

Efficacy of Dental Services for Reducing Adverse Events in Those Receiving Chemotherapy for Cancer



Main Points

- A search of the MEDLINE database and professional society websites identified 27 primary research studies, 7 systematic reviews, and 5 practice guidelines that addressed the benefits and harms of dental evaluation and treatment prior to initiating cancer chemotherapy regimens.
- Evidence from randomized controlled trials indicates that pre-chemotherapy dental care does not reduce the incidence of oral mucositis, but such care does appear to reduce the severity of mucositis when it occurs.
- The bulk of the remaining evidence base consists of cohort studies that compared groups of patients who did or did not receive pre-treatment dental care. The evidence from these studies suggests that pre-treatment dental care may:
 - Reduce the incidence of oral infections during chemotherapy.
 - Reduce the incidence of osteonecrosis of the jaw during and after treatment with bisphosphonates or other agents used to treat malignant bony lesions.
- The available evidence does not permit conclusions regarding the effect of pre-treatment dental care on patient survival or adherence to cancer treatment regimens.
- Four professional society guidelines have recommended pre-treatment dental care prior to cancer chemotherapy or treatments for malignant bony lesions.
- A meaningful portion of the U.S. population lacks insurance coverage for dental care and may also lack personal financial resources to pay for that care.



Background

Disorders of the teeth, gums, and their supporting structures are important threats to a person's overall health.¹ However, the workforce that provides evaluation and treatment of dental disorders is not strongly integrated into the system of overall healthcare delivery in the United States. Dental professionals (dentists, dental hygienists, and dental assistants) are often trained in separate schools of dentistry or in colleges that do not have affiliated schools of

medicine or nursing. After completing training, the majority practice in privately owned dental offices that are not affiliated with medical clinics or hospitals.²

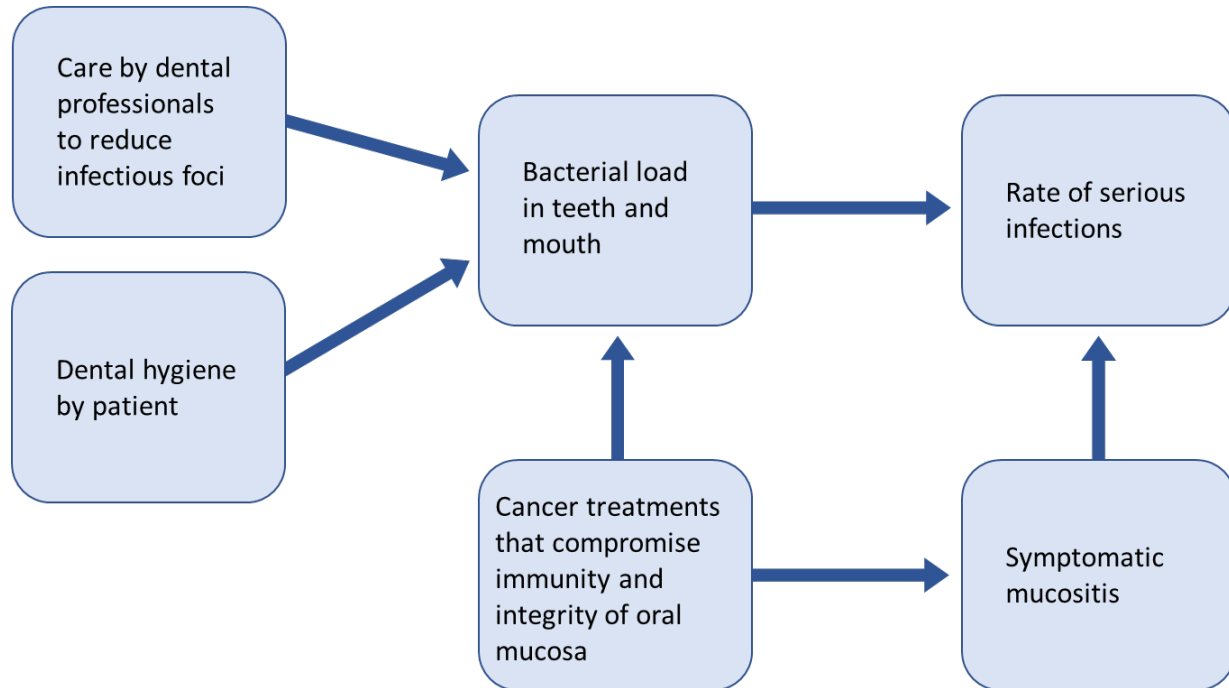
Financial barriers impede access to dental services. About one-third of U.S. citizens lack both dental insurance and other financial resources to pay for dental care. The number of people lacking dental insurance is triple the rate of those lacking medical insurance, and there are serious gaps in the U.S. safety net system for providing dental care to uninsured adults and children.³ For patients with cancer, lack of private health insurance is associated with less favorable clinical outcomes.⁴ Optimizing insurance coverage for necessary clinical services is an important priority.⁵

The Centers for Medicare & Medicaid Services (CMS) administers a major component of the U.S. health insurance system. While one of its programs (Medicaid) provides financial support for dental care to some people who would otherwise be uninsured, its largest program (Medicare) generally does not. While the statutes that define Medicare policies do not permit payment for most types of dental care, they have allowed some exceptions when the dental care is closely tied to the outcomes of complex medical procedures.⁶ For example, in the current regulations governing Medicare, CMS states that Medicare payment is permitted for “An oral or dental examination performed on an inpatient basis as part of comprehensive workup prior to renal transplant surgery or performed in an RHC/FQHC [Rural Health Clinic/Federally Qualified Health Center] prior to a heart valve replacement.”⁶ This payment policy addresses an important medical scenario in which the mouth and teeth are a potential source of infection in patients who undergo medical treatments that suppress the immune system and increase the patient’s susceptibility to serious complications.

Immunosuppression is commonly understood to be a reduction in the performance of the cells that comprise the body’s immune system, leading to impairment of resistance to infections and other disorders.⁷ Renal transplantation is not the only type of medical treatment that entails immunosuppression and an associated increased risk of infection. Other types of solid organ transplantation require long-term immunosuppression, while transplantation of hematologic cells (stem cells derived from either peripheral blood or bone marrow) induces major immunosuppression as part of the procedure itself.⁸ Treatment of a broad range of malignancies often requires the use of chemotherapeutic agents that suppress the body’s production of white blood cells, thereby impairing the body’s ability to resist serious (often life-threatening) bacterial and fungal infections. The route of entry of these offending bacteria can be the mouth.⁹⁻¹¹

There is abundant worldwide experience in the care of patients whose medical conditions require chemotherapy regimens that induce immunosuppression.^{12, 13} This experience has led to an understanding of how improved dental care potentially can reduce the incidence of serious infections and improve overall patient outcomes.¹⁴ The causal model for these concepts is diagrammed in Figure 1.

Figure 1. Causal model underlying the justification for performing dental evaluation, patient education, and medically necessary treatment prior to cancer treatment



A broad base of scientific knowledge provides justification for this causal model. Chemotherapy regimens cause short-term suppression of both neutrophils and lymphocytes, and the immunosuppression (such as reduced levels of B-lymphocytes and circulating antibodies) can last several months.^{15,16} Neutropenia is associated with an increased risk of septicemia, with patients aged 65 years and older having increased mortality from such infections.^{15,17} The bacteria causing these infections are frequently part of the oral biome.¹⁸ About half of adults in the United States have periodontitis, and the prevalence is 65% in those aged 65 years and older.¹⁹ Periodontitis is a gum disease that impairs the oral mucosa and predisposes to bacteremia and possible serious infection in the context of immunosuppression induced by chemotherapy. Periodontitis can be identified in routine dental examinations, thereby facilitating local treatments to reduce its severity. Studies examining the progression of periodontitis after a single episode of dental treatment prior to initiation of chemotherapy have shown that the severity of periodontitis improved²⁰ or remained stable²¹ for periods of 6 to 9 months.

Another common downstream complication of the drugs used in chemotherapy regimens is oral mucositis, which is a breakdown of the integrity of the oral mucosa.²² Mucositis can last for weeks, is painful, and interferes with the maintenance of oral nutrition. In addition to being a serious adverse event, mucositis also facilitates entry of oral bacteria into the bloodstream. The combination of resident bacteria in the mouth and compromise of the barrier to entry of these bacteria can increase the risk of bacteremia. Mucositis is associated with systemic infections in patients receiving high-dose chemotherapy.^{23,24} A potential benefit of dental care is that it can reduce the entry of bacteria through damaged oral mucosa by modifying the oral environment.²⁵

Performance of a thorough dental evaluation before commencing some types of cancer chemotherapy provides at least three potential benefits. The first is that examination by a dentist can identify local sources of active infection, such as oral abscesses or infected teeth or gums. By then treating those foci, the bacterial load in the mouth can be reduced. The second rationale is to provide teaching to the patient on proper daily self-care of the teeth and gums, through

brushing, flossing, and (in some cases) use of antibacterial mouth rinses. Such daily maintenance can minimize the overgrowth of pathogenic bacteria in the mouth and deter progression of dental disease that could contribute to negative systemic outcomes such as septicemia. Third, the education component is also important for alerting the patient that initiation of chemotherapy frequently leads to xerostomia, a severe form of dry mouth that diminishes local oral innate immunity and predisposes to worsened dental disease and inflammation. Poorer oral health and inflamed mucosa can also impair the intake of adequate nutrition. It is both feasible and practical to incorporate the examination, local treatment, and patient education components into one or two dental visits that will not delay initiation of the chemotherapy regimen on a timely basis.^{26, 27}

The potential value of conducting dental care prior to cancer treatment depends on defining which cancer patients would receive the greatest benefit from this care. An integral part of the causal model is that the chemotherapy regimen has a substantial impact on immunity to infection (largely through the suppression of white blood cells). Chemotherapy regimens are often complex, involving both the use of multiple drugs and defining the dosage intensity of those drugs.²³ Nevertheless, some guidance has been provided through expert consensus (supporting information provided in Appendixes A, B, and C).

Some cancer treatments are associated with an increased risk of severe deterioration of the bones of the jaw, known as osteonecrosis. Osteonecrosis greatly impairs patient function by causing mucosal and gingival breakdown that leads to chronically exposed bone and eventual bone death.²⁸ This process causes persistent pain, disfigurement, and impairment of eating and chewing. Published series of affected patients have identified the major risk factors for its occurrence to be high-dose radiotherapy to the jaw, osteoporosis, the use of drugs to suppress bony metastases (denosumab, high-dose bisphosphonates, or anti-angiogenic therapy) and tooth extractions following cancer treatments.²⁹⁻³¹ Because the risk factors appear to be additive, clinicians have advocated a thorough dental evaluation and removal of compromised teeth prior to commencing either local radiotherapy or drugs that directly affect the bone. Thus, the rationale for early dental care is to reduce the need to perform tooth extractions during or after the course of cancer treatment. Prior research has shown that dental evaluation and treatment prior to commencing cancer treatment reduced the number of tooth extractions after the treatment had ended.³² Osteonecrosis does not have an infectious etiology, and it is not related to the causal model summarized in Figure 1. However, it is a serious adverse event occurring in some cancer patients, and early dental evaluation and treatment can potentially reduce its rate of occurrence.

