ASCO special articles

Salivary Gland Hypofunction and/or Xerostomia Induced by Nonsurgical Cancer Therapies: ISOO/MASCC/ASCO Guideline

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abstract

PURPOSE To provide evidence-based recommendations for prevention and management of salivary gland hypofunction and xerostomia induced by nonsurgical cancer therapies.

METHODS Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) and ASCO convened a multidisciplinary Expert Panel to evaluate the evidence and formulate recommendations. PubMed, EMBASE, and Cochrane Library were searched for randomized controlled trials published between January 2009 and June 2020. The guideline also incorporated two previous systematic reviews conducted by MASCC/ISOO, which included studies published from 1990 through 2008.

RESULTS A total of 58 publications were identified: 46 addressed preventive interventions and 12 addressed therapeutic interventions. A majority of the evidence focused on the setting of radiation therapy for head and neck cancer. For the prevention of salivary gland hypofunction and/or xerostomia in patients with head and neck cancer, there is high-quality evidence for tissue-sparing radiation modalities. Evidence is weaker or insufficient for other interventions. For the management of salivary gland hypofunction and/or xerostomia, intermediate-quality evidence supports the use of topical mucosal lubricants, saliva substitutes, and agents that stimulate the salivary reflex.

RECOMMENDATIONS For patients who receive radiation therapy for head and neck cancer, tissue-sparing radiation modalities should be used when possible to reduce the risk of salivary gland hypofunction and xerostomia. Other risk-reducing interventions that may be offered during radiation therapy for head and neck cancer include bethanechol and acupuncture. For patients who develop salivary gland hypofunction and/or xerostomia, interventions include topical mucosal lubricants, saliva substitutes, and sugar-free lozenges or chewing gum. For patients with head and neck cancer, oral pilocarpine and oral cevimeline, acupuncture, or transcutaneous electrostimulation may be offered after radiation therapy.

Additional information can be found at www.asco.org/supportive-care-guidelines.

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Saliva plays a crucial role in the maintenance of tooth integrity, dilution of food detritus and bacteria, mechanical cleansing of the oral cavity, and oral comfort. Saliva also provides antimicrobial activity preventing oral infections and plays an important part in the upper GI functions including taste perception, formation of food bolus, facilitation of mastication, swallowing and speech, as well as lubrication of oropharyngeal and upper esophageal mucosa.[1] Thus, salivary gland hypofunction is associated with an increased risk for oral infections,[2,3] eg, candidiasis,[4] carious destruction of teeth,[5,6] dysgeusia,[7] oral mucosal discomfort,[8] and a worsened nutritional state.[9,10] Definitions for salivary gland hypofunction and other key terms are provided in Table 1.

Patients with cancer may experience salivary gland hypofunction and xerostomia as a consequence of cancer therapy. This is most notable in patients with head and neck cancer treated with external-beam radiation therapy.[8] In this setting, salivary gland hypofunction and xerostomia may be severe and permanent. This results in a profound, potentially life-long adverse impact on oral health and oral

THE BOTTOM LINE

Salivary Gland Hypofunction and/or Xerostomia Induced by Nonsurgical Cancer Therapies: ISOO/MASCC/ASCO Guideline

Guideline Question

What are the most effective interventions to prevent, minimize, and manage salivary gland hypofunction and xerostomia in the oncology patient receiving nonsurgical cancer therapy?

Target Population

Adult patients with cancer who are scheduled to receive or who have received nonsurgical cancer therapy.
Cancer diagnoses included head and neck cancer (radiation therapy in the head and neck region, chemotherapy, and chemoradiotherapy); hematologic malignancies (hematopoietic stem cell therapy, systemic chemotherapy, and total body irradiation); thyroid cancer (radioactive iodine); other solid cancer (systemic cancer chemotherapy); and all cancers treated by biologic cancer therapy including targeted therapies.

Target Audience

Oncologists and other physicians, dentists, dental specialists, dental hygienists, oncology nurses, clinical researchers, advanced practitioners, and patients with cancer, with particular emphasis on those individuals with head and neck cancer.

Methods

A multidisciplinary Expert Panel was convened by MASCC/ISOO and ASCO to develop clinical practice guideline recommendations based on a systematic review of the medical literature.

Recommendations

Clinical question 1. What is the efficacy of available pharmacologic and nonpharmacologic interventions (including the effects of radiation dose, type, and regimen) for the prevention of salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies?

