

A systematic review of dental disease in patients undergoing cancer therapy

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Abstract

Introduction This purpose of this systematic review was to evaluate the literature and update our current understanding of the impact of present cancer therapies on the dental apparatus (teeth and periodontium) since the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies.

Review method A systematic literature search was conducted with assistance from a research librarian in the databases MEDLINE/PubMed and EMBASE for articles published between 1 January 1990 and 31 December 2008. Each study was independently assessed by two reviewers. Taking into account predetermined quality

measures, a weighted prevalence was calculated for the prevalence of dental caries, severe gingival disease, and dental infection. Data on DMFT/dmft, DMFS/dmfs, plaque, and gingival indexes were also gathered. The level of evidence, recommendation, and guideline (if possible) were given for published preventive and management strategies.

Results Sixty-four published papers between 1990 and 2008 were reviewed. The weighted overall prevalence of dental caries was 28.1%. The overall DMFT for patients who were post-antineoplastic therapy was 9.19 (SD, 7.98; $n=457$). The overall plaque index for patients who were post-antineoplastic therapy was 1.38 (SD, 0.25; $n=189$). The GI

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for patients who were post-chemotherapy was 1.02 (SD, 0.15; $n=162$). The weighted prevalence of dental infections/abscess during chemotherapy was reported in three studies and was 5.8%.

Conclusions Patients who were post-radiotherapy had the highest DMFT. The use of fluoride products and chlorhexidine rinses are beneficial in patients who are post-radiotherapy. There continues to be lack of clinical studies on the extent and severity of dental disease that are associated with infectious complications during cancer therapy.

Keywords Cancer therapy · Dental caries · Periodontal disease

Introduction

Surgical resection, radio-, and chemotherapy, either used singly or in combination, are the three most common modalities used in head and neck cancer treatment. Although these modalities are effective in eradicating the tumor, they also negatively impact the normal head and neck structures surrounding the tumor. Direct damage to the oral structures (soft and hard tissue) frequently occurs from radio- and chemotherapy, and indirect damage may also arise from systemic toxicity. These oral complications may occur during and following cancer therapy and are generally grouped into two broad categories: acute and chronic. This review will focus on the acute and chronic effects of cancer therapy on the dental apparatus (i.e., teeth and periodontium). Because of the known long-term impact of cancer therapy on the dental apparatus, in particular, the increased risk of dental caries, this article will also examine the evidence for various preventive and treatment approaches of dental disease in such patients.

Another important issue covered by this review was the evidence for pre-cancer therapy dental clearance. The rationale for dental examination and treatment prior to cancer therapy is based on reports in the literature linking increased incidence of intra-therapy complications and viridans streptococcal bacteremia in patients with poor dental health [1–3]. One of the concerns is the occurrence of acute dental infections while patients are undergoing cancer therapy. Even though this has not been extensively reported in patients who are immunosuppressed from chemotherapy, from theoretical reasoning, it is possible for a minor odontogenic infection to develop into a systemic infection and result in a life-threatening event. Another frequently cited reason for pre-cancer therapy dental clearance is the risk of post-radiation jaw osteoradionecrosis in patients who receive radiation doses above 6,000 cGy in the head and neck region. The estimated

incidence of osteoradionecrosis in radiated (conventional radiation) jaw bone is approximately 7% and occurs more frequently in the mandible than in the maxilla [4]. The process may occur spontaneously, may be caused by trauma (e.g., accidental injury to oral mucosa from masticatory activity or iatrogenically from dental extractions) or oral infections (e.g., periapical and periodontal infections). Due to the concern of oral and systemic sequelae from dental infection, the dentist is often part of the pre-cancer therapy work up in many treatment centers.

The purpose of this systematic review was to evaluate the literature and update our current understanding of the impact of present cancer therapies on the dental apparatus (teeth and periodontium) and the role of pre-cancer treatment dental protocols since the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [5].

Historical perspective (prior to 1990)

The historical perspective was summarized from the 1989 National Institute of Health (NIH) Development Consensus Conference on the oral complications of cancer therapies.

Dental disease and the necessity of pre-cancer therapy dental clearance

Patients with chronic dental disease and poor oral hygiene were thought to be at increased risk for the development of acute odontogenic infections and potentially life-threatening systemic infections during periods of immunosuppression, though this appeared to occur less frequently than other acute mucosal oral infections [6, 7]. Oncology centers employed empiric guidelines to prevent these odontogenic infections, which often entailed the implementation of pre-cancer treatment dental protocols. These protocols typically included restoration of carious teeth, root canal therapy (if time permits), extraction of hopeless teeth, and dental prophylaxis with or without scaling and root planning. The guidelines for endodontic care and extractions proposed during the consensus in 1990 are illustrated in Tables 1 and 2, respectively.