We sought to assemble and evaluate the published evidence supporting the efficacy of specific types of dental care that are intended to reduce adverse event rates in patients with cancer. If the evidence base is judged to be sufficient, this information potentially can inform policy initiatives (including changes to Medicare payment policies) that can improve access to specific dental services for people with cancer. The primary question for this review is: *For people who will undergo certain types of cancer treatments, does dental care prior to the treatment improve adverse event rates and other relevant outcomes?*



Methods

The goal of this Rapid Response report was to identify evidence pertinent to the medical necessity of dental evaluation and treatment prior to commencing certain kinds of cancer treatment. The review focused on the relationship between pre-treatment dental services and these outcomes of interest:

- Serious infections
- Oral mucositis
- Osteonecrosis of the jaw
- Cancer survival
- Adherence to cancer treatment regimens
- Quality of life

We reviewed peer-reviewed literature and professional guidelines from the last 50 years to identify research and standards of practice on the need for and effectiveness of dental screening and pre-treatment prior to beginning acute immunosuppressive therapies or medical therapies for treatment of cancerous lesions of the bone. A medical librarian with extensive experience conducting searches for systematic and rapid reviews developed and conducted a literature search of Ovid MEDLINE ALL on December 16, 2022 (Appendix A). Our review of the search results focused on identifying primary research studies, systematic reviews, and clinical guidelines published by professional societies. We also reviewed a literature set collected by CMS and scanned the reference lists of all included studies.

Each abstract was reviewed by one team member. We excluded those that did not examine dental services that were performed prior to beginning cancer therapy. For the rest, a team member read the full-text article and applied a set of inclusion and exclusion criteria to guide decisions on including studies in this Rapid Response. A comparison group (patients who did not receive pre-treatment dental care) was not a criterion for including a study. We excluded reports of small numbers of patients (such as case reports) and studies that reported on patients treated only with radiation therapy or surgery. Prior research has found that chemotherapy is a stronger risk factor for short-term infectious complication than monotherapy with radiation therapy.³³ The specific criteria that formed the basis for inclusion or exclusion of individual studies are summarized in Table 1. We also included systematic reviews that addressed the effectiveness of dental care prior to initiation of cancer treatments. If a reviewer was unsure regarding the appropriate disposition of a study (either at the abstract or full-text stage of review), then the study was flagged for the lead author to screen. Agreement was reached after discussion by the two reviewers.

Table 1. Inclusion and exclusion criteria used in full-text review

Category	Inclusion Criteria	Exclusion Criteria
Patient population	Patients with serious cancers for which treatment is planned to be initiated within 2 months	Patients who do not have cancer or for whom cancer treatment has already been initiated or completed
Type of dental care	Dental examination, targeted dental treatments, and/or patient education on oral hygiene prior to starting cancer treatment	Dental care that occurred only after starting the cancer treatment
Type of cancer treatment	Chemotherapy agents or other medications used to treat malignant bony lesions	Treatment only with radiation therapy or surgery
Outcomes studied	Rates of serious adverse events, quality of life, cancer relapse rates, mortality, or adherence to cancer treatment	Outcomes confined only to dental conditions that do not require urgent intervention (caries, degree of periodontitis) or no outcomes reported (only pre-treatment data reported)
Scope of study	Reports of outcomes for 10 or more patients who received pre-treatment dental care	Case reports, series of fewer than 10 patients, or narrative review articles

To find additional relevant practice guidelines, we conducted a gray literature search using the websites of the American Society of Clinical Oncology, the National Comprehensive Cancer Network, the American Society for Radiation Oncology, the American Cancer Society, the International Society of Oral Oncology, and the Multinational Association of Supportive Care in Cancer. All sites were searched for the following terms: dental, dentistry, oral, teeth, gingivitis, cavities, cavity, and caries. All results of these searches were reviewed at the title/abstract level, and any potentially relevant guidelines were then reviewed at the full-text level by one reviewer.

We scored each included primary research study for its study design, using the categories of randomized controlled trial, prospective cohort, retrospective cohort, or registry-based study. We also recorded whether the statistical analysis had used methods to adjust for confounding, such as matching or propensity score methods. For systematic reviews, we summarized the date ranges of the search, the primary conclusions, and any strength of evidence assessments that were performed.

All reported patient outcomes in the included studies were recorded. We did not perform quantitative meta-analysis of the included primary research studies. Instead, we conducted a narrative synthesis of all included studies for this report.

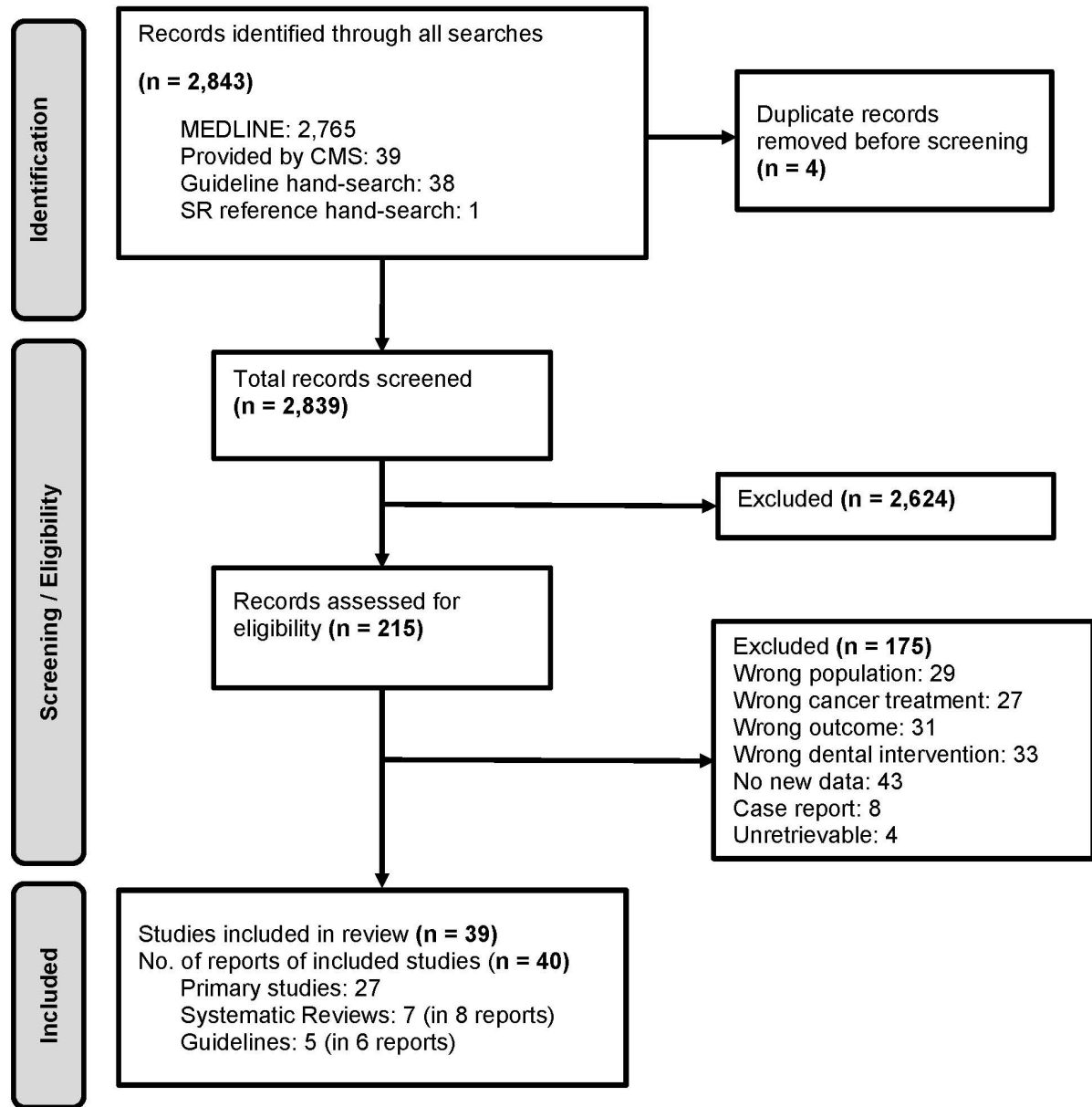
Results

The literature search yielded 2,765 records. After the title and abstract screening, 176 were assigned for full-text review. An additional 39 full-text articles not already found in the literature search were provided by CMS and its partner organizations. From these 215 full-text records, 26^{10, 23, 26, 28-30, 34-53} were judged to be original reports providing evidence relevant to our primary study question. The literature search also yielded seven systematic reviews contained in eight publications.⁵⁴⁻⁶¹ One additional research study was identified through review of the reference lists of the systematic reviews,⁶² yielding a total of 26 included primary studies. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram

of the review process can be found in Figure 2. Table 2 summarizes the research designs, major results, and patient populations of the 27 primary studies. Four of the studies examined the outcome of major infection,^{10, 26, 44, 45} 9 examined the outcome of clinically significant mucositis,^{34-37, 43, 46, 47, 50, 53} 10 examined the outcome of osteonecrosis,^{28-30, 38-42, 52, 62} and 1 examined both mucositis and infection rates.²³ In addition, two examined mortality rates,^{49, 51} and one examined outcomes related to quality of life.⁴⁸ None of the studies evaluated differences in other cancer outcomes (such as relapse rates or adherence to cancer treatment regimens) among patients who received dental care prior to initiating specific treatments for the underlying cancer. Seventeen of the studies had comparison groups; usually the comparison groups were patients who had not undergone a pre-treatment dental evaluation. Three of the studies were randomized controlled trials,³⁴⁻³⁶ 12 were prospective cohort studies,^{10, 23, 30, 39, 40, 43, 45-48, 51, 62} 10 were retrospective cohort studies,^{26, 29, 37, 38, 41, 42, 44, 49, 50, 52} and 2 were cross sectional analyses of nationwide databases.^{28, 53} Four of the studies were conducted in the United States,^{10, 29, 45, 51} 1 was conducted in Canada,²⁶ 16 in Europe,^{23, 30, 34-36, 38-42, 46, 48-50, 52, 62} 2 in India,^{43, 47} 2 in Taiwan,^{28, 53} and 1 each in Brazil³⁷ and Japan.^{44, 28}

The gray literature search identified 38 practice guidelines, of which three guidelines (contained in 4 publications) were relevant (Appendix C).⁶³⁻⁶⁶ Two additional relevant guidelines were identified in the review of full-text records.^{67,68}

Figure 2. PRISMA flow diagram



Abbreviations: CMS=Centers for Medicare & Medicaid Services; MA=meta-analysis; n=number; PRISMA=preferred reporting items for systematic reviews and meta-analyses; SR=systematic review.

Table 2. Table of included studies

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Greenberg, 1982 ¹⁰ United States Funding source not reported	Septicemia	Prospective cohort	25%	78%	33	Acute nonlymphocytic leukemia	Chemotherapy (not further described)	Only patients who developed persistent fever during chemotherapy were enrolled. Blood cultures revealed a lower rate of infections from apparent oral sources in the group that received pre-treatment dental care (p=0.01).
Shimada, 2017 ⁴⁴ Japan National Center for Global Health and Medicine	Dental and systemic infections	Retrospective cohort	3.6%	No control group; all patients received dental care prior to chemotherapy.	75	Hematological malignancies	Chemotherapy (not further described)	This study provides an estimate of the expected rate of dental infections during chemotherapy (following pre-treatment dental care).