Recommendation 1.1. Intensity-modulated radiation therapy should be used to spare major and minor salivary glands from a higher dose of radiation to reduce the risk of salivary gland hypofunction and xerostomia in patients with head and neck cancer (type: evidence-based; evidence quality: high; strength of recommendation: strong).

Recommendation 1.2. Other radiation modalities that limit cumulative dose to and irradiated volume of major and minor salivary glands as or more effectively than intensity-modulated radiation therapy may be offered to reduce salivary gland hypofunction and xerostomia (type: informal consensus; evidence quality: low; strength of recommendation: strong).

Recommendation 1.3. Acupuncture may be offered during radiation therapy for head and neck cancer to reduce the risk of developing xerostomia (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 1.4. Systemic administration of the sialogogue bethanechol may be offered during radiation therapy for head and neck cancer to reduce the risk of salivary gland hypofunction and xerostomia (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 1.5. Vitamin E or other antioxidants should not be used to reduce the risk of radiation-induced salivary gland hypofunction and xerostomia because of the potential adverse impact on cancer-related outcomes and the lack of evidence of benefit (type: informal consensus; evidence quality: low; strength of recommendation: weak).

Recommendation 1.6. Evidence remains insufficient for a recommendation for or against the use of submandibular gland transfer administered before head and neck cancer treatment to reduce the risk of salivary gland hypofunction and xerostomia because of insufficient evidence with contemporary radiation modalities.

Recommendation 1.7. Evidence remains insufficient for a recommendation for or against the use of the following interventions during radiation therapy for head and neck cancer: Oral pilocarpine, amifostine (with contemporary radiation modalities), or low-level laser therapy.

Recommendation 1.8. Evidence remains insufficient for a recommendation for or against the use of the following interventions to reduce the risk of salivary gland hypofunction or xerostomia in patients with head and neck cancer: n-acetylcysteine oral rinse, traditional Chinese medicine–based herbal mouthwash, local clonidine, concurrent chemotherapy with nedaplatin, boost radiation therapy, hyperfractionated or hypofractionated radiation therapy, intra-arterial chemoradiation, minocycline, melatonin, nimotuzumab, zinc sulfate, propolis, viscosity-reducing mouth spray, transcutaneous electrical nerve stimulation (TENS), parotid gland massage, thyme honey, and human epidermal growth factor.

Clinical question 2. What is the efficacy of available pharmacologic and nonpharmacologic interventions for the management of salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies?

(continued on following page)

THE BOTTOM LINE (CONTINUED)

Recommendation 2.1. Topical mucosal lubricants or saliva substitutes (agents directed at ameliorating xerostomia and other salivary gland hypofunction-related symptoms) may be offered to improve xerostomia induced by nonsurgical cancer therapies (type: evidence-based; evidence quality: intermediate; strength of recommendation: strong).

Recommendation 2.2. Gustatory and masticatory salivary reflex stimulation by sugar-free lozenges, acidic (nonerosive and sugar-free special preparation if dentate patients) candies, or sugar-free, nonacidic chewing gum may be offered to produce transitory increased saliva flow rate and transitory relief from xerostomia by stimulating residual capacity of salivary gland tissue (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 2.3. Oral pilocarpine, and cevimeline where available, may be offered after radiation therapy in patients with head and neck cancer for transitory improvement of xerostomia and salivary gland hypofunction by stimulating residual capacity of salivary gland tissue. However, improvement of salivary gland hypofunction may be limited (type: evidence-based; evidence quality: high; strength of recommendation: strong).

Recommendation 2.4. Acupuncture may be offered after radiation therapy in patients with head and neck cancer for improvement of xerostomia (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 2.5. Transcutaneous electrostimulation or acupuncture-like transcutaneous electrostimulation of the salivary glands may be offered after radiation therapy in patients with head and neck cancer for improvement of salivary gland hypofunction and xerostomia (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 2.6. Evidence remains insufficient for a recommendation for or against the use of the following interventions for improvement of salivary gland hypofunction and xerostomia: Extract of ginger and mesenchymal stem cell therapy.