These guidelines varied greatly amongst centers due to the lack of outcome-oriented trials to assess efficacy of a specific pre-cancer therapy dental protocol. Ultimately, the decision on the type of dental treatment rendered was based on the clinician's assessment of the clinical and radiographic condition of the pulpal and periodontal status of the tooth involved, the time available prior to cancer treatment initiation, and patient's immune status at the time of dental treatment.

Experts concluded that larger scale prospective studies were needed to examine the risk-benefit ratio of dental

Table 1 Empiric guidelines for endodontic care in patients scheduled to receive myelosuppressive chemotherapy [7]

Diagnosis	Management
Reversible pulpitis	Caries control
Irreversible pulpitis	Initial biomechanical preparation of canal(s); temporary double closure
Necrotic pulp with chronic periapical pathosis	No endodontic treatment unless patient has 7 days from completion of endodontic therapy to onset of myelosuppression (<1,000 granulocytes/mm ³)
Necrotic pulp with acute periapical infection	Endodontic therapy or extraction depending on systemic status of patient and scheduling of chemotherapy

procedures prior to myelosuppressive chemotherapy. In addition, studies should also focus on the extent of periodontal, pericoronal, and dental disease that were likely to cause serious complications during chemotherapy.

Long-term effect of cancer therapies on teeth and periodontium

Prior to 1990, data on the caries profile in patients who have undergone chemotherapy were limited and conflicting [8]. Some studies reported increase caries incidence, while others did not find any changes in caries activity. Similar findings were found regarding the periodontium of these patients. In patients who had received head and neck radiotherapy, the ensuing xerostomia caused by damage to the salivary glands predisposed these patients to post-radiation caries. Fluoride therapy was considered to be the best option for prevention of post-radiation caries. The role of long-term use of chlorhexidine rinses and saliva substitutes was uncertain.

Aims

The aim of the present review was to expand on the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [5]. The specific goals of this systematic review of dental disease as an oral complication of cancer therapies were as follows:

1. Determine the prevalence of dental caries in cancer survivors.
2. Determine prevalence of periodontal disease in cancer survivors.
3. Determine the prevalence of local and systemic infections caused by dental disease during cancer therapy.

Table 2 Guidelines for dental extractions [7]

Primary wound closure with multiple interrupted sutures
Ten days between extraction date and granulocyte count <500/mm ³
Avoidance of intra-alveolar hemostatic packing agents
Platelet transfusion if platelet count <40,000/mm ³
Prophylactic antibiotics if granulocyte count <2,000/mm ³

4. Determine the efficacy of preventive and treatment approaches in managing dental disease in cancer survivors.
5. Determine the efficacy of pre-cancer therapy dental clearance in preventing oral complications during and after cancer therapy.

Systematic review methodology

Search strategy and criteria for selecting studies

A systematic literature search was conducted with assistance from a research librarian in the databases MEDLINE/PubMed and EMBASE for articles published between 1 January 1990 and 31 December 2008. The primary outcome was to retrieve all literature containing original data on dental caries and periodontal disease and pre-cancer dental clearance protocols in cancer patients undergoing head and neck radiotherapy, chemotherapy, or combined treatment modalities.

The following publication types were eliminated from this systematic review: systematic and non-systematic reviews; microbiology studies; growth and development studies; organ transplant studies; studies eliciting dental complications through questionnaires, studies reporting data from previous publications; phase I and II studies, opinion papers, and case reports; articles published before 1990; and publications from the 1990 NCI Monographs [9] based on the 1989 NIH Development Consensus Conference on the Oral Complications of Cancer Therapies [5]. The search was limited to the English language. Gender and age were not limited.

Review methodology

Each article was independently evaluated by two reviewers (BH, CH, JIN, MS, and VM) with pilot-tested collection forms customized for reviewing dental disease data. Dental caries was assessed by the presence (Y/N), DMFT/dmft (decayed, missing, and filled teeth: DMFT for permanent, adult teeth and dmft signifying deciduous teeth), and DMFS/dmfs indexes (decayed, missing, and filled surfaces: DMFS for permanent, adult teeth and dmfs signifying deciduous teeth) if available. Periodontal health was assessed using the plaque and gingival indexes. Further

data collected for each article such as type of study, blinding, presence of control group, scale validity, and sample size were used to determine quality outcomes utilized to determine the weighted prevalence of caries and dental infection. Further details of this methodology can be reviewed in the publication by Brennan MT et al. [10].

The following assumptions were made regarding cancer diagnosis and treatment modality in this review:

1. There were several articles that only described the treatment modality but did not include the cancer diagnosis. If the treatment modality involved head and neck radiation, the assumption was made that this treatment was for head and neck cancer. No assumptions were made regarding the type of head and neck malignancy.
2. Although, the modality of cancer treatment (i.e., radiotherapy and chemotherapy) was described in detail in the majority of the studies, many did not specify or clarify whether this was the only treatment approach. Therefore, if only one mode of antineoplastic therapy (e.g., chemotherapy, radiotherapy, and surgery) was described in the manuscript, we made the assumption that this particular treatment was the only therapy rendered, unless otherwise stated by the authors.

