 5 year from start of treatment.	(i) Deceased patients showed significantly higher SM counts at 2 months ($p < 0.05$) and 1 year ($p < 0.05$) compared to survivors. (ii) Significantly lower SM values ($p < 0.05$) were observed in both groups after starting CT* when compared to baseline values. (iii) Deceased group showed higher LB counts than survivors but this was not statistically significant.
O' Sullivan et al. [45]	Cohort	HE[ß] cancer $N = 34$ Median age: 5.3 years Healthy Control: $N = 18$	Concomitant CT* and cranial radiation.	Microbial sampling done prior to and during anticancer therapy, methotrexate stage, maintenance stage and infection stage.	(i) There was significant association between treatment states and SM counts ($p < 0.0001$). SM counts decreased significantly from before treatment to during treatment, rose slightly during methotrexate stage and increased to original value during maintenance stage. (ii) There was no change in the flora composition in the study group during different stages of treatment. (iii) A significant difference was between the study and control for S.viridans ($p = 0.012$) and Haemophilus ($p = 0.029$).
Ou-Yang et al. [46]	Cross-sectional	HE[ß] cancer $N = 46$ Age: 7.5 years Healthy Control: $N = 46$ (age and gender matched)	CT* only	Microbial sampling done once during cancer treatment maintenance stage.	(i) The SM counts of the cancer group were significantly lower ($p < 0.001$) than the control group. ii) The LB counts did not significantly differ between groups ($p = 0.47$).

CT*: Chemotherapy

H&N[α]: Head and neck cancer

HE[ß]: Hematological

RT^: Head and neck radiation

SCT[#]: Stem cell transplant (including bone marrow transplant)

significantly higher failures due to recurrent caries (p <0.05) compared to GIC restorations. Even so, the overall failure rate of GIC restorations (due to poorer marginal adaptation and disintegration) was still higher than composite resin restorations in non-fluoride users [32].

The use of fluoride was not previously considered in the 2010 systematic review. As such, extraction of this data from papers included in the 2010 publication was conducted; all studies retrieved were in post head and neck radiation patients. As with the DeMoor et al. study [32], McComb et al. [33] also found that GIC restorations had significantly less failures due to recurrent caries than composite resin restorations in non-fluoride users. In a study by Wood et al. who compared conventional GIC and amalgam restorations, authors found that GICs had significantly higher failures (due to marginal adaptation, anatomical form, and caries) compared to amalgam restorations in fluoride users [34]. This study was done in 1993, and it is likely that the properties of glass ionomer cements used were different from later studies and as such may be more sensitive to fluoride ion damage.

(iv) Toothpaste

There were no new studies involving toothpaste use in cancer patients since the 2010 systematic review.

Summary and recommendations

1. Recommend the use of fluoride products to prevent dental caries in post head and neck radiation patients. This remains unchanged from the 2010 systematic review. It is important to reinforce its use as compliance decreases with time. The type of fluoride delivery system did not significantly influenced caries activity. (*Level of Evidence: II, Grade of Recommendation: B*)
2. Recommend the use of chlorhexidine mouth rinse in concentrations ranging from 0.12% - 0.2% once or twice daily for the reduction of plaque accumulation and SM counts in patients undergoing head and neck radiotherapy. This remains unchanged from the 2010 systematic review [3]. The amounts of Lactobacillus (LB) or periodontal pathogens were not affected by the use of chlorhexidine. The potential side effects of increased staining, calculus build up and temporary taste changes should be taken into account with use of chlorhexidine. (*Level of Evidence: II, Grade of Recommendation: B*)
3. Recommend the use of composite resins, resin modified GIC and amalgam restorations over conventional GIC in post head and neck radiation patients who are compliant fluoride users. In non-fluoride users, GIC restorations may be considered to reduce the rate of recurrent caries but would require frequent replacements due to breakdown in structure integrity. *(Level of Evidence: II, Grade of Recommendation: B)*