Additional Resources

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

MASCC/ISOO and ASCO believe that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

health–related quality of life.[13] Although radioactive iodine, total body irradiation, and high-dose chemotherapy with hematopoietic stem cell transplantation as well as moderate-dose chemotherapy for solid tumors may also cause salivary gland hypofunction, in these settings, function loss and associated symptoms tend to be less severe and often less long-lasting.[14-16]

Under resting (unstimulated or when not chewing) conditions, the majority of saliva (ie, approximately two-thirds) is produced by the submandibular glands, which are composed of both serous and mucous acinar cells and produce a viscous mucin-rich fluid, with the sublingual glands also contributing with a mainly mucous secretion. The parotid glands produce a serous watery and protein-rich fluid relatively devoid of mucins that accounts for approximately 20% of the total volume of unstimulated whole saliva (10% from each parotid gland) and about 50% of the total volume of stimulated whole saliva (ie, 25% from each parotid gland). Although the minor salivary glands produce only 10% of the total volume of saliva, they play a key role in lubricating the mucosa by secreting a significant amount of salivary mucins.[1] As mucins bind water molecules, their presence on the mucous membranes help maintain a hydrated state on the mucosal surface contributing to the patient's sense of relative oral moisture.[17]

Strategies can be used to prevent or reduce salivary gland hypofunction and xerostomia induced by nonsurgical cancer therapies, to provide comfort, and to ameliorate adverse effects of salivary gland hypofunction and xerostomia. Limiting the radiation dose to the major and minor salivary glands through various modalities has demonstrated reduction in salivary gland hypofunction, xerostomia, and decrease in the incidence and severity of late effects.[18-23] Although other approaches have been investigated, they have not been widely adopted either because of lack of compelling data or barriers to adoption.[24] Unfortunately, management strategies for salivary gland hypofunction provide only limited relief of associated symptoms, including xerostomia, thus emphasizing the importance of preventive measures.[25] Salivary substitutes and topical therapies such as moisturizing agents may transiently minimize symptoms. Furthermore, the impact of therapeutic interventions for salivary gland hypofunction and its associated symptoms has rarely extended to the assessment of critical adverse effects such as oral infections, mucosal pain and sensitivity, dental decay, chemosensory dysfunction (taste and smell), nutritional status, and chronic inflammation. Nonetheless, it is important to encourage appropriate oral health behaviors (oral hygiene and fluoride application) to lessen the adverse effects on

TABLE 1. Definitions Related to Dysfunction of the Salivary Glands

Salivary gland hypofunction	Reduced salivary flow rate as measured objectively. Saliva flow rate is considered low when < 0.2 ml/min for unstimulated whole saliva[11]
Hyposalivation	Pathologic low saliva secretion, commonly defined as an unstimulated whole saliva flow rate of ≤ 0.1 ml/min or a stimulated whole saliva flow rate of ≤ 0.7 ml/min measured by sialometry[11]
Xerostomia	Patient-reported, subjective sensation of oral dryness. Although xerostomia most frequently occurs when the unstimulated whole saliva flow rate is reduced by about 45%-50% of the normal secretion of that person,[12] there are no specific threshold levels of salivary flow rate that characterize xerostomia. The degree of xerostomia may be affected by factors other than salivary flow rates
Whole saliva	Derives from the major salivary glands (the parotid, submandibular, and sublingual glands, which account for 90% of the saliva secretion) and the minor salivary glands (which account for the remaining 10%)

oral health and to provide dietary counseling to minimize the adverse impact on nutritional outcomes.[24] Improvement in these salient outcomes would provide compelling support for effective interventions.

The systematic review conducted for this guideline updates the findings of two previous systematic reviews published in 2010 by Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) (Data Supplement, online only).[26,27] The purpose of this systematic review–based guideline is to provide evidence-based recommendations for the prevention and management of salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies including all types of radiation regimens (eg, head and neck radiation therapy, radioactive iodine, and total body irradiation in combination with hematopoietic stem cell transplantation), chemotherapy, and biologic cancer therapy including targeted therapies.

GUIDELINE QUESTIONS

This clinical practice guideline addresses two clinical questions: (1) What is the efficacy of available pharmacologic and nonpharmacologic interventions (including the effects of radiation dose, type, and regimen) for the prevention of salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies? (2) What is the efficacy of available pharmacologic and nonpharmacologic interventions for the management of salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies?

METHODS

Guideline Development Process

This systematic review-based guideline was developed by a multidisciplinary Expert Panel convened by MASCC/ISOO and ASCO, which included collective expertise in oral medicine, head and neck oncology, medical oncology, radiation oncology, radiation biology, oral and maxillofacial surgery, and biostatistics. The Expert Panel also included a patient representative and an ASCO guidelines staff member with health research methodology expertise. The literature search interval was January 1, 2009, through June 12, 2020.