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Toljanic, 1999 ⁴⁵ United States Funding source not reported	Dental infections	Prospective cohort	4%	No control group; all patients received dental care prior to chemotherapy.	48	Hematological malignancies and solid tumors	Chemotherapy regimens that induced neutropenia	This study provides an estimate of the expected rate of dental infections during chemotherapy (following pre-treatment dental care).
*Watson, 2020 ²⁶ Canada Funding source not reported	Dental Infections	Retrospective cohort	0.7%	4.2% in concurrent control group; 4.3% in historical control group	641	Acute leukemia	Combination chemotherapy	Dental infections during chemotherapy were lower in the group that received pre-treatment dental care (p=0.05).

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Zecha, 2022 ²³ Netherlands Funding source not reported	Mucositis and febrile neutropenia	Prospective cohort	Febrile neutropenia: 11%. Oral mucositis: 53%	No control group; all patients received dental care prior to chemotherapy.	88	Solid tumors and lymphoma	Myelosuppressive chemotherapy	Patients who received high risk chemotherapy regimens had a higher risk of developing febrile neutropenia ($p = 0.0004$) than patients who received low risk regimens. Patients who developed febrile neutropenia had greater severity of mucositis than patients who did not develop febrile neutropenia ($p=0.005$)
*Borowski, 1994 ³⁴ France Funding source not reported	Mucositis	Randomized controlled trial	85%	93%	150	Leukemias and lymphomas	Bone marrow transplantation	Mucositis incidence did not differ significantly between groups, but pre-transplant dental care reduced its severity over time ($p < 0.01$).

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
da Silva Santos, 2011 ³⁷ Brazil Funding source not reported	Mucositis	Retrospective cohort	Oral mucositis incidence 86%; mean duration of symptoms 10 days	Oral mucositis incidence 97%; mean duration of symptoms 20 days	70	Hematological malignancies	Stem cell transplantation	Mucositis incidence did not differ significantly between groups, but pre-transplant dental care shortened its duration (p<0.001).
Dahllof, 1988 ⁴⁶ Sweden Funding source not reported	Mucositis	Prospective cohort	65%	No control group; all patients received dental care prior to chemotherapy.	49	Acute leukemias or aplastic anemia	Bone marrow transplantation	All patients were under 12 years of age. This study provides an estimate of oral mucositis in children receiving this treatment modality.
Dholam, 2021 ⁴⁷ India Funding source not reported	Mucositis	Prospective cohort	78%	No control group; all patients received dental care prior to chemotherapy.	135	Head and neck cancer	Neoadjuvant chemotherapy (2 or 3 agents)	Mucositis incidence is moderately high in patients receiving this type of chemotherapy.

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Djuric, 2006 ³⁵ Serbia & Montenegro Funding source not reported	Mucositis	Randomized controlled trial	40%	53%	34	Acute leukemia	Multi-agent chemotherapy	Mucositis incidence did not differ between groups, but dental care slightly reduced its severity (not statistically significant either for incidence or severity).

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Huang 2021 ⁵³ Taiwan Taiwan Ministry of Health and Welfare; Tseng-Lien Lin Foundation	Mucositis	Cross sectional analysis comparing patients who did and did not develop osteonecrosis after receiving 5-fluorouracil chemotherapy	5.0%	2.5%	13,969	Head and neck cancer	Chemotherapy regimen using 5-fluorouracil. Seventy two percent of the patients also received concurrent radiotherapy.	Preventive dental care with plaque scaling was associated with a higher risk of developing oral mucositis during chemotherapy: "After adjustment for gender, age, comorbidities, and cancer treatments, patients receiving scaling both within 3 weeks, and from 3 weeks to 6 months, before the index date had a higher risk of OM than those without scaling (OR = 2.25, 95% CI = 1.81–2.81; OR = 1.51, 95% CI = 1.19–1.92, respectively)."

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Jena, 2022 ⁴³ India Funding source not reported	Mucositis	Prospective cohort	10%	No control group; all patients received dental care prior to chemotherapy.	138	Solid tumors	Chemotherapy (not further described)	The mucositis incidence of 10% is a lower rate than in other published studies. The publication does not clarify whether the chemotherapy regimens may have been less intensive than in the other studies having oral mucositis as the clinical outcome.
Radochova, 2021 ⁵⁰ Czech Republic Czech Health Research Council	Mucositis	Retrospective cohort	63%	No control group; all patients received dental care prior to chemotherapy.	496	Acute leukemia, multiple myeloma, or non-Hodgkin lymphoma	Stem cell transplantation	When patients were stratified by presence of periodontitis prior to transplantation, the rate of mucositis did not differ, but the severity was higher in patients with pre-existing periodontitis (p=0.015).

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Ruggiero, 2018 ³⁶ Italy Funding source not reported	Mucositis	Randomized controlled trial	86%	88%	137	Hematological malignancies	Stem cell transplantation	Mucositis incidence did not differ between groups, but pre-transplant dental care slightly reduced its severity (statistical significance not reported).
Bacci, 2021 ³⁸ Italy No external funding	Osteonecrosis	Retrospective cohort	0%	25%	99	Multiple myeloma	Bisphosphonates	The incidence of osteonecrosis in the patients who received dental evaluation and treatment prior to starting bisphosphonates was significantly lower ($p < 0.0001$) than in the patients who did not receive dental care.

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Bonacina, 2011 ³⁰ Italy Funding source not reported	Osteonecrosis	Prospective cohort	0%	11%	282	Solid tumors with bony metastases	Zoledronic acid	The incidence of osteonecrosis in the patients who received dental evaluation and treatment prior to starting ZA was significantly lower ($p < 0.00001$) than in the patients who did not receive dental care prior to starting ZA.
Bramati, 2015 ³⁹ Italy No external funding	Osteonecrosis	Prospective cohort	0%	8.6%	398	Solid tumors with bony metastases	Bisphosphonates	Patients who had dental evaluation and treatment before starting bisphosphonates had a lower incidence of osteonecrosis than patients who did not receive dental care prior to bisphosphonate treatment ($p < 0.0001$).

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Coello-Suanzes, 2018 ⁴⁰ Spain Funding source not reported	Osteonecrosis	Prospective cohort	7%	36%	255	Solid tumors with bony metastases	Zoledronic acid	Patients who received dental evaluation and treatment before starting ZA had a lower incidence of osteonecrosis than patients who did not receive dental care prior to ZA treatment (p=0.06).
Dimopoulos, 2009 ⁴¹ Greece Funding source not reported	Osteonecrosis	Retrospective cohort	6.7%	26%	128	Multiple myeloma	Zoledronic acid	Patients who received dental evaluation and treatment before starting ZA had a lower incidence of osteonecrosis than patients who did not receive dental care prior to ZA treatment (p=0.03).

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Huang, 2020 ²⁸ Taiwan Taiwan Ministry of Health and Welfare; Academia Sinica Taiwan; Tseng-Lien Lin Foundation; Taiwan Brain Disease Foundation; Katsuzo and Kiyo Aoshima Memorial Funds	Osteonecrosis	Cross sectional analysis comparing patients who did and did not develop osteonecrosis after receiving bisphosphonate therapy	2.7% incidence of osteonecrosis in entire cohort	Not applicable	7,394	Oral cancer	Neoadjuvant chemotherapy	Dental extractions performed less than 2 weeks prior to starting radiation therapy were associated with a higher risk of developing osteonecrosis compared with dental extractions performed more than 2 weeks before starting radiation therapy (hazard ratio 1.49; 95% confidence interval 1.01, 2.19). Administration of chemotherapy did not increase the risk in these patients.

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
*Owosho, 2018 ²⁹ United States National Cancer Institute Cancer Center Support Grant	Osteonecrosis	Retrospective cohort	1%	11%	2216	Solid tumors with bony metastases	Bisphosphonates, denosumab, antiangiogenic medications	The rate of osteonecrosis in patients who received dental care before starting one or more medications was significantly lower than in patients who did not have pre-treatment dental care (p<0.00001).
Ripamonti, 2009 ⁴² Italy Funding source not reported	Osteonecrosis	Retrospective cohort	1.3% incidence in patients receiving any bisphosphonate; 1.7% incidence in patients receiving ZA	3.2% incidence in patients receiving any bisphosphonate; 7.8% incidence in patients receiving ZA	966 for entire sample; 322 for sub-group who received ZA	Solid tumors with bony metastases	Bisphosphonates	The differences in rates between groups was not statistically significant either for the entire patient sample or for the sub-group who received ZA.

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Turner, 2016 ⁵² United Kingdom Funding source not reported	Osteonecrosis	Retrospective cohort	0%	20%	45	Solid tumors with bony metastases	Denosumab and/or zoledronic acid	The rate of osteonecrosis in patients who received dental care before starting one or more medications was significantly lower than in patients who did not have pre-treatment dental care (p<0.05).
Vandone, 2012 ⁶² Italy Funding source not reported	Osteonecrosis	Prospective cohort	3.9%	Concurrent control group: 1.2%. Historical control group: 5.5%	411	Solid tumors	Bisphosphonates	Rate of osteonecrosis in the group receiving pre-treatment dental care was higher than in one comparison group but lower than in the other. No differences were statistically significant.

Author, Year Country Funding Source	Outcome	Design	Rate of Outcome in Dental Care Group	Rate of Outcome in Control Group (No Dental Care Immediately Prior to Cancer Treatment)	Total N	Cancer Conditions	Cancer Treatments	Key Findings
Patel, 2022 ⁴⁹ United Kingdom Funding source not reported	Overall survival	Retrospective cohort	37% overall survival (with varying lengths of follow-up)	No control group; all patients received dental care prior to chemotherapy.	492	Solid tumors with bony metastases	Bone targeting agents (not further described)	Due to incomplete reporting and lack of a comparison group, the impact of pre-treatment dental care on patient survival cannot be determined.
Slotman, 1992 ⁵¹ United States Funding source not reported	Overall survival	Prospective cohort	Median survival 45 months; 5-year survival 43%	No control group; all patients received dental care prior to chemotherapy.	53	Head and neck cancer	Neoadjuvant chemotherapy and surgical resection	Due to lack of a comparison group, the impact of pre-treatment dental care on patient survival cannot be determined.
Nunez-Aguilar, 2018 ⁴⁸ Spain Spanish Society of Oral Surgery	Quality of life	Prospective cohort	Trend toward improvement from baseline to 12 months following the baseline assessment	Trend toward lower quality of life between the baseline and 12-month time points	81	Oral cancer	Neoadjuvant chemotherapy	Due to multiple quality of life scales being used and the small sample size, a definitive conclusion cannot be reached.

Abbreviations: CI=confidence interval; OM=oral mucositis; OR=odds ratio; ZA=zoledronic acid. Studies denoted by an asterisk (*) provide the strongest evidence (based on study design and/or sample size) for the effect of pre-treatment dental care on each of the three main outcomes.