Changes in dental related oral microorganisms during cancer therapy

Fourteen studies examined the temporal effect of cancer therapy on dental related oral microorganisms (Table 3). Two studies were not included in the table [47, 48]. One study [48], unlike the other studies where raw SM and LB values was used, this particular study arbitrarily categorized the amount of SM and LB into low to high levels and thus was excluded. Another study compared the oral microbiota of caries free patients versus those with radiation caries at 1 year post head and neck radiation [47]. However, there was no baseline measure, changes due to radiation was unclear [47]. All studies examined SM and LB changes; of which two studies also evaluated periodontal pathogens [35, 38].

Head and neck radiation resulted in increases in both SM and LB oral colonization, although this was not always to statistically significant levels [35, 36, 39–41]. Other than chlorhexidine, hyperbaric oxygen therapy was also evaluated by one study which resulted in reduction of SM and LB[10]. Studies on periodontal flora reported shifts in periodontal pathogens in patients who were post head and neck radiation; however no clear pattern could be observed [35, 38]. More studies are needed to examine the effect of cancer therapy on periodontal related microorganisms and the clinical relevance of this change.

Unlike in head and neck radiation patients, anti-neoplastic chemotherapy did not appear to increase SM or LB oral colonization. In fact, these organisms remain either unchanged or reduced in amounts during anti-neoplastic chemotherapy [42–46, 49]. The reduction of SM and LB during anti-neoplastic chemotherapy was most pronounced during the induction and treatment phase. This is likely due to the antimicrobial effect of certain cytotoxic agents used in these regimens (e.g., doxorubicin).

Summary

1. The colonization of SM and LB increased in post head and neck radiation patients. (*Level of Evidence: III*)
2. The colonization of SM and LB remain unchanged or decreased during anti-neoplastic chemotherapy. (*Level of Evidence: III*)

Discussion

As expected, there were no randomized clinical trials on pre-cancer therapy dental evaluation/treatment protocols as there are obvious ethical concerns with providing no treatment in cancer patients in a prospective study. However, since the

2010 systematic review, a well-executed non-randomized clinical trial [24] and several studies examining different protocols ranging from minimal to complete dental evaluation/treatment protocols prior to cancer therapy have been published [18, 19, 27]. An appraisal of all the studies retrieved in this current and the previous review suggest that patients who underwent partial dental evaluation/treatment protocols prior to chemotherapy and HSCTs involving removal of moderate and severe dental pathologies experienced no or minimal odontogenic related complications during cancer therapy [24, 25, 26]. Even in minimal pre-cancer dental evaluation/treatment protocols, whereby only acute and symptomatic dental pathology were addressed prior to chemotherapy and HSCTs, only 3–4% of patients developed dental related complications [16, 18]. In a retrospective review of the Nationwide Inpatient sample, Allareddy et al. found that leukemia adults who had gingivitis/ periodontitis were at higher risk for septicemia, bacterial infections and mycoses [50]. However, the conclusions made in this paper must be interpreted with great caution as it was unclear how (i.e., who, when) the inpatient diagnosis of periodontal disease was made; and thus the prevalence of periodontal disease may be grossly inaccurate. The overall weighted prevalence of dental infections during cancer therapy in this review (5.4%) was low and comparable to that reported in the 2010 systematic review (5.8%). However, we noted that the pre-existing oral conditions and the type of pre-cancer dental evaluation/treatment protocols of patients in these studies were unclear which could potentially bias the results. Nonetheless, the option for partial dental evaluation/treatment protocols should be considered in patients where there is an urgency to start cancer therapy as soon as possible; leaving little time for complete dental evaluation/treatment. Complete dental evaluation/treatment protocols though ideal must be reconsidered if the time taken to eliminate all active and potential sources of infections in a patient completely and for healing to occur would result in a delay in cancer therapy initiation and negatively impact prognosis. Another concern is the risk for complications arising from pre-cancer therapy dental treatment, which in this group of medical vulnerable patients is significant. Such complications may cause delay in cancer therapy initiation and, in severe cases, result in a systemic infection [20, 22, 23]. Although beyond the scope of this review, in view of the low incidence of dental adverse events, it may be of interest to evaluate the cost and benefits for such pre-cancer dental evaluation/treatment protocols prior to commencement of cancer therapy. The cost of such protocols should be weighed against the cost and burden of managing adverse oral events during cancer therapy that may be prevented with dental evaluation and treatment prior to cancer therapy.