Results

The electronic searches identified over a thousand titles and abstracts. After examination of the abstracts and full-text articles by the review group, 64 articles satisfied the inclusion criteria. Forty-six studies were observational, and 18 were interventional studies. Of the 64 studies included, 31 studies recruited adult patients, 24 recruited pediatric patients, 4 included both pediatric and adult patients, and 5 did not provide the age of the population sampled. The two most common malignancies were head and neck cancer and hematological malignancies (Table 3). The majority of studies reported the type of cancer treatment rendered (Table 4).

Observational studies

Of the 46 observational studies, 24 were cohort, 8 were case control, and 14 were cross-sectional studies. The majority of studies were conducted in single institution settings. Only one observational study did not report the type of antineoplastic therapy rendered.

(A) Teeth

1. Dental infection/abscess

Dental infections/abscess during chemotherapy was reported in three studies, and the weighted prevalence was

5.8% [11–13] (standard of error, 0.009; 95% confidence interval, 1.8–9.7).

1. Dental caries (Table 5)

The weighted overall prevalence of dental caries was 28.1% and was determined from 19 studies [14–32]. The weighted prevalence of dental caries in patients who received only chemotherapy was 37.3%. The weighted prevalence of dental caries in patients who were post-radiotherapy and those who were post-chemo- and radiotherapy were 24% and 21.4%, respectively.

2. DMFT

The overall DMFT for patients who were post-antineoplastic therapy was 9.19 (SD, 7.98; $n=457$) [14, 17, 25, 29, 30, 33–36]. The DMFT for patients who were post-chemotherapy [17, 25, 33] and post-radiotherapy [14, 30, 36] was 4.5 (SD, 2.88; $n=132$) and 17.01 (SD, 9.14; $n=157$), respectively. The mean DMFT value in patients prior to treatment was 8.2 (SD, 0.71; $n=80$) [14, 35]. The mean DMFT for healthy controls was 4.4 (SD, 4.07; $N=275$) [14, 17, 25, 29, 34].

3. dmft

The overall dmft for patients who were post-cancer therapy (all modalities) was 3.23 (SD, 2.42; $n=128$) [29, 33, 34]. The mean dmft for healthy controls was 2.15 (SD, 1.77; $n=103$) [29, 34].

4. DMFT/dmft

The overall DMFT/dmft for patients who were post-chemotherapy was 5.63 (SD, 0.88; $n=66$) [37, 38]. The mean DMFT/dmft for healthy controls was 4.7 (SD, 0.14; $n=56$) [37, 38].

5. DMFS

The overall DMFS for patients who were post-cancer therapy (all modalities) was 11.8 (SD, 9.01; $n=128$) [17, 34, 35]. The mean DMFS for healthy controls was 4.1 (SD, 0.28; $n=86$) [17, 34].

6. DMFS/dmfs

The overall DMFS/dmfs for patients who were post-chemotherapy was 8.01 (SD, 2.14; $n=66$) [37, 38]. The mean DMFS/dmfs for healthy controls was 1.08 (SD, 0.04; $n=56$) [37, 38].

(B) Periodontium

1. Severe gingivitis

The weighted prevalence of severe gingivitis from three studies was 20.3% (standard of error, 0.49; 95% confidence interval, 0–41.4) [12, 13, 39]. All three studies were conducted on patients undergoing chemotherapy.

2. Plaque index (PI)

Table 3 Cancer diagnosis ($n=64$)

Cancer diagnosis	Number of studies (references)	Number of patients ^a
Cancers in the head and neck region		
Squamous cell carcinoma	9 [18, 56, 63–69]	385
Head and neck cancer	12 [22, 26, 36, 40, 43, 44, 46, 49, 51, 53, 57, 58]	550
Head and neck cancer (assumptions made by reviewers)	3 [45, 52, 54]	77
Nasopharyngeal cancer	8 [14, 27–30, 70–72]	272
Cancer requiring radiation to the ENT/H&N region	2 [21, 50]	2,507
Tumors in the salivary gland areas	3 [48, 63, 67]	17
Hematologic malignancies		
Hematologic malignancies/diseases (exclude lymphoma if possible)	16 [12, 13, 17, 19, 24, 29, 33, 39, 41, 55, 73–78]	2,008
Lymphoma (Hodgkin's, non-Hodgkin's disease, NOS)	15 [12, 25, 29, 35, 37, 38, 41, 42, 47, 55, 67, 69, 70, 74, 78]	325
Other diagnosis		
Rhabdomyosarcoma	7 [12, 15, 20, 25, 29, 32, 74]	264
Osteosarcoma/Ewing sarcoma	2 [12, 25]	15
Wilms tumor/nephroblastoma	5 [12, 23, 25, 29, 74]	64
Neuroblastoma	4 [12, 16, 29, 69]	59
Small cell cancer	1 [11]	21
Breast cancer	1 [41]	1
Childhood cancer	1 [34]	52
Thyroid cancer	1 [31]	121
Diagnosis not specified	5 [12, 25, 29, 69, 74]	25