Serious Infection

Five studies examined major infections during courses of intensive chemotherapy (Table 2). The largest was a retrospective cohort study that reported on 641 patients hospitalized for induction chemotherapy to treat newly diagnosed acute myelogenous leukemia (AML).²⁶ A total of 147 of these patients underwent a dental screening and treatment program prior to starting the chemotherapy. The dental care included a thorough visual examination of the teeth and gums, with local treatment of observed infections (usually tooth extractions). The study included two comparison groups of AML patients who did not receive dental evaluations prior to starting chemotherapy. The first was comprised of 190 patients treated in the same time period, and the second was comprised of 304 patients admitted for induction chemotherapy in the 26 prior months (before the hospital had initiated the dental screening program). Serious dental infections during chemotherapy occurred in slightly more than 4% of the patients in both control groups and in fewer than 1% of the patients in the group that received dental screening ($p < 0.05$ for comparisons to each of the control groups). Six of the patients in the screened group were found to have localized infections that were treated prior to starting chemotherapy. This study did not provide information about the rates of any other types of infection, such as bacteremia or septicemia. No statistical methods were used to adjust for differences in patient characteristics among the groups, but the use of two different control groups added some protection against confounding.

A prospective cohort study published in 1982 examined rates of sepsis among adults who were hospitalized for chemotherapy to treat acute leukemia.¹⁰ Patients were enrolled in the cohort if they developed persistent fever during the hospitalization. The study used an interrupted time series design, with a pre-treatment dental care program (visual examination, radiographs, and treatment of any local sources of infection) implemented after the first nine patients had been enrolled in the cohort. The rate of documented sepsis in these febrile patients was high: 25% in the patients who received dental care prior to starting chemotherapy, compared to a rate of 78% among patients enrolled prior to implementation of the dental care program ($p = 0.01$ for the comparison between groups). The design of this small study has limitations, but the results support the contention that the dental care program reduced the occurrence of sepsis from oral bacteria.

Three uncontrolled studies reported on infection occurrence in cohorts (2 prospective and 1 retrospective) of patients who received dental screenings prior to undergoing chemotherapy.^{23, 44, 45} These studies provide additional context to the studies that included comparison groups.^{10, 26} Two of these patient series examined serious dental infections during chemotherapy, and the infection rates were 4% in each.^{44, 45} The third study examined incidence of febrile neutropenia in patients treated with chemotherapy for solid tumors and lymphoma.²³ It found the incidence of febrile neutropenia to be 12% in the patients who had received dental screenings. This study also provided a classification of the intensity of the chemotherapy regimens administered to the patients, designated as either “high risk” or “low risk.” The classification system is reproduced in Appendix B.²³ Among 34 patients who received high risk chemotherapy, febrile neutropenia occurred in 9 (26%). Among 54 patients who received low risk chemotherapy, febrile neutropenia occurred in only 1 (1.9%). This difference between groups is statistically significant ($p = 0.0004$). While this study does not demonstrate whether pre-treatment dental care provided protection against febrile neutropenia, it does provide insight into the rates of this outcome in different patient subgroups.

Oral Mucositis

Of the 10 studies that examined the occurrence and severity of oral mucositis as the main outcome, 3 were randomized controlled trials (RCTs), 2 had a retrospective cohort design, 4 had a prospective cohort design, and 1 was a cross-sectional analysis of a nationwide database. The three RCTs³⁴⁻³⁶ were conducted in European countries and ranged in size from 37 to 150 total participants. The participants in these trials were patients with hematological malignancies treated with induction chemotherapy, bone marrow transplantation, or stem cell transplantation. All studies examined a pre-treatment regimen consisting of dental examination, plaque removal, and patient instruction on daily oral hygiene. Participants were randomized into groups either receiving the dental care regimen or not receiving it. The most recent RCT³⁶ also used a factorial design in which patients were re-randomized to receive either a local treatment for mucositis or a daily antiseptic mouth rinse. As shown in Table 2, none of the RCTs found that pre-treatment dental care significantly reduced the incidence of mucositis when measured at about 14 days after initiation of chemotherapy. The incidence of mucositis across the three trials ranged between 40 and 86% in the study arms that received pre-treatment dental care and between 53 and 93% in the study arms that did not receive pre-treatment dental care. The trials also measured severity of the symptoms of mucositis over time. In all the trials there was a trend toward lower severity in the groups who received baseline dental care. This was statistically significant ($p < 0.01$) in one trial,³⁴ non-significant in one,³⁵ and not analyzed in one³⁶ (Table 3).

Table 3. Severity of mucositis reported in randomized controlled trials

Author, Year Country	N Participants	Comparison of Mucositis Severity Between Study Arms That Did or Did Not Receive Dental Care Prior to Starting Chemotherapy
Borowski, 1994 ³⁴ France	150	Daily measurements of mucositis severity during period of immunosuppression. Rates of moderate or severe mucositis were slightly lower in the Dental Evaluation group in each day of follow-up ($p < 0.01$)
Djuric, 2006 ³⁵ Serbia & Montenegro	34	Weekly measurements of mucositis severity. Severity was consistently lower in group randomized to pre-treatment dental care, but this was not statistically significant.
Ruggiero, 2018 ³⁶ Italy	137	Daily measurements of mucositis severity, but these results were reported only as average scores. Scores trended lower in the patients randomized to dental care prior to the immunosuppressive treatment, but no statistical analyses were reported.

A retrospective cohort study examining mucositis as the clinical outcome reported on 70 patients hospitalized for stem cell transplantation.³⁷ Thirty-five were treated at a single hospital that provided pre-treatment dental evaluation and treatment, but these patients did not receive training on daily dental hygiene. The comparison group of 35 patients received care at a second hospital that did not provide pre-treatment dental evaluations or dental hygiene training. In addition, the chemotherapy regimens used in the two hospitals differed somewhat. The study results were similar to those found in the three RCTs. Patients had a high incidence of mucositis (greater than 85%) at both hospitals (without significant difference in the rates), but the duration of symptoms attributable to mucositis was significantly ($p < 0.001$) shorter at the hospital that provided pre-treatment dental care.

A cross-sectional study based on a nationwide database in Taiwan⁵³ examined the incidence of oral mucositis among patients with head and neck cancer who received a chemotherapy regimen

containing 5-fluorouracil. The study excluded any patients who had signs of mucositis in prior rounds of chemotherapy, which might explain the study's low overall incidence of mucositis (3.5%). The study stratified patients by whether they had received plaque scaling in the 6 months prior to receiving chemotherapy and also classified the timing of the plaque scaling (within 3 weeks prior to chemotherapy versus between 3 weeks and 6 months prior to chemotherapy). Plaque scaling was associated with significantly ($p < 0.001$) higher rates of mucositis in both crude analyses and analyses adjusted for patient characteristics. The highest incidence of mucositis (5.9%) occurred in the patients who underwent plaque scaling within 3 weeks prior to receiving chemotherapy, but patients who had a longer time interval between the dental treatment and receiving chemotherapy also had an increased mucositis incidence. These results suggest that pre-treatment dental care can adversely influence the incidence of mucositis after chemotherapy.

Four prospective cohort studies and one retrospective cohort study were case series that did not include comparison groups. The rates of mucositis in these studies ranged from 10% to 78% (Table 2).

The variation in mucositis incidence may have been due to the intensity of the chemotherapy regimens that the patients received. One study²³ classified the patients by the intensity of the chemotherapy used (Appendix B). The incidence of mucositis was 76% in patients receiving chemotherapy regimens classified as high-risk and 39% in patients receiving low-risk regimens. This difference was reported to be statistically significant ($p = 0.001$). This study also found that, when comparing patients who did and did not develop febrile neutropenia, the patients with febrile neutropenia had both higher incidence and greater severity of oral mucositis ($p = 0.005$).

Osteonecrosis

Nine cohort studies have reported data on the incidence of osteonecrosis in patient groups that did and did not receive dental care prior to initiating treatment for malignant bony lesions (Table 2). The participants in these studies all had metastatic solid cancers or multiple myeloma and were treated with bisphosphonates, denosumab, bevacizumab, or ipilimumab. Four studies used a prospective cohort design; five used a retrospective cohort design. All of the studies found that the incidence of osteonecrosis was lower in patients who received pretreatment dental care.

The four prospective cohort studies had total sample sizes ranging from 255 to 411.^{30, 39, 40, 62} The study participants were consecutively enrolled when they presented for care at the participating dental clinics and were stratified by whether bisphosphonate therapy had begun prior to that time. If there had been no prior bisphosphonate therapy, the patients were placed in the group that received pre-treatment dental care. Otherwise, they were placed in the comparison group. All patients in both groups received (or continued to receive) bisphosphonate therapy. In one study³⁹ the comparison group was a historical cohort of patients who had not received pre-treatment dental care. Another study included both contemporaneous and historical (assembled retrospectively) control groups.⁶² For patients who had not yet begun therapy, the dental care consisted of oral examination, plaque removal, treatment of diseased teeth, and teaching on oral hygiene. Duration of follow-up was at least 18 months. None of the four studies used statistical methods to adjust for confounding between groups. In two of the studies the incidence of osteonecrosis was significantly lower ($p < 0.0001$) in the group that received pre-treatment dental care.^{30, 39} In both studies, the incidence of osteonecrosis at 18 months in the groups receiving pre-treatment dental care was 0. The other two prospective cohort studies^{40, 62} identified cases of osteonecrosis in patients who received pre-treatment dental care and also in patients who did not. The differences among groups did not reach statistical significance ($p < 0.05$) in either of these studies.

Five studies having retrospective cohort designs examined osteonecrosis incidence in patients with multiple myeloma or metastatic solid cancers. The largest of these had a sample size of 2216 patients who were followed at a single cancer center in the United States.²⁹ Pre-treatment dental evaluation was conducted in 872 of these patients. The dental care regimen included a full examination, treatment of diseased teeth, and education on dental hygiene. The follow-up period was relatively short (about 1 year). Osteonecrosis occurred in 1% of the patients who had pre-treatment dental care and in 10.5% of patients who did not have pre-treatment dental care, which was highly significant ($p < 0.00001$). No statistical adjustments for confounding were performed.

The other four studies having retrospective cohort designs had smaller sample sizes, with the number of patients who received pre-treatment dental care ranging from 35 to 154.^{38, 41, 42, 52} The pre-treatment dental regimens included complete examinations, plaque removal, and treatment of diseased teeth. The mean duration of follow-up ranged from 11 to 24 months. All four studies found a reduced incidence of osteonecrosis when the patients received pre-treatment dental care. The incidence of osteonecrosis was 0 to 6.7% in the patients receiving pre-treatment dental care and 3.2% to 26.3% in the groups not receiving pre-treatment dental care. The differences between groups reached statistical significance in three of the studies^{38, 41} but not in the fourth.^{42, 52}

A retrospective cross-sectional study evaluated patients diagnosed with oral cancer, most of whom received neoadjuvant chemotherapy.²⁸ This study differs from the other studies examining osteonecrosis incidence, in that patients did not receive bisphosphonates or other drugs that target bone tissue. However, the patients did receive targeted radiation therapy to the jaw and mouth. The study included data on 7394 patients who were enrolled in a national clinical database, of whom 198 (2.7%) developed osteonecrosis. The data included detailed information about the types and timing of dental treatments received by the patients. The overall incidence of osteonecrosis was 2.7%, and all patients had at least 4 years of follow-up. Comparisons were made between patients with and without osteonecrosis, after adjustments for various clinical covariates. It was found that the osteonecrosis patients had significantly higher adjusted rates of major dental treatments (tooth extractions and periodontal treatments) less than 1 month before the start of radiation therapy. When examining rates of these procedures in the period of 1–3 months prior to radiation therapy, there were no significant differences between the patients who developed osteonecrosis and those who did not.