The systematic review that formed the basis for this guideline was conducted by the Oral Care Study Group of ISOO. It followed the Cochrane risk-of-bias tool for randomized trials (RoB version 2)[28] criteria to assess elements of quality related to study design, methodology, and the risk of bias in randomized trials included in systematic reviews. PubMed, EMBASE, and Cochrane Library were searched for randomized controlled trials (RCTs) published in the English language that investigated interventions that addressed prevention or management of salivary gland hypofunction and/or xerostomia. The search strategy is provided in the Data Supplement.

The abstract of each article was reviewed by the Salivary Gland Hypofunction and Xerostomia Cosection Heads (V.M. and S.B.J.) from the Oral Care Study Group, MASCC/ISOO. RCTs of salivary gland hypofunction were included when objective measurement of salivary gland function was performed by sialometry (salivary flow rate). The selected full-text articles were distributed to the reviewer team along with an evaluation form customized in a Research Electronic Data Capture (REDCap) database for reviewing salivary gland hypofunction and xerostomia data. All reviewers completed a calibration exercise before data collection, and feedback was submitted by e-mail correspondence. Two independent reviewers extracted information regarding study design, study population, interventions, outcome measures, methods, results, risk of bias, and conclusions for each article. The evaluation results were compared and re-evaluated until consensus was reached per arbitration via a third reviewer (Expert Panel Cochair V.M.). The review team was recruited from the Oral Care Study Group, MASCC/ISOO.

The included studies were descriptively merged with the relevant RCTs included in the 2010 systematic reviews (Data Supplement)[26,27] to form the evidentiary basis for the guideline recommendations.

The Expert Panel met via teleconference and corresponded through e-mail. Based upon the evidence provided by the systematic review, the Expert Panel was asked to provide critical review with the subsequent development of recommendations for the prevention and management of salivary gland hypofunction and xerostomia. The guideline

recommendations were made available for an open comment period of 2 weeks, allowing the public to review and comment on the recommendations. These comments were taken into consideration while finalizing the recommendations. Members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review to specialists in radiation oncology and oral diseases, and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are reviewed and approved by the Expert Panel and the ASCO Clinical Practice Guidelines Committee before publication. This guideline was also reviewed and approved by the MASCC/ISOO Guideline Committee. All funding for the administration of the project was provided by MASCC/ISOO and ASCO.

Articles were selected for inclusion in the systematic review of the evidence based on the following criteria:

- Population: Adult patients with cancer who are scheduled to receive or who have received nonsurgical cancer therapy. Cancer types included:
  - Head and neck cancer (radiation therapy in the head and neck region, chemotherapy, or chemoradiotherapy)
  - Hematologic malignancies (hematopoietic stem cell therapy, systemic chemotherapy, and total body irradiation as cancer treatment and conditioning regimen)
  - Thyroid cancer (radioactive iodine)
  - Other solid cancer (systemic cancer chemotherapy)
  - All cancers treated by biologic cancer therapy including targeted therapies.
- Fully published RCTs.

Articles were excluded from the systematic review if they were (1) meeting abstracts not subsequently published in peer-reviewed journals; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; or (3) published in a non-English language. The guideline recommendations are crafted, in part, using the *Guidelines Into Decision Support* (GLIDES) methodology.[29] In addition, a guideline implementability review was conducted (Data Supplement). Based on the implementability review, revisions were made to the draft to clarify recommended actions for clinical practice. Ratings for the type and strength of recommendation, bias, and quality of the evidence are provided with each recommendation (Data Supplement).

The Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. Based on formal review of the emerging literature, MASCC/ISOO and ASCO will determine the need to update its recommendations on Salivary Gland Hypofunction and/or Xerostomia Induced by Nonsurgical Cancer Therapies. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology Inc (ASCO) and the Multinational Association of Supportive Care in Cancer (MASCC)/International Society of Oral Oncology (ISOO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. MASCC/ISOO and ASCO do not endorse third-party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. MASCC/ISOO and ASCO provide this information on an "as is" basis and makes no warranty, express or implied, regarding the information. MASCC/ISOO and ASCO specifically disclaim any warranties of merchantability or fitness for a particular use or purpose. MASCC/ISOO and ASCO assume no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at http://www.asco.org/rwc). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely

to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

RESULTS

Characteristics of Studies Identified in the Literature Search

A total of 58 RCTs met eligibility criteria and, together with the 2010 systematic reviews,[26,27] form the evidentiary basis for the guideline recommendations.[30-50,51-70,71-86] A QUOROM flow diagram is provided in the Data Supplement. The identified trials included 46 preventive studies and 12 therapeutic studies. The outcomes assessed were xerostomia (38), salivary gland hypofunction (5), and both xerostomia and salivary gland hypofunction (15).