^a Healthy controls were excluded

The overall PI for patients who were post-antineoplastic therapy was 1.38 (SD, 0.25; $n=189$) [25, 37, 38, 40]. The PI for patients who were post-chemotherapy was 1.46 (SD, 0.23; $n=162$) [25, 37, 38]. The mean PI for healthy controls was 0.91 (SD, 0.12; $n=152$) [25, 37, 38].

3. Gingival index (GI)

The GI for patients who were post-chemotherapy was 1.02 (SD, 0.15; $n=162$) [25, 37, 38]. The mean GI for healthy controls was 0.76 (SD, 0.10; $n=152$) [25, 37, 38].

(C) Febrile episodes from oral source

One study reported the incidence of patients with febrile episode originating from a dental problem was 4% [41].

Another study found that an oral source was the only identifiable foci of infection in 42% of recorded febrile episodes [42]. The same study also reported that patients with febrile episodes had more severe dental infection (57.6%) than those without (23.3%) [42].

Interventional studies

Fluoride therapy

The anticariogenic benefits of fluoride therapy are well documented in the literature. Water fluoridation has been touted to be responsible for the dramatic decrease in dental caries in the twentieth century. There are several studies

Table 4 Breakdown of studies and patients with reference to treatment modality ($n=64$)

Treatment modality	Number of studies (references)	Number of patients ^a
Chemotherapy only±surgery	22 [11, 13, 15–17, 19, 23, 25, 29, 32, 33, 37–39, 41, 42, 47, 73–76, 78]	710
Radiation only±surgery	30 [14, 21, 22, 26, 30, 36, 40, 43–46, 48–54, 56, 57, 63–72]	3,477
Radiation and chemotherapy±surgery	19 [15–18, 20, 26–29, 32, 33, 40, 41, 64, 72, 75–78]	696
No breakdown or vague description of cancer therapy or other type of therapy	7 [6, 12, 24, 31, 35, 55, 58]	1,812

^a Healthy controls and patients who have not yet underwent treatment were excluded

Table 5 Weighted prevalence of dental caries following cancer therapy ($n=19$)

Treatment modality	Number of studies	Mean prevalence (%)	STD error	95% confidence interval
Chemotherapy only	5	37.3	0.17	0–85.7
Radiotherapy only	4	24.1	0.13	0–66.2
Chemoradiotherapy	9	21.4	0.06	6.9–35.8

that have extrapolated and investigated the benefits of fluoride use in the general population for management of dental caries in patients have undergone head and neck radiation. Because of the damage to the salivary glands during radiation and the ensuing xerostomia that follows, these patients are at higher risk than the average person for the development of dental caries. We retrieved five randomized control trials on fluoride therapy in patients who have undergone antineoplastic therapy [43–47]; four studies were on patients who were post-radiation, and one was on patients who were undergoing chemotherapy (Table 6). Two studies compared different types and methods of fluoride application on the caries activity [43, 44]. In both studies, they found no difference in caries activity between the treatment groups. Al Joburi et al. noted that patients who were noncompliant with their fluoride therapy had a significantly higher caries increment compared to the fluoride treatment groups [43]. Two articles investigated the use of an intraoral fluoride releasing system, and in both studies, there were no significant differences in dental caries between groups that used the system and those that used regular fluoride gels in custom fabricated trays [45, 46]. Meurman et al. compared the use of chlorhexidine 0.12% to amine-stannous fluoride mouth rinses in patients undergoing chemotherapy [47]. They found that both rinses reduced the gingival bleeding scores and plaque scores as well as the levels of streptococcus mutans in the saliva.

Toothpaste

There were three studies that investigated the use of various toothpastes [48–50] (Table 7). Two studies examined the benefits of toothpaste containing lactoperoxidase in patients who have undergone radiotherapy for head and neck cancer [48, 49]. Toljanic et al. found that the toothpaste containing salivary lactoperoxidase provided slight improvement in plaque and gingival index scores compared to placebo toothpaste, but this was not significant [49]. In the other study by Van Steenberghe et al., authors found that patients using toothpaste containing lactoperoxidase (Biotene) significantly reduced sulcular bleeding index after 10 days of use [48]. In addition, when only interdental spaces were considered, there was significantly lower plaque seen in the Biotene group compared to patients who were using Sensodyne toothpaste. The third article retrieved in this

category compared a dual phase remineralizing toothpaste to conventional toothpaste [50]. The authors found significantly ($p=0.03$) lower net root surface caries increment/year in patients using Enamelon toothpaste compared to those using conventional toothpaste.