Other Cancer-Related Outcomes

Three additional published studies were identified in the MEDLINE search. Two reported overall survival among patients who had received dental care prior to initiating cancer treatment,^{49, 51} and one evaluated patient reports of quality of life.⁴⁸ No studies were identified that evaluated other outcomes, such as adherence to cancer treatments.

Both studies examining overall survival were case series that did not include comparison groups of patients who had not received pre-treatment dental care. One reported on patients receiving bone-targeting agents for bony metastases,⁴⁹ and the other reported on patients receiving neoadjuvant chemotherapy for head and neck cancer.⁵¹ Survival was modest in both studies, reflecting the severity of the underlying cancer conditions. Because of the lack of comparison groups, no conclusion can be drawn about the importance of pre-treatment dental care for prolonging survival.

The study examining use of a quality of life (QOL) measure reported on 81 patients scheduled to receive neoadjuvant chemotherapy for oral cancer.⁴⁸ Half of the patients received dental evaluation and treatment prior to starting the chemotherapy. The QOL instrument was administered before, during, and after the course of chemotherapy. The patients who received dental care showed a general trend toward

greater improvement of scores compared to the group that did not receive dental care. This study was limited by the small sample size and multiple QOL scales that were administered (with a risk of spurious associations).

Practice Guidelines

Our searches identified five practice guidelines that provide recommendations on the provision of dental care prior to initiation of cancer treatments (Appendix B). The cancer treatments addressed in the guidelines include hematopoietic stem cell transplantation (HSCT), multi-agent chemotherapeutic regimens, treatments for head and neck cancer, and medications directed at bony metastases.^{63-67,68} Two guidelines in three publications were produced for the Multinational Association of Supportive Care in Cancer (MASCC) and the International Society of Oral Oncology (ISOO) collaboration.⁶⁴⁻⁶⁶ A third guideline was produced for a collaboration between MASCC/ISOO and the American Society of Clinical Oncology (ASCO).⁶³ Topics for these clinical practice guidelines were the management of mucositis secondary to cancer therapy, prevention and management of medication-related osteonecrosis of the jaw (MRONJ), and basic oral care for hematology-oncology patients and HSCT recipients. The American Academy of Pediatric Dentistry has disseminated a guideline on dental care for children undergoing immunosuppressive chemotherapy or radiation therapy to the head and neck.⁶⁸ Seven specialty associations involved in the care of head and neck cancer patients in the United Kingdom also published a guideline for dental evaluation and treatment before and after treatments for head and neck cancer.⁶⁷ The guideline ([5th edition of the UK Multi-Disciplinary Guidelines for Head and Neck Cancer](#)) is based on guidance from the National Institute for Health and Care Excellence (NICE) and expert recommendations.⁶⁷

These guidelines vary in complexity and breadth, but they consistently advocate for a thorough dental evaluation prior to commencing intensive cancer therapies. The stated goals of recommended evaluation and treatment are to educate patients on adherence to good oral hygiene protocols during treatment,⁶³⁻⁶⁸ to balance the composition of bacterial species in the oral microbiome,⁶⁶ to prevent serious post-treatment sequelae such as MRONJ,^{63, 67} to eradicate potential sources of infection,^{64, 68} and to lessen toxicity and ease symptoms of oral mucositis.^{65, 66, 68}

The MASCC/ISOO/ASCO and American Academy of Pediatric Dentistry guideline documents include reviews of the published literature.^{63-66, 68} However, upon review of the literature, each guideline group determined that the evidence base was insufficient to create guidance solely on published studies. The guideline developers thereby convened expert panels to develop consensus-based recommendations. Among these five guidelines, the strongest claim for evidence backing the guideline recommendations were for MRONJ prevention.⁶³

Systematic Reviews

The literature search also identified seven previously published systematic reviews related to cancer patients who may require medically necessary dental services. The systematic reviews were published between 2010 and 2022. Of these, two were conducted in the United States,^{58, 61} one in Spain,⁵⁵ one in Brazil,^{59, 60} and one in the United Kingdom.⁵⁴ The remaining two were conducted by multi-national collaborations.^{56, 57} The two multi-national reviews represent an original review followed by an update of that review 8 years later.^{56, 57} Some systematic reviews focused primarily on a particular type of cancer such as hematological⁵⁴ or head and neck cancers,^{59, 60} while others focused on specific complications such as medication-related osteonecrosis of the jaw.^{58, 61} Others were more broadly

focused on general protocols for medically necessary dental treatments for multiple types of malignancies.⁵⁵⁻⁵⁷ These systematic reviews consistently cited a shortage of high-quality evidence and the lack of consistent clinical guidance for confidently defining medically necessary dental protocols prior to beginning cancer treatments. One of the reviews⁵⁵ had a scope similar to this Rapid Response but did not include publications from the last 10 years. A review published in 2018⁵⁸ focused on prevention of medication-related osteonecrosis. Its search yielded six included studies. One was a prospective cohort study not identified in our literature search.⁶² That study was added to our Rapid Response and is described above. Two additional studies^{69, 70} were not identified in our search but addressed other types of intervention than dental care prior to starting bisphosphonate therapy.

A recent review^{59, 60} focused on the timing of pre-treatment dental care and concluded that there is limited evidence supporting the recommendation that cancer treatment be delayed at least 2 weeks after dental procedures. Another recent review⁵⁴ sought to assess the evidence-based components of pre-treatment dental management. It found a lack of consistency across studies in the individual components of this management. Two other systematic reviews focused on rates of dental problems in cancer patients.^{56, 57} The earlier review⁵⁶ assessed rates of caries and other tooth lesions (not addressed in this Rapid Response), while the second review⁵⁷ assessed rates of dental infections. The synthesis found that the infection rates during treatment ranged from 0 to 4%, which aligns with the findings of this Rapid Response (Table 2).

One systematic review searched for reports on the costs of care for oral mucositis and osteonecrosis.⁶¹ This review found that mucositis costs had been reported in 16 publications, while the costs for bisphosphonate-associated osteonecrosis had been reported in only 1. However, eight additional publications reported on costs for osteonecrosis attributed to radiation therapy. The reported costs varied widely but generally supported the conclusion that these adverse events meaningfully contribute to higher costs of care. For mucositis, it is estimated that it also generally lengthens inpatient stays, resulting in higher costs.



Discussion

To prepare this Rapid Response, a thorough search of the MEDLINE database compiled all relevant published studies through the end of 2022. The evidence base includes 27 primary studies that vary considerably in their sample sizes, study designs, and methodological rigor. The patient data included in these studies are drawn from a well-defined group of cancer conditions. Most participants included in the studies had severe life-threatening types of cancer for which short-term aggressive therapy was planned. The cancer conditions included acute leukemias, clinically advanced multiple myeloma, solid tumors with bony metastases, head and neck cancers, and a limited number of other conditions for which multi-agent chemotherapy, bone marrow transplantation, or stem-cell transplantation was planned. The chemotherapy regimens administered to these patients had meaningful impacts on the integrity of the oral mucosa and (in some cases) the integrity of bony tissue. Most of the studies used observational study designs, and many did not employ methods to adjust for sources of confounding between the patient groups that were compared. The studies focused on rates of side effects of the cancer treatments over short and medium timeframes. Few studies examined cancer control outcomes, such as cancer-free or overall survival. Nevertheless, while it may be unlikely that a single episode of dental care has an effect on long-term control of the underlying cancer, reducing the rate of side effects potentially can improve morbidity, quality of life, and total cost of care.

The strongest body of evidence is the set of studies examining the effects of pre-treatment dental care on the rates of osteonecrosis among patients who will undergo cancer treatments that target bony tissue (summarized in Table 2). Agents that are effective for suppressing bony lesions due to multiple myeloma or metastatic disease include RANK ligand inhibitors, antiangiogenic agents, and high-dose bisphosphonates. The rationale for providing pre-treatment dental care to patients who will undergo such treatments is that this care may reduce the need to undergo tooth extractions after initiating the treatment and thereby possibly triggering osteonecrosis.⁷¹ While the evidence base on osteonecrosis prevention does not include RCTs, it does include cohort studies compiled from the experiences of cancer centers in the United States, Europe, and Japan, with a total sample size of more than 12,000 cancer patients. Of the nine studies that directly compared groups who did and did not receive dental care prior to initiation of the cancer treatment regimens, all showed trends of lower osteonecrosis rates in the groups that had received dental care (statistically significant in all studies but 2^{42, 62}). The rates of osteonecrosis were consistently 7% or lower in the groups receiving pre-treatment dental care and trended higher (sometimes much higher) in the groups that had not received dental care. The largest study was conducted at a U.S. cancer center²⁹ and found a highly significant reduction in the osteonecrosis rate following pre-treatment dental care.

Cancer patients who undergo multi-agent chemotherapy have a high risk of neutropenia in the first few weeks and immunological suppression that can last as long as a year.¹⁶ Impaired immunity increases the risk of serious infections that can lead to prolonged hospitalizations and patient morbidity.¹⁷ Two comparative studies have examined the impact of pre-treatment dental care on the rate of serious infections, and both showed a significantly lower infection rate in the patients who had received pre-treatment dental care.^{10, 26} The premise that dental care will reduce the incidence of subsequent serious infection is based on a compelling biological model, and retrospective analyses of cancer patients treated with thoracic surgeries have also shown that patients who received pre-surgical dental care had lower incidence of postoperative pneumonia.^{72, 73} While additional studies examining this issue would be valuable, the present evidence base does support the provision of dental care prior to intensive chemotherapy regimens for the purpose of preventing infection.

The five comparative studies that addressed the effect of pre-treatment dental care on the occurrence of mucositis did not demonstrate that dental care lowers the actual incidence of mucositis (as shown by the reported rates in Table 2). These findings are not surprising, in that the primary cause of mucositis is oral mucosal damage aggravated by the direct effect of chemotherapy agents on the mucosa. Instead, the potential benefit of dental care is that it may reduce the severity and duration of mucositis (statistically significant in 1 cohort study³⁷ and 1 of 3 RCTs³⁴). Prior research has suggested that bacterial load in the mouth aggravates chemotherapy-induced mucositis.⁷⁴ Plaque removal by dental professionals can modify the oral mucosa, potentially reducing the severity of mucositis,²⁵ although one study using a large national database⁵³ found that plaque removal also can lead to a small increased incidence of mucositis. It is thereby possible (supported by a small body of evidence) that dental care (including daily dental hygiene) optimizes the bacterial load and, in turn, facilitates healing of the damaged oral mucosa. Mucositis most often occurs with high-intensity chemotherapy regimens (such as induction treatment for acute leukemias and conditioning regimens for stem cell transplantation). This is the same population for which pre-treatment dental care may be useful to prevent serious infections, so a beneficial effect on the severity of mucositis provides an additional justification for the provision of dental care in such patient groups.

Eleven U.S. and international professional societies have endorsed clinical practice guidelines that recommend dental evaluation, treatment of diseased dental structures, and patient education prior to the initiation of specified cancer treatments for adults and children (Appendix C). These guidelines

were developed through the consensus of experts and are based on much of the evidence summarized in this Rapid Response document. As shown in Appendix C, the guidelines are consistent in the types of recommended practices and the stated justifications for those practices. It is a reasonable inference that these guidelines represent the generally accepted current standard of care.