Because of the limitations of the available evidence, a majority of the recommendations focus on patients who receive radiation therapy for head and neck cancer. There were no eligible RCTs that investigated treatment strategies for immunotherapies. Details of included studies are provided in the Data Supplement.

Overall, 14 studies were judged to be at high risk of bias, 15 at low risk of bias, and 29 were identified as having some concern with regards to the risk of bias according to the Cochrane risk-of-bias tool for randomized trials (RoB version 2). All the included studies were parallel studies except for two studies that were cross-over with wash-out period ranging from 1 to 8 weeks.

RECOMMENDATIONS

Clinical Question 1

What is the efficacy of available pharmacologic and nonpharmacologic interventions (including the effects of radiation dose, type, and regimen) for the prevention of salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies?

Recommendation 1.1. Intensity-modulated radiation therapy (IMRT) should be used to spare major and minor salivary glands from a higher dose of radiation to reduce the risk of salivary gland hypofunction and xerostomia in patients with head and neck cancer (type: evidence-based; evidence quality: high; strength of recommendation: strong).

Recommendation 1.2. Other radiation modalities that limit cumulative dose to and irradiated volume of major and minor salivary glands as or more effectively than IMRT may be offered to reduce salivary gland hypofunction and xerostomia (type: informal consensus; evidence quality: low; strength of recommendation: strong).

Recommendation 1.3. Acupuncture may be offered during radiation therapy for head and neck cancer to reduce the risk of developing xerostomia (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 1.4. Systemic administration of the sialogogue bethanechol may be offered during radiation therapy for head and neck cancer to reduce the risk of salivary gland hypofunction and xerostomia (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 1.5. Vitamin E or other antioxidants should not be used to reduce the risk of radiation-induced salivary gland hypofunction and xerostomia because of the potential adverse impact on cancer-related outcomes and the lack of evidence of benefit (type: informal consensus; evidence quality: low; strength of recommendation: weak).

Recommendation 1.6. Evidence remains insufficient for a recommendation for or against the use of submandibular gland transfer administered before head and neck cancer treatment to reduce the risk of salivary gland hypofunction and xerostomia because of insufficient evidence with contemporary radiation modalities.

Recommendation 1.7. Evidence remains insufficient for a recommendation for or against the use of the following interventions during radiation therapy for head and neck cancer: Oral pilocarpine, amifostine (with contemporary radiation modalities), or low-level laser therapy.

Recommendation 1.8. Evidence remains insufficient for a recommendation for or against the use of the following interventions to reduce the risk of salivary gland hypofunction or xerostomia in patients with head and neck cancer: n-acetylcysteine oral rinse, traditional Chinese medicine–based herbal mouthwash, local clonidine, concurrent chemotherapy with nedaplatin, boost radiation therapy, hyperfractionated or hypofractionated radiation therapy, intra-arterial chemoradiation, minocycline, melatonin, nimotuzumab, zinc sulfate, propolis, viscosity-reducing mouth spray, transcutaneous electrical nerve stimulation (TENS), parotid gland massage, thyme honey, and human epidermal growth factor.

Literature Review and Analysis

Tissue-sparing radiation modalities. Three RCTs[44,50,65] (N = 166 total) compared patients treated with three-dimensional conformal radiation therapy to IMRT in head and neck squamous cell carcinoma and demonstrated a statistically significant improvement in xerostomia with one study also confirming improvement in long-term salivary gland hypofunction (Data Supplement). One RCT[87] (N = 616) that compared the clinical outcomes and late

toxicities of two-dimensional conventional radiation therapy and IMRT for the treatment of nasopharyngeal carcinoma demonstrated a reduced incidence and severity of xerostomia in the IMRT group.