Chlorhexidine

Chlorhexidine is a bisguanide with bactericidal activity against gram-positive and -negative bacteria. Its mechanism of action is through disruption of bacterial membranes and enzyme systems. There were three studies that evaluated the effect of chlorhexidine mouth rinse on oral hygiene indexes in patients who have undergone antineoplastic therapy [39, 47, 51] (Table 8). Two studies found that chlorhexidine rinse reduced plaque scores as well as the levels of salivary streptococcus mutans count [47, 51]. However, in both studies, the lactobacillus counts were either higher or did not change with the use of chlorhexidine. One study compared the use of chlorhexidine with and without mechanical removal of plaque and calculus on day 1 of chemotherapy and found that the plaque scores and bleeding scores were significantly lower in the group that had mechanical removal of plaque and calculus [39].

Dental restorations

There were three studies that investigated the use of various dental restorative materials in patients who have undergone head and neck radiation [52–54] (Table 9). In studies by McComb et al. [52] and Wood et al. [53], conventional glass ionomer cements performed more poorly than the comparative materials, specifically amalgam, resin-modified glass ionomer, and composite resin restorations. Hu et al. compared Ketac molar (KM) to Fuji IX (FIX) restorations and found that there was statistically ($p=0.01$) higher number of KM restorations (30%) lost compared to FIX (12.5%) restorations at the 12- and 24-month follow up [54].

Others

There were two articles on oral care protocols, one [41] examined the benefits of a minimal intervention pre-cancer therapy dental protocol, and the other [55] examined the impact of an intensive preventive protocol on patients

Table 6 Summary of fluoride studies (5)

Author	Dx	Tx	Study type	Time of assessment	Final N/intervention 1	Final N/intervention 2	Final N/intervention 3
Al Joburi et al. 1995 [43]	H&N ^a	RT ^b	RCT ^c Single blind (operator)	Post-RT ^b Patients recalled at intervals ranging 4 to 6 months, all patients reexamined after one year during recall appointments	N=69 Sodium fluoride gel in custom trays daily for 5 min for 3 months Remineralizing mouth rinse twice a day for next 3 months Continued use of regular dentifrice	N=56 Brush with stannous fluoride gel instead of dentifrice	N=18 Noncompliant with fluoride therapy
Chambers et al. 2007 [46]	H&N ^a	RT ^b	RCT ^c Single blind (operator)	3 months post-RT ^b At placement of intraoral fluoride releasing system (IFRS) retainers, at 4, 8, 12, 24, 36, and 48 weeks	N=9 Placement of IFRS retainers on bilateral maxillary molars for all patients and all used 1,100 ppm toothpaste twice daily, oral hygiene instructions N=11 Sustained release fluoride tablet replaced every 3 months Sodium fluoride/hydroxy ethyl methacrylate/methyl methacrylate (50:50 ratio of HEMA/MMA)	0.4% Stannous fluoride gel in custom trays daily for 10 min	
Meurman et al. 1991 [47]	Hodgkin's and non-Hodgkin's disease	CT ^d	RCT ^c Double-blind cross-over study	During combination CT ^d Assessed prior to anticancer treatment, and before and after each period of rinsing with different type of mouthwash	N=51 (self control) All patients went through a rinse period with 0.05% sodium fluoride solution from weeks 2 to 4 In addition, patients in the amine-stannous fluoride group also had 0.05% sodium fluoride solution from weeks 6 to 8 N=51 (self control) 0.12% Chlorhexidine (CHLX) rinse	0.025% Amine-stannous fluoride mouth rinse	
Meyerowitz et al. 1998 [45]	Not specified (assumed H&N ^a)	H&N ^a RT	RCT ^c Single blind (operator)	Post-RT ^b (completed >3 months before study) Assessments at baseline (before placement of IFRS), 1, 2, 3, 4, 5, and 6 (end of study) months	N=13 Intraoral fluoride releasing system (IFRS), fluoride pellet: sodium fluoride/hydroxy ethyl methacrylate/methyl methacrylate (50:50 ratio of HEMA/MMA)	N=10 1.1% Neutral sodium fluoride in custom trays, 5 min daily	
Spak et al. 1994 [44]	H&N ^a	RT ^b	RCT ^c Double blind	Assessed immediate prior to RT ^b , 6 and at 12 months after RT ^b	N=19 0.42% Fluoride gel daily from start of radiation until 2 weeks after end of radiation, then daily use of 1.23% fluoride gel for 4 weeks. Thereafter, switched to 0.42% fluoride gel and use until 1 year after baseline exam	N=18 0.42% Fluoride gel daily from start of radiation until 1 year after baseline exam	