The underlying causal model that provides the rationale for pre-treatment dental care is that improved oral health can mitigate the direct toxic effects of the chemotherapy agents used in cancer treatment (Figure 1). The individual studies included in this Rapid Response usually included only patients with a limited number of cancer types, but the range of cancer conditions across all the studies is fairly broad. The chemotherapy regimens examined in the studies are well established and can be used for a wide range of cancer conditions. Therefore, the findings of many of the included studies could be generalized to patients who have other types of cancer treated with high-intensity chemotherapy. However, some newer cancer treatments, such as targeted therapies or CAR T-cell therapy, have not been evaluated in the studies of pre-treatment dental care.

There are limitations to the present evidence base. A recently published meta-analysis based on five published case series found that patients who had regular dental visits before, during, and after treatment for head and neck cancer had better overall survival compared with patients who had few dental visits.⁷⁵ However, individual studies that evaluated oral health habits (tooth brushing and flossing) have not shown that regular dental hygiene improved cancer outcomes.^{76, 77} Few studies have specifically examined whether dental care within 1 month of beginning cancer treatment has a favorable effect on outcomes such as survival and quality of life. The studies that have addressed these outcomes have serious methodological limitations (Table 2). In addition, the influence of dental care on other aspects of cancer management (such as adherence to treatment regimens) has not been studied.

Pre-treatment dental care potentially can influence the costs of cancer care. As shown in Table 3, some studies have found that pre-treatment dental care reduced the severity of oral mucositis. Both a systematic review and a more recent individual study concluded that mucositis lengthens hospital stays and increases overall costs for both adults⁶¹ and children.⁷⁸ A beneficial effect of dental care potentially can lower the impact of mucositis on costs and the length of inpatient stays.

It is standard practice to delay beginning bisphosphonates or other agents that act directly on bones after a patient undergoes invasive dental treatment. A published systematic review examined the evidence for the optimal duration of this delay.^{59, 60} That review cited two studies, one of which examined patients who received only radiation therapy. The other study was included in this Rapid Response.²⁸ The conclusion of that review was that the cancer treatment should be delayed for at least 2 weeks, which is consistent with the published evidence. This evidence comes only from patients with head and neck cancer treated with radiation therapy and chemotherapy. Timing of the treatment delay was not addressed in the cohort studies of patients with multiple myeloma or bony metastases. In another study of mucositis incidence in head and neck cancer patients receiving chemotherapy, delaying chemotherapy until 3 weeks or longer after plaque scaling was associated with a lower incidence of oral mucositis.⁵³ Another study evaluating patients with hematologic malignancies found that the time interval of initiating chemotherapy after a tooth extraction had a significant impact on the incidence of a dental complication (delayed socket healing) that potentially increases risk of infection.⁷⁹ These studies support the contention that chemotherapy regimens or treatment with agents active on bone should be delayed for approximately 2–3 weeks after tooth extractions or other dental treatments.

All of the studies used a fairly broad range of dental services as part of the pre-treatment dental programs. Most used a combination of thorough examinations, immediate treatment of serious abnormalities, and patient education. It is not possible to determine which of the components of the dental programs had greater or lesser impact. A systematic review⁵⁴ noted the lack of consistency across

studies in the specific components of patient evaluation and dental treatment. Among the 26 primary studies in this review, the completeness of descriptions of the dental care programs varied considerably. However, the regimens generally included physical examinations by a dentist, plaque removal, other treatments that were targeted at local foci of infection, and training of patients on daily dental hygiene. Overly aggressive dental procedures (particularly tooth extractions) can be problematic. Patients identify extractions as having substantial negative impact on quality of life,⁸⁰ and poorly healing tooth sockets can increase the risk of osteonecrosis.²⁸

It is unlikely that this literature search failed to identify other relevant studies or sources of information. Most of the research on dental care performed prior to cancer treatment has been conducted outside of the United States, and the number of new studies each year has been small. Based on these past patterns, it is unlikely that the evidence base will change substantially over the next 2-3 years.

This Rapid Response has addressed a set of adverse outcomes whose incidence or severity potentially can be reduced by an episode of pre-treatment dental care. While the current evidence base has limitations, it does provide guidance on when dental care may be beneficial in the care of people with certain types of cancer. The linkages between dental care and the medical treatments for cancer (and the benefits of linking such care) are summarized in Appendix D. Essential to these linkages is communication and coordination between dental providers and the oncology treatment teams. While there may be barriers to such coordination, such obstacles can be overcome.



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This Rapid Response was prepared by the AHRQ Evidence-based Practice Center (EPC) Program using streamlined literature review methods to assist end-users in making specific decisions in a limited timeframe. To shorten timelines, reviewers made strategic choices about which processes to abridge compared to a comprehensive systematic review. The adaptations made for expediency may limit the certainty and generalizability of the findings from the review.

None of the investigators have any affiliations or financial involvement that conflicts with the material presented in this report.

The information in this report is intended to help healthcare decision makers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of healthcare services. This report is not intended to be a substitute for the application of clinical judgment. Anyone who makes decisions concerning the provision of clinical care should consider this report in the same way as any medical reference and in conjunction with all other pertinent information, i.e., in the context of available resources and circumstances presented by individual patients.

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Afterword

Recognized for excellence in conducting comprehensive systematic reviews, the Agency for Healthcare Research and Quality (AHRQ) Evidence-based Practice Center (EPC) Program is developing a range of rapid evidence products to assist end-users in making specific decisions in a limited timeframe.

To shorten timelines, reviewers make strategic choices about which review processes to abridge. However, the adaptations made for expediency may limit the certainty and generalizability of the findings from the review, particularly in areas with a large literature base. Transparent reporting of the methods used and the resulting limitations of the evidence synthesis are extremely important.

AHRQ expects that these rapid evidence products will be helpful to health plans, providers, purchasers, government programs, and the healthcare system as a whole. Transparency and stakeholder input are essential to the Effective Health Care Program.

If you have comments on this report, they may be sent by mail to the Task Order Officer named below at: Agency for Healthcare Research and Quality, 5600 Fishers Lane, Rockville, MD 20857, or by email to epc@ahrq.hhs.gov.

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Appendix A. MEDLINE Search Strategy

Ovid MEDLINE ALL 1946 to December 15, 2022

Date searched: December 16, 2022

1 Bone Marrow Transplantation/ or exp Immunosuppression Therapy/ or exp Neoplasms/ or exp Radiotherapy/ or exp Stem Cell Transplantation/ or exp Vasculitis/ or (chemotherapy or radiation or radiotherapy).hw. (4216009)

2 (((marrow or cell) adj transplant*) or cancer* or carcinom* or chemo* or haematopoi* or hematopoi* or HSCT or immunosuppress* or irradiat* or leukemia* or lymphom* or malig* or neoplas* or onco* or radiat* or radiotherap* or "radio-therap*" or tumor* or tumour* or vasculitis).ti,ab. (5002402)

3 or/1-2 (6077617)

4 ((caries or cavity or cavities or extracted or extraction\$1 or gingivitis or ((dental or oral) and (assess* or care or consult* or evaluat* or foci or health* or infect* or inflam* or manag* or screen* or treat*)) or integrat* or molar or odont* or periodont* or pulpitis or "root canal" or stomatitis or teeth or tooth*) and (advance or ahead or before or early or initial* or "medically necessary" or prechemo* or "pre-chemo" or prehabilitation or prehaematopoi* or prehematopoi* or "pre-haematopoi*" or "pre-hematopoi*" or preirradiat* or "pre-irradiat*" or preliminary or preonco* or "pre-onco*" or preoperat* or "pre-operat*" or preparat* or "pre-RT" or preradiat* or "pre-radiat*" or preradio* or "pre-radio*" or prestem or "pre-stem" or presurg* or "pre-surg*" or pretherap* or "pre-therap*" or pretransplant* or "pre-transplant*" or prior or prophyl* or time* or timing or undergoing)).ti. (23276)

5 (dental adj2 (caries or cavity or cavities or extracted or extraction\$1 or gingivitis or integrat* or molar or odont* or periodont* or pulpitis or "root canal" or scaling or stomatitis or teeth or tooth* or assess* or care or consult* or evaluat* or foci or health* or infect* or inflam* or manag* or screen* or treat*) adj3 (advance or ahead or before or early or initial* or "medically necessary" or prechemo* or "pre-chemo" or prehabilitation or prehaematopoi* or prehematopoi* or "pre-haematopoi*" or "pre-hematopoi*" or preirradiat* or "pre-irradiat*" or preliminary or preonco* or "pre-onco*" or preoperat* or "pre-operat*" or preparat* or "pre-RT" or preradiat* or "pre-radiat*" or preradio* or "pre-radio*" or prestem or "pre-stem" or presurg* or "pre-surg*" or pretherap* or "pre-therap*" or pretransplant* or "pre-transplant*" pretreat* or "pre-treat*" or prior or prophyl* or time* or timing or undergoing)).ab. (2495)

6 or/4-5 (25388)

7 and/3,6 (3428)

8 7 not ((exp Animals/ not Humans/) or (animal model* or bitch\$2 or bovine or canine or capra or cat or cats or cattle or cow\$1 or dog\$1 or equine or ewe\$1 or feline or goat\$1 or hamster\$1 or horse\$1 or invertebrate\$1 or macaque\$1 or mare\$1 or mice or monkey\$1 or mouse or murine or nonhuman or non-human or ovine or pig or pigs or porcine or primate\$1 or rabbit\$1 or rat\$1 or rattus or rhesus or rodent* or sheep or simian or sow\$1 or vertebrate\$1 or zebrafish or palliative).ti.) (3122)

9 limit 8 to english language (2816)

10 remove duplicates from 9 (2807)

11 10 not (comment or editorial or news).pt. (2721)

12 (meta-analysis or "systematic review").pt. or (meta-anal* or metaanal* or ((evidence or review or scoping or systematic or umbrella) adj3 (review or synthesis))).ti. (789366)

13 and/11-12 (123)

14 (controlled clinical trial or randomized controlled trial).pt. or (control* or placebo\$1 or random* or trial*).ti. (1389803)

15 and/11,14 (255)

16 15 not 13 (244)

17 Case-Control Studies/ or Cohort Studies/ or Comparative Study/ or Controlled Before-After Studies/ or Cross-Sectional Studies/ or Epidemiologic Studies/ or exp Evaluation Studies as Topic/ or Follow-Up Studies/ or Historically Controlled Study/ or Interrupted Time Series Analysis/ or Longitudinal Studies/ or Prospective Studies/ or Retrospective Studies/ or ("case-control" or cohort\$1 or "before-after" or ((comparative or epidemiologic or evaluation) adj3 study) or cross-sectional or follow-up or (historic* adj4 control*) or "interrupted time" or longitudinal\$2 or prospective\$2 or retrospective\$2).ti,ab,kf. (6856231)

18 and/11,17 (1339)

19 18 not (13 or 15) (1127)

20 11 not (13 or 16 or 19) (1227)

Appendix B. Chemotherapy Regimens and Potential Myelotoxicity

Table B-1. Classification of chemotherapy regimens by potential for myelotoxicity^a