In post head and neck radiation patients, oral colonization with SM and LB was significantly higher than at baseline [35, 36, 39–41]. Chlorhexidine and to a lesser extent sodium fluoride reduced SM and perhaps caries risk in these patients [30]. The recommendations that both chlorhexidine and fluoride products are effective in reducing caries activity in post head and neck radiation patients from the 2010 systematic review are thus still valid. However, compliance with fluoride use was found to decrease drastically over time; with one study reporting an extremely low compliance of 12% for fluoride gel delivered in a custom tray at 24 months [29]. It is therefore imperative that clinicians managing post head and neck radiation cancer survivors emphasize the continued use of fluoride products for caries prevention. Since, there are no differences in the type of fluoride products, a strategy may be to recommend trying the various products available and using the one most acceptable to the patient.

There is evidence for the cariostatic properties of GIC in the literature and its benefits in patients with high caries risk. However, in this systematic review, GIC restorations had significantly higher failure rates than composite resin restorations in post head and neck radiation patients [32, 33]. Most of the failures were due to structural degradation. We hypothesize that since GIC maintains its structural strength when hydrated; in a post- head and neck radiation patient suffering from salivary gland hypofunction, the structural integrity of GIC may be compromised which may explain their high number of failures. That withstanding, in non-fluoride users, the overall GIC restorations resulted in less failures due to secondary caries compared to composite resin restorations [32, 33]. This suggests that in patients who are non-compliant fluoride users, GIC restorations may be considered with the caveat that these restorations will require regular maintenance and replacements due to breakdown in structural integrity.

Conclusions

1. The weighted prevalence of dental infections during cancer therapy is relatively low (5.4%) and is comparable to that reported in the 2010 systematic review (5.8%).
2. Post extraction complications ranged from 3 to 40% in cancer patients and were most common after third molar extractions.
3. In view of the relatively low dental infections during cancer therapy and the complications after third molar extractions, partial dental evaluation/treatment protocols prior to anti-neplastic therapy and HSCT whereby minor caries (within dentin), asymptomatic third molars or asymptomatic teeth without excessive probing depth (<8 mm), mobility (I and II) or with periapical lesions of <5 mm were obseved; appear to be a viable option; if there is insufficient time for complete dental evaluation/treatment protocols.

4. The guideline for use of fluoride products remains unchanged from the 2010 systematic review and they are recommended to prevent dental caries in post head and neck radiation patients. It is important to reinforce its use as compliance decreases with time.
5. The use of chlorhexidine mouth rinse (in concentrations ranging from 0.12 to 0.2% once or twice daily) remains unchanged from the 2010 systematic review and is recommended for the reduction of plaque accumulation and SM counts in post head and neck radiation patients.
6. The use of composite resins, resin modified GIC and amalgam restorations is recommended over conventional GIC in post head and neck radiation patients who are fluoride users. In non-fluoride users, GIC restorations are suggested to reduce the rate of recurrent caries but may require frequent replacements due to breakdown in structure integrity.
7. There was an increase in cariogenic microbes (SM and LB) in post head and neck radiation patients which was not observed in patients receiving anti-neoplastic chemotherapy.

Acknowledgements The authors thank Ms. Sim Yu Fan for helping with the statistical analyses for this manuscript. We would like to also thank Dr. Sharon Tan for assisting with the data management.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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