^a Head and neck^b Radiation^c Randomized control trial^d Chemotherapy

Table 7 Summary of toothpaste studies (3)

Author	Cancer Dx	Cancer Tx	Study type	Time of assessment	Final N/intervention 1	Final N/intervention 2
Papas et al. 2008 [50]	Not specified (assumed H&N ^a)	H&N ^a RT ^b	RCT ^c Double blind	Some post-RT ^b (0–15 years), some still actively treated with RT ^b Assessed at baseline, then 1, 2, 4, 6, 8, 10, and 12 months	N=23 Enamelon (dual phase remineralizing toothpaste)	N=19 Conventional toothpaste
Tojamic et al. 1996 [49]	H&N ^a	RT ^b	RCT ^c Double blind	Post-RT ^b Assessments done at start of study, 1, 2, 3, 4, 5, and 6 months	All were given a toothbrush and 1.1% neutral sodium fluoride gel every night for 5 min, cross-over at 3 months N=19 (self control) Group 1 (10), group 2 (9) Group 1: toothpaste with lactoperoxidase and glucose oxidase then placebo toothpaste	N=19 (self control) Group 1 (10), group 2 (9) Group 2: placebo toothpaste then toothpaste with lactoperoxidase and glucose oxidase
van Steenberghe et al. 1994 [48]	Tumors in the major salivary gland area	RT ^b	RCT ^c Single blind (patient)	Minimum 3 months post-RT ^b Assessments done at days 0, 10, 42, and 52	Prior to study, all patients received 2 sessions of oral hygiene instructions (OHI) which included supervised toothbrushing and interproximal plaque control. At baseline, all patients received a professional cleaning. Cross-over on day 42 N=12 (self control) 6 On each group Biotene toothpaste then Sensodyne toothpaste on day 42	N=12 (self control) 6 On each group Sensodyne toothpaste then Biotene toothpaste on day 42

^a Head and neck^b Radiation^c Randomized control trial^d Chemotherapy

Table 8 Summary of chlorhexidine studies (3)

Author	Cancer Dx	Cancer Tx	Study type	Time of assessment	Final N/intervention 1	Final N/intervention 2
Bergmann et al. 1992 [39]	Acute myelogenous leukemia	CT ^d	RCT ^c Blinding unknown	During antineoplastic treatment Assessed on days 1, 14, and 28 of CT ^d	N=10 0.1% Chlorhexidine rinse with mechanical removal of plaque and calculus on day 1	N=10 0.1% Chlorhexidine rinse
Joyston-Bechal et al. 1992 [51]	H&N ^a	RT ^b	Before and after	Assessed 1 week before RT ^b , once weekly during 4 weeks of treatment, and at approximately 6, 8, 10, 12, 26, 40, and 52 weeks after start of RT ^b	N=25 0.2% Chlorhexidine, diluted 1:1 with water twice a day for 1 week before RT, during RT, and 4 weeks after radiation	NA
Meurman et al. 1991 [47]	Hodgkin's and non-Hodgkin's disease	CT ^d	RCT ^c Double-blind cross-over study	During combination CT ^d Assessed before anticancer treatment began and before and after each period of rinsing with different type of mouthwash	All patients went through a rinse period with 0.05% sodium fluoride solution from weeks 2 to 4 In addition, patients in the amine-stannous fluoride group also had 0.05% sodium fluoride solution from weeks 6 to 8 N=51 (self control) 0.12% Chlorhexidine rinse	N=51 (self control) 0.025% Amine-stannous fluoride mouth rinse

^a Head and neck^b Radiation^c Randomized control trial^d Chemotherapy

Table 9 Summary of studies on dental restorations (3)

Author	Cancer Dx	Cancer Tx	Study type	Time of assessment	Final N/intervention 1	Final N/intervention 2	Final N/intervention 3
Hu et al. 2002 [54]	Malignant tumors (assumed H&N ^a)	Cervicofacial RT ^b	Cohort	Post-RT ^b Assessment at placement 6, 12, and 24 months	N=73 restorations 15 patients Ketac molar restorations	N=73 restorations 15 patients Fuji IX GP restorations	
McComb et al. 2002 [52]	Not specified (assumed H&N ^a)	H&N ^a RT ^b	Cohort/N-RCS	Post-RT ^b Recall at 6, 12, 18, and 24 months	N=39 patients/44 class V restorations (initial) Conventional glass ionomer (GI) restorations	N=39 patients/44 class V restorations Resin-modified glass ionomer restorations (RMGI)	N=39 patients/44 class V restorations Composite restorations
Wood et al. 1993 [53]	H&N ^a	RT ^b	Before and after Split mouth design	Post-RT ^b Placement before RT then 6 month assessment	N=54 (36 patients/self control) Glass ionomer cement restorations	N=54 (36 patients/self control) Amalgam restorations	

^a Head and neck^b Radiation^c Randomized control trial^d Chemotherapy

undergoing chemotherapy (Table 10). Both studies had several flaws in them, including small sample size or lack of comparison groups. There was one article each on the benefits of amifostine [56], cheese [57], and honey on dental health [58]. Results from these studies should be interpreted with caution because of the lack of additional randomized control trials.