High Risk of Myelotoxicity	Low Risk of Myelotoxicity
5FU 400mg/m ² + continuously 2400mg/m ² for 46h, Oxaliplatin 85mg/m ² , Irinotecan 180mg/m ² , Leucovorin 400mg/m ²	Bevacizumab 10mg/kg, Doxorubicin 40mg/m ²
Bleomycin 30USP, Cisplatin 20mg/m ² , Etoposide 100mg/m ²	Bevacizumab 15mg/kg, Carboplatin AUC 4, Gemcitabin 1000mg/m ²
Bleomycin 10 USP, Dacarbazin 375mg/m ² , Doxorubicin 25mg/m ² , Vinblastin 6mg/m ²	Bevacizumab 15mg/kg, Cisplatin 50mg/m ² , Paclitaxel 175mg/m ²
Capecitabin 1000mg/m ² , Epirubicin 50mg/m ² , Oxaliplatin 130mg/m ²	Capecitabin 1000mg/m ² , Oxaliplatin 65mg/m ² , NAB-Paclitaxel 80mg/m ²
Cisplatin 20mg/m ² , Etoposide 100mg/m ²	Capecitabin 1000 mg/m ² , Oxaliplatin 130mg/m ²
Cisplatin 60mg/m ² , Doxorubicin 37,5mg/m ² , MTX 12g/m ²	Capecitabin 750mg/m ² , Oxaliplatin 130mg/m ²
Cisplatin 80mg/m ² , Etoposide 100mg/m ²	Carbazitaxel 25mg/m ² , Prednison 5mg 2dd
Cisplatin 80mg/m ² , Dactinomycin 2mg, Doxorubicin 30mg/m ²	Carboplatin AUC 2, Paclitaxel 50mg/m ²
Cyclophosphamide 300mg/m ² , Prednison 40mg/m ² , MTX intrathecal, Vincristin 2mg	Carboplatin AUC 4, Gemcitabin 1000mg/m ²
Cyclophosphamide 600mg/2, Docetaxel 75 mg/m ²	Carboplatin AUC5, liposomaal doxorubicin 30mg/m ²
Cyclophosphamide 600mg/m ² , Doxorubicin 60mg/m ² , Paclitaxel 80mg/m ²	Carboplatin AUC 6, Paclitaxel 175 mg/m ²
Cyclophosphamide 600mg/m ² , Dactinomycin 0,5mg, Etoposide 100mg/m ² , MTX 300mg/m ² , Vincristin 0,8mg/m ²	Carboplatin AUC2, Paclitaxel 50mg/m ²
Cyclophosphamide 750mg/m ² , Doxorubicin 50mg/m ² , MTX high dose, Rituximab 375mg/m ² , Vincristin 2mg	Carboplatin + Paclitaxel + Trastuzumab + Pertuzumab
Cyclophosphamide 750mg/m ² , Doxorubicin 50mg/m ² , Prednison, Rituximab 375mg/m ² , Vincristine 2mg	Cisplatin 40mg/m ²
Dactinomycin 2mg, Ifosfamide 3gr/m ² , Vincristine 2mg	Cyclophosphamide 60mg/m ² , Doxorubicin 60mg/m ² , Paclitaxel 80mg/m ²
Docetaxel 75mg/m ² , Gemcitabin 900mg/m ²	Dacarbazin 375mg/m ² , Doxorubicin 25mg/m ² , Vinblastin 6mg/m ²
Doxorubicin 37,5mg/m ² , Ifosfamide 3000 mg/m ²	Doxorubicin 75mg/m ²
Doxorubicin 20mg/m ² , Etoposide 150mg/m ² , Ifosfamide 3000mg/m ² , Vincristin 2mg	Doxorubicin 75mg/m ² , Olaratumab 15mg/kg
Etoposide 100mg/m ² , Ifosfamide 3000mg/m ² , Vincristin 2mg	Gemcitabin 1000mg/m ² , NAB-Paclitaxel 125mg/m ²
Folfiri: 5FU + Irinotecan: Irinotecan 180mg/m ² , Folinezuur 400mg/m ² , Fluorouracil 400mg/m ²	Liposomal Doxorubicin 45mg/m ²
DA-EPOCH-R (Cyclophosphamide Etoposide, Prednisolon, Vincristin, Hydroxoanurubicine, Rituximab) + MTX it	NR

Abbreviations: 5FU = 5-Fluoruracil, USP = United States Pharmacopeia, MTX = methotrexate, AUC = area under the curve, NAB = nanoparticle albumin-bound, It = intrathecal.

^aSource: Zecha J, Raber-Durlacher JE, Laheij A, et al. The Potential Contribution of Dental Foci and Oral Mucositis to Febrile Neutropenia in Patients Treated With Myelosuppressive Chemotherapy for Solid Tumors and Lymphoma. *Frontiers in Oral Health*. 2022;3:940044. doi: <https://dx.doi.org/10.3389/froh.2022.940044>. PMID: 35846111.

Appendix C. Guideline Recommendations

Table C-1. Relevant guideline recommendations

Author, Year Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
Elad, 2020 ⁶⁵ and Hong, 2019 ⁶⁶ MASCC/ISOO	MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy	2019/2020	Adult and pediatric patients with mucositis secondary to cancer therapy	<p><u>Basic Oral Care:</u></p> <ul style="list-style-type: none"> • The panel suggests that implementation of multiagent combination oral care protocols is beneficial for the prevention of oral mucositis OM during CT. • The panel suggests that implementation of multiagent combination oral care protocols is beneficial for the prevention of OM during H&N RT. • The panel suggests that implementation of multiagent combination oral care protocols is beneficial for the prevention of OM during HSCT. • No guideline was possible regarding the use of professional oral care for the prevention of OM in patients with hematologic, solid, or H&N cancers because of limited and inconsistent data. <ul style="list-style-type: none"> ○ An expert opinion complements this guideline: Although there was insufficient evidence to support the use of professional oral care for OM prevention, the panel is of the opinion that dental evaluation and treatment as indicated before cancer therapy are desirable to reduce risk for local and systemic infections from odontogenic sources. • No guideline was possible regarding the use of patient education for the prevention of OM in patients with hematologic cancer during HSCT or CT because of limited and inconsistent data. <ul style="list-style-type: none"> ○ An expert opinion complements this guideline: The panel is of the opinion that educating patients about the benefits of basic oral care strategies is still appropriate because this may improve self-management and adherence to the recommended oral care protocol during cancer treatment. • No guideline was possible regarding the use of saline or sodium bicarbonate rinses in the prevention or treatment of 	<p>LOE defined as follows: I=Recommendation II=Suggestion III=No guidelines possible</p> <p>Basic oral care: All items LOE=III Anti-inflammatory agents: See text PBM: See text Cryotherapy: All items LOE=II Growth factors and cytokines: KGF-1 item LOE=I; GM-CSF item LOE=II Natural and misc.: See text</p>

Author, Year Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
				<p>OM in patients undergoing cancer therapy because of limited data.</p> <ul style="list-style-type: none"> ○ An expert opinion complements this guideline: Despite the limited data available for both saline and sodium bicarbonate, the panel recognizes that these are inert, bland rinses that increase oral clearance, which may be helpful for maintaining oral hygiene and improving patient comfort. <p><u>Growth factors and cytokines:</u></p> <ul style="list-style-type: none"> • The use of KGF-1 intravenously is recommended for the prevention of OM in patients with hematologic cancer undergoing autologous HSCT with a conditioning regimen that includes high-dose CT and TBI. • The evidence suggests that topical GM-CSF should not be used for the prevention of OM in patients undergoing HSCT. <p><u>Natural and miscellaneous:</u></p> <ul style="list-style-type: none"> • Chewing gum is not suggested for the prevention of OM in pediatric patients with hematological or solid cancer who receive CT. (LOE=III) 	
Yarom, 2019 ⁶³ ASCO MASCC/ISOO	Medication-Related Osteonecrosis of the Jaw: MASCC/ISOO/ASCO Clinical Practice Guideline	2019	Adult cancer patients who are receiving BMAs for any oncologic indication	<p><u>Recommendation 2.1. Coordination of care:</u> For patients with cancer who are scheduled to receive a BMA in a nonurgent setting, oral care assessment (including a comprehensive dental, periodontal, and oral radiographic exam when feasible) should be undertaken before initiating therapy. Based on the assessment, a dental care plan should be developed, implemented, and coordinated between the dentist and the oncologist to ensure that medically necessary dental procedures are undertaken before BMA initiation. Follow-up by the dentist should then be performed on a routine schedule (e.g., every 6 months) once BMA therapy has commenced.</p> <p><u>Recommendation 2.2. Modifiable risk factors:</u> Members of the multidisciplinary team should address modifiable risk factors for MRONJ with the patient as early as possible. These risk factors include poor oral health, invasive dental procedures, ill-fitting dentures, uncontrolled diabetes mellitus, and tobacco use.</p>	2.1: Moderate 2.2: Moderate 2.3: Moderate 2.4: Moderate 2.5: Weak

Author, Year Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
				<p><u>Recommendation 2.3. Elective dentoalveolar surgery:</u> Elective dentoalveolar surgical procedures (e.g., non-medically necessary extractions, alveoloplasties, and implants) should not be performed during active therapy with a BMA at an oncologic dose. Exceptions may be considered when a dental specialist with expertise in the prevention and treatment of MRONJ has reviewed the benefits and risks of the proposed invasive procedure with the patient and the oncology team.</p> <p><u>Recommendation 2.4. Dentoalveolar surgery follow-up:</u> If dentoalveolar surgery is performed, patients should be evaluated by the dental specialist on a systematic and frequently scheduled basis (e.g., every 6 to 8 weeks) until full mucosal coverage of the surgical site has occurred. Communication with the oncologist regarding the status of healing is encouraged, particularly when considering future use of BMA.</p> <p><u>Recommendation 2.5. Temporary discontinuation of BMAs before dentoalveolar surgery:</u> for patients with cancer who are receiving a BMA at an oncologic dose, there is insufficient evidence to support or refute the need for discontinuation of the BMA before dentoalveolar surgery. Administration of the BMA may be deferred at the discretion of the treating physician, in conjunction with discussion with the patient and the oral health provider.</p>	
Butterworth, 2016 ⁶⁷	Restorative dentistry and oral rehabilitation: United Kingdom National Multidisciplinary Guidelines	2016	H&N cancer patients	<p>Recommendations:</p> <ol style="list-style-type: none"> 1. Preventive oral care must be delivered to patients whose cancer treatment will affect the oral cavity, jaws, salivary glands, and oral accessibility 2. Close working and communication between the surgeons, oncologists and restorative dental specialists is important in ensuring optimal oral health outcomes. 3. If patients are deemed at risk of trismus they should be warned, and its progressive and potentially irreversible nature explained. 4. Where it is known that adjuvant radiotherapy will be given, extractions should take place at primary surgery to maximize the time for healing and minimize the number of surgical events for patients. 	<p>Where the multidisciplinary team of authors considered the recommendation to be based on clinical experience, they gave their statement a “G” rating.</p> <p>All recommendations recorded in this</p>