Summary and recommendations

1. The use of fluoride products reduces caries activity in patients who are post-radiotherapy. However, the type of fluoride gel or fluoride delivery system used did not significantly influence caries activity (*Level of Evidence: II, Grade of Recommendation: B, Recommend the use of fluoride to prevent dental caries in patients who are post-radiotherapy*).
2. The use of chlorhexidine rinse reduces plaque scores and oral streptococcus mutans scores. This reduction was not seen with lactobacillus counts (*Level of Evidence: II, Grade of Recommendation: B, Recommend the use of chlorhexidine to improve oral hygiene, although potential side effect of tooth staining, increased calculus, and taste changes need to be taken into account*).
3. There is evidence suggesting that conventional glass ionomer restorations performed more poorly than resin-modified glass ionomer, composite resin, and amalgam restorations in patients who had been treated with radiotherapy (*Level of Evidence: III, Grade of Recommendation: B, Suggest the use of resin-modified glass ionomer, composite resin or amalgam restoration, and not a conventional glass ionomer restoration in patients who have been treated with radiotherapy*).
4. More studies are needed to determine the benefits of various types of toothpaste, pre-cancer therapy dental intervention, honey, and cheese on dental health (*Level of Evidence: III, Grade of recommendation: C, No guideline possible can be made at this juncture due to the lack of well designed studies*).

Discussion

In this systematic review, the weighted prevalence of dental caries amongst cancer survivors were surprisingly highest in patients who only received chemotherapy compared to those who received radiotherapy or chemoradiotherapy. This discrepancy may be attributed to the distinct differences in the dental management of patients prior to radiotherapy versus those being prepared for chemotherapy. Patients undergoing head and neck radiotherapy are at lifelong risk of developing osteoradionecrosis; subsequently,

Table 10 Other interventions (5)

Author	Cancer Dx	Cancer Tx	Study type	Time of assessment	Final <i>N</i> /intervention 1	Final <i>N</i> /intervention 2
Rojas de Morales et al. 2001 [55]	Hematologic malignancies (defined)	Not provided	RCT ^c	All were seen pre-treatment then assessed twice a week during hospitalization, once a week if outpatient; seen until CT ^d completed and hematological parameters reestablished 154 evaluations Average evaluations per patient: 13 (2–30)	<i>N</i> =5	<i>N</i> =7
Rudat et al. 2000 [56]	Squamous cell carcinoma	RT ^b	Cohort	Before and 1 year post-RT ^b	<i>N</i> =17 Preventive protocol Reinforce oral physiotherapy, removal of plaque, non-alcoholic 0.05% fluoride mouth rinse, topical application of 20% miconazole during chemotherapy, use of toothpaste 4 times a day before and after chemotherapy, toothpaste substituted with sodium bicarbonate during chemotherapy	Oral physiotherapy <i>N</i> =18
Sela et al. 2000 [58]	H&N ^a	Not provided (RT ^b assumed)	N-RCS	Post-RT ^b	Intravenous Amifostine (200 mg/m ²) Honey from wildflowers, swish 5 ml for 5 min and swallow	Nothing
Sela et al. 1994 [57]	H&N ^a	RT ^b	N-RCS	Assessment before and after rinse (same visit) Post-RT ^b	<i>N</i> =12 radiated patients Appliance with etched (in vitro exposure to cola for 60 min) enamel slabs (extracted human molars), for radiated and non-radiated patients <i>N</i> =14 (8 RT, 6 non-RT)	<i>N</i> =12 healthy controls <i>N</i> =14 (8 RT, 6 non-RT)
Toljanic et al. 1999 [41]	Hematologic malignancies (defined) and breast cancer	CT ^d : 46 CT ^d and RT ^b : 2	Cohort	Pre-cancer treatment then daily exam during treatment	Chew on a piece 20 g hard cheese for 5 min <i>N</i> =48 Minimal intervention pretherapy dental treatment	Chewing parafilm

^a Head and neck^b Radiation^c Randomized control trial^d Chemotherapy

dental management protocols prior to radiation often entail aggressive approaches such as extractions. Another explanation for the unanticipated caries prevalence may be because the majority of the studies were carried out on children (12/19 studies) [14–17, 20, 23–25, 27–29, 32], and a high proportion of the diagnoses in children was hematologic malignancies that were treated largely with curative chemotherapy. These children are ill for a long period of time and could have higher caries activity because of the need to frequently consume highly cariogenic dietary supplements for weight maintenance or are taking sucrose-rich medications. In addition, caregivers are often overwhelmed by their child's medical diagnosis and often neglect the oral health component. In contrast to the caries prevalence, the DMFT index is expectedly highest in patients who were post-radiation therapy compared to patients who were post-chemotherapy and healthy controls. The DMFT/S index is a means to obtain an estimation of dental disease in a population and is recommended by the World Health Organization (WHO) for the measurement of caries experience, thereby allowing for easy comparison among international studies [59]. Despite the shortcomings of the DMFT/S index (e.g., failure to detect dental decay between posterior teeth surfaces due to the lack of dental radiographs, failure to distinguish the various reasons for missing teeth) and the suggestions by several authors to switch to alternative indices, the DMFT/S index is still the most widely utilized caries assessment tool presently [60, 61]. It would have been helpful to look at the caries activity trends longitudinally in this systematic review; however, it was not possible to compile this information due to the lack of specification, standardization, and/or wide ranges of time periods of DMFT data collection.

Similarly, attempts to describe periodontal health and periodontal disease beyond that of plaque and gingival indexes in cancer patients were difficult in this review. PI is a measure of oral hygiene that synthesizes both number of surfaces covered and the amount of hard and soft deposits on the teeth, and gingival index is a measurement of the amount of inflammation present in the gingival tissues. Although, there were other measurements of periodontal health such as oral health index-simplified (OHI-S), probing depth, clinical attachment loss, gingival recession, and bleeding index, each of these parameters were only reported in a single study and therefore could not be combined or compared with other studies to have any meaningful results. Other difficulties encountered include the various reports of outcome variables (raw data versus percentages) and the categorization of periodontal health without clear definition. The measurements of DMFT/S, PI, and GI are important clinical considerations for dental practitioners because they are predictive indicators for the determination of future disease [62].

The majority of the intervention studies were carried out on patients who were post-head and neck radiotherapy, likely because these individuals are thought to be at a much higher risk for the development of dental caries compared to their post-chemotherapy counterparts. Expectedly, the use of fluoride products and chlorhexidine rinses are beneficial in reducing caries activity and levels of streptococcus mutans, respectively.

There continues to be a lack of clinical trials to evaluate the extent of dental disease associated with complications during cancer therapy, despite recommendations from the 1989 NIH consensus for more studies in this area [5]. In this review, the weighted prevalence of an odontogenic infection during chemotherapy is approximately 6%. However, these studies had small sample sizes, did not report pre-existing oral conditions, and had varied styles of reporting results, making it tricky to draw conclusions. In addition, the pre-existing oral conditions in these patients were unknown. Despite the low prevalence of dental infections, there is some evidence in the literature that these infections may cause bloodstream bacteremia and become potentially life-threatening in immunosuppressed individuals. Based on this theoretical reasoning and indirect evidence, it appears reasonable to propose that all acute and potential sources of oral infections should be eradicated. Although, large prospective studies are required to definitively address this theoretical concern for oral infection.

Another area with poor evidence is the necessity for pre-cancer therapy dental clearance, and if required, the extent of disease that needs to be eradicated. However, conducting a prospective randomized controlled trial to evaluate eradicating all oral infections prior to patients undergoing cancer therapy versus no dental treatment may likely pose ethical concerns, especially if there is sufficient time for dental clearance. Eradicating acute dental problems versus eradicating both acute and chronic dental issues may be a more practical research design. At the time of this review, there was one cohort study that examined the viability of a minimal dental intervention clearance protocol in patients prior to chemotherapy. They found a 4% conversion rate of previously diagnosed chronic dental disease to acute inter-therapy pathology and a relative incidence of 10% conversion rate of acute conversion of previously diagnosed severe chronic periodontal disease [41]. Based on their findings, the authors felt that patients with chronic dental pathology could proceed safely with chemotherapy, as the conversion rate to an acute condition was infrequent. Due to the distinct differences in the implications of the presence of dental disease in patients who are pre-chemotherapy versus those who are pre-radiotherapy, the results of this study cannot be extrapolated to patients undergoing radiotherapy. There are presently no studies that have investigated or assessed which dental treatment protocol may be the most superior and appropriate in patients undergoing radiotherapy.

Conclusions

1. Patients who were post-radiotherapy had the highest DMFT compared to those who were post-chemotherapy and healthy controls.
2. Patients who were post-antineoplastic therapy had higher PI and GI than healthy patients.
3. The use of fluoride products and chlorhexidine rinses are beneficial in patients who are post-radiotherapy.
4. Conventional glass ionomer restorations performed more poorly than resin-modified glass ionomer, composite resin, and amalgam restorations in patients who were post-radiotherapy.
5. There continues to be lack of clinical studies on the extent and severity of dental disease that is associated with infectious complications during cancer therapy.

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Conflict of interest statement None to declare.

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