Author, Year Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
				5. Osseointegrated implants should be considered for all patients having resection for H&N cancer.	table received a "G" rating.
American Academy of Pediatric Dentistry, 2022 ⁶⁸	Dental management of pediatric patients receiving immunosuppressive therapy and/o head and neck radiation	2022	Children diagnosed with cancer	<p>Recommendations included in Best Practices document:</p> <p>The objectives of a dental/oral examination before therapy starts are three-fold:</p> <ul style="list-style-type: none"> • to identify and stabilize or eliminate existing and potential sources of infection and local irritants in the oral cavity—without needlessly delaying the treatment or inducing complications. • to communicate with the medical team regarding the patient's oral health status, plan, and timing of treatment. • to educate the patient and parents about the importance of optimal oral care to minimize oral problems and dis-comfort before, during, and after treatment and to inform them about the possible acute and long-term effects of the therapy in the oral cavity and the craniofacial complex. <p>Oral/dental assessment: should include a thorough head, neck, and intraoral examination, oral hygiene assessment, and radiographic evaluation based on history and clinical findings.</p> <p>Ideally, all dental care should be completed before immunosuppressive therapy is initiated. When that is not feasible, temporary restorations may be placed and non-acute dental treatment may be delayed until the patient's hematological status is stable.</p> <p>Education: Patient and parent education includes the importance of optimal oral care in order to minimize oral problems and discomfort before, during, and after treatment and the possible acute and long-term effects of the therapy in the craniofacial complex.</p> <p>Communication: The dentist's communication of the comprehensive oral care plan with the medical team is vital. Information to be shared includes</p>	

Author, Year Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
				the extent of non-elective dental treatment needed, need for supportive care (e.g., hospital admission, blood product replacement, antibiotic coverage) and the amount of time needed for stabilization of oral disease and healing from the dental procedures. Discussions with the medical team can ensure ideal coordination between needed dental services and planned cancer therapy.	
Elad, 2015 ⁶⁴ MASCC/ISOO	Basic oral care for hematology–oncology patients and hematopoietic stem cell transplantation recipients: a position paper from the joint task force of the MASCC/ISOO and EBMT	2014	Adult and pediatric hematology–oncology patients and patients undergoing HCST	<p>The information below is an abridged summary of recommendations provided throughout this position paper, sourced from Figure 2 in this publication.</p> <p><u>Before HCST/CT</u> Prevention of infection: Oral/dental examination - refer for dental evaluation; focus: eliminate foci of infection, traumatic surfaces Pain control: Prevention of local trauma - refer for dental evaluation; eliminate causes for local trauma Maintain oral function: Chewing capacity – ask patient about difficulty to chew; refer to dentist to restore occlusion, if applicable Managing oral complications of the underlying cancer or anti-cancer treatment: Oral examination – refer for an oral medicine specialist/dentist Quality of life: Education – inform about future possible oral complications</p> <p><u>During HCST/Chemotherapy</u> Prevention of infection:</p> <ul style="list-style-type: none"> • Oral hygiene: Ensure cleaning teeth and tongue (soft bristled toothbrush, floss if capable without trauma) • Decontamination: <ul style="list-style-type: none"> ○ Advise using bland rinses (e.g., saline), repeated rinses/day ○ Advise rinsing with chlorhexidine in alcohol free solution x2/day ○ If unable to rinse, apply solution to sterile gauze or toothette 	NA

Author, Year Organization(s)	Title	Year	Population	Recommendation(s)	Stated Recommendation Strength
				<ul style="list-style-type: none"> • Prophylaxis: Apply the institute protocol for prophylaxis for oral candidiasis & viral reactivation Maintain oral function: <ul style="list-style-type: none"> • Speaking, oral moisture. Utilize: Sugar free chewing gum/candy (non-acidic); dentifrices for oral dryness; saliva substitute 1st line; frequent sips of water • Diet: Promote non-cariogenic, low-acid atraumatic diet Managing oral complications of the underlying cancer or anti-cancer treatment: Detection <ul style="list-style-type: none"> • Detect possible signs & symptoms • Consult with oral medicine specialist/dentist treatment Quality of life: <ul style="list-style-type: none"> • Taste change: Encourage patient to maintain oral intake • For dry mouth, utilize: Sugar free chewing gum/candy (non-acidic); dentifrices for oral dryness; saliva substitute 1st line; frequent sips of water • Awareness of future dental problems: Educate patient regarding late effects of therapy 	

Abbreviations: 5-FU=5-fluorouracil; AAOM=American Academy of Oral Medicine; ASCO=American Society of Clinical Oncology; BMA= bone-modifying agents; CT=chemotherapy; EBMT= European Society for Blood and Marrow Transplantation; HSCT= hematopoietic stem-cell transplantation; H&N=head and neck; ISOO=International Society of Oral Oncology; IMRT= intensity-modulated radiotherapy; KGF-1=keratinocyte growth factor 1; LOE=level of evidence; MASCC=Multinational Association of Supportive Care in Cancer; MRONJ=medication related osteonecrosis of the jaw; NA=not applicable; OM=oral mucositis; PBM=photobiomodulation; RT=radiotherapy; TBI=total body irradiation.

Note: Appendix C reference numbers correspond to those in the main section of this report.

Appendix D. Linkages Between Certain Medical and Dental Services

Table D-1. Linkages between certain medical and dental services

Study Name	Citation	E1: Standard of Care Requires Dental Services	E2: Improved Healing/Quality of Surgery/Reduced Likelihood of Readmission	E3: Improved Clinical Outcomes and Success of Medical Procedure	E4: Improvement in Quality and Safety Outcomes (i.e., Fewer Readmissions; More Rapid Healing; Quicker Discharge)	Additional Comments
Multinational Association of Supportive Care in Cancer (MASCC) / International Society of Oral Oncology (ISOO) Clinical Practice Guideline	Elad, 2020 ⁶⁵	"Although there was insufficient evidence to support the use of professional oral care for OM [oral mucositis] prevention, the panel is of the opinion that dental evaluation and treatment as indicated before cancer therapy are desirable to reduce risk for local and systemic infections from odontogenic sources...The panel is of the opinion that educating patients about the benefits of basic oral care strategies is still appropriate because this may improve self-management and adherence to the recommended oral care protocol during cancer treatment."	Not applicable	Not applicable	Not applicable	Not applicable
MASCC/ISOO/ ASCO Clinical Practice Guideline	Yarom, 2019 ⁶³	"For patients with cancer who are scheduled to receive a [bone-modifying agent] BMA in a nonurgent setting, oral care assessment (including a comprehensive dental, periodontal, and oral radiographic exam when feasible) should be undertaken before initiating therapy. Based on the assessment, a dental care plan should be developed, implemented, and coordinated between the dentist and the oncologist to ensure that medically necessary dental procedures are undertaken before BMA initiation. Follow-up by the dentist should then be performed on	Not applicable	Not applicable	Not applicable	Not applicable

		a routine schedule (e.g., every 6 months) once BMA therapy has commenced."				
American Academy of Pediatric Dentistry Best Practices Document	American Academy of Pediatric Dentistry 2022 ⁶⁸	"children undergoing immunosuppressive therapy and/or head and neck radiation...have unique oral health needs and are at risk of developing multiple associated oral and systemic complications. Dentists play an essential role in diagnosing, preventing, stabilizing, and treating oral health problems that can compromise a patient's quality of life before, during, and following such therapies. All children undergoing immunosuppressive therapy and/or head and neck radiation should have an oral examination before such treatment commences. Dental interventions must be performed promptly, efficiently, and with attention to the patient's unique circumstances and treatment protocol... Preventive strategies include oral hygiene, diet, fluoride, and patient education. When completing all dental care prior to therapy is not feasible, priorities should be treatment of odontogenic and periodontal infections, extractions, periodontal care, and removal of sources of tissue irritation."	Not applicable	Not applicable	Not applicable	Not applicable
Clinical Practice Guideline	Butterworth, 2016 ⁶⁷	"Preventive oral care must be delivered to patients whose cancer treatment will affect the oral cavity, jaws, salivary glands and oral accessibility."	Not applicable	Not applicable	Not applicable	Not applicable
Systematic Review	Mazzetti, 2022 ⁵⁹	"Meta-analyses showed a higher risk of ORN [osteoradionecrosis] development in patients with Exo [dental extractions] performed < 2 weeks before oncological treatment than in those who Exo was performed > 2 weeks ≤ 1 month	Not applicable	Not applicable	Not applicable	This review highlights the need for collaboration and careful pre-treatment planning between medical and dental

		before oncological therapy (RR 1.29; 95 % CI 1.12–1.48; p < 0.01). There was a higher prevalence of oral mucositis (OM) in patients who received periodontal treatment ≤ 3 weeks before oncological therapy than those who received dental procedures > 3 weeks ≤ 6 months before."				providers to avoid the most serious oral and dental adverse events associated with cancer treatments.
Retrospective cohort study on pre-treatment dental care to reduce symptoms of oral mucositis	da Silva Santos, 2011 ³⁷	Not applicable	Patients who received dental care prior to stem cell transplantation had shorter duration of symptomatic mucositis than patients who did not receive pre-treatment dental care (p<0.001).	Not applicable	Not applicable	Lower severity of oral mucositis leads to higher quality of life for patients undergoing cancer treatment.
RCT on pre-treatment dental care to reduce symptoms of oral mucositis	Borowski, 1994 ³⁴	Not applicable	Patients who received dental care prior to bone marrow transplantation experienced less severe oral mucositis than patients who did not receive pre-treatment dental care (p<0.01).	Not applicable	Not applicable	Lower severity of oral mucositis leads to higher quality of life for patients undergoing cancer treatment.
Retrospective cohort study on pre-treatment dental care to reduce dental infections requiring emergency treatment during intensive chemotherapy	Watson, 2020 ²⁶	Not applicable	Not applicable	Serious dental infections were significantly (p=0.05) less frequent in the patients who received dental evaluation and treatment prior to beginning chemotherapy.	Not applicable	Not applicable
Prospective cohort study of febrile patients undergoing intensive chemotherapy for acute	Greenberg, 1982 ¹⁰	Not applicable	Not applicable	Blood cultures revealed that patients who had received pre-treatment dental care had a lower rate of infections	Not applicable	Not applicable

nonlymphocytic leukemia				from apparent oral sources (p=0.01).		
Retrospective cohort study on pre-treatment dental care to reduce the incidence of osteonecrosis among patients receiving treatment for solid tumors with bony metastases	Owosho, 2018 ²⁹	Not applicable	Not applicable	Not applicable	The rate of osteonecrosis in patients who received dental care before starting one or more bone-active medications was significantly lower than in patients who did not have pre-treatment dental care (p<0.00001).	Not applicable
Cross-sectional study examining the effect of certain types of dental care on the incidence of osteonecrosis during radiation therapy and chemotherapy for head and neck cancer	Huang, 2020 ²⁸	Not applicable	Not applicable	Not applicable	Dental extractions performed less than 2 weeks prior to starting radiation therapy were associated with a higher risk of developing osteonecrosis (hazard ratio 1.49; 95% confidence interval 1.01, 2.19). Administration of chemotherapy did not increase the risk in these patients.	Not applicable

Abbreviations: ISOO=International Society of Oral Oncology; MASCC=Multinational Association of Supportive Care in Cancer; 5-FU=5-fluorouracil; AAOM=American Academy of Oral Medicine; ASCO=American Society of Clinical Oncology; BMA= bone-modifying agents; CT=chemotherapy; EBMT= European Society for Blood and Marrow Transplantation; HSCT= hematopoietic stem-cell transplantation; H&N=head and neck; IMRT= intensity-modulated radiotherapy; KGF-1=keratinocyte growth factor 1; LOE=level of evidence; MRONJ=medication related osteonecrosis of the jaw; NA=not applicable; OM=oral mucositis; PBM=photobiomodulation; RT=radiotherapy; TBI=total body irradiation.

Note: Appendix D reference numbers correspond to those in the main section of this report.