In terms of IMRT techniques, one RCT[78] (N = 122) compared sequential versus simultaneous integrated boost IMRT in patients with nasopharyngeal carcinoma, showing similar outcomes in terms of acute adverse events and toxicities for the two techniques. An RCT[80] (N = 60) comparing simultaneous modulated accelerated radiation therapy versus simultaneous integrated boost IMRT in the treatment of locally advanced head and neck cancer demonstrated similar adverse outcomes.

A third RCT with limited sample size[57] (N = 23) that compared the efficacy and late adverse effects of IMRT combined with recombined humanized endostatin and IMRT combined with concurrent chemotherapy in patients with locally advanced nasopharyngeal carcinoma found nonsignificant differences in the xerostomia score between the two groups.

It is important to note that all the included studies used IMRT, with no available literature on novel radiation modalities (see Clinical Interpretation).

Preventive acupuncture. Two RCTs[61,62] (N = 109 total) compared patients with nasopharyngeal and oropharyngeal cancers undergoing radiation therapy treated with acupuncture versus standard of care (no intervention) or sham acupuncture (Data Supplement 1). Although acupuncture was associated with less xerostomia up to 6 months after radiation therapy completion, it did not demonstrate a statistically significant effect on salivary gland hypofunction.

One RCT[42] (N = 339) compared true acupuncture with sham acupuncture and a standard-of-care control in patients with oropharyngeal or nasopharyngeal carcinoma undergoing radiation therapy. Patients receiving acupuncture reported a reduction in xerostomia compared with standard of care 1 year after radiation therapy. There was no difference in xerostomia between the sham acupuncture and standard-of-care arm.

Muscarinic agonist stimulation (bethanechol) during radiation therapy. One RCT[54] (N = 97) in patients with head and neck cancer undergoing radiation therapy compared systemic administration of bethanechol versus placebo (Data Supplement). Bethanechol was associated with a reduction in xerostomia incidence and severity 2 months after radiation therapy, as well as an increase in unstimulated and stimulated whole saliva flow rates. An earlier study on bethanechol, included in the 2010 review,[26,27] reported a significant increase in unstimulated whole saliva flow rate (Data Supplement).[88]

Vitamin E and antioxidants. Two RCTs assessed the use of vitamin E to prevent salivary gland hypofunction and xerostomia because of radiation therapy (Data Supplement). One RCT[74] (N = 60) compared the use of pentoxifylline and vitamin E on the incidence and severity of radiation-induced oral mucositis and dysphagia in patients with head and neck cancer with measurement of acute xerostomia as a secondary outcome and did not report a difference in the incidence of xerostomia between the intervention arm and the control arm. A second RCT[39] (N = 36) that tested the preventive efficacy of vitamin C or E complex supplementation for radiation-induced xerostomia in patients with head and neck cancer did not show a difference in salivary gland hypofunction between experimental and control arms. This trial did, however, report improvement of xerostomia from 1 to 6 months after radiation therapy in the intervention arm compared with the control arm.

Importantly, randomized data in the head and neck cancer population demonstrated an adverse impact of antioxidant therapy on cancer-related outcomes.[89-91]

Submandibular gland transfer. Two RCTs assessed the use of submandibular gland transfer to prevent salivary gland hypofunction and xerostomia because of radiation therapy (Data Supplement). One RCT[55] (N = 120) compared the preventive use of submandibular gland transfer to oral pilocarpine and showed higher unstimulated and stimulated whole saliva flow rates in the surgical group compared with the oral pilocarpine group. No adverse effects were reported in this study. A second RCT[86] (N = 65) compared submandibular gland transfer versus a nonsurgical control and reported lower long-term incidence of moderate to severe xerostomia and higher unstimulated saliva flow rate in the experimental group than in the control group. There is no evidence on the use of submandibular gland transfer with contemporary radiation modalities including IMRT.

Oral pilocarpine, amifostine, and low-level laser therapy. The results of the RCTs on preventive pilocarpine published before January 1, 2009, were not consistent.[26,27] In addition, the improvement of salivary gland hypofunction was shown to be limited. No new evidence was identified in the current systematic review. The dissimilar results on sparing of salivary gland function by administration of oral pilocarpine during radiation therapy are thought to be highly dependent on the wide range of cumulative radiation doses applied. In one study comparing pilocarpine and placebo, no significant difference in salivary flow rate was noted.[92] However, in an exploratory analysis, salivary gland hypofunction and xerostomia were reduced by the use of pilocarpine in the subset of patients whose mean parotid doses exceeded 40 Gy.[92] Confirmatory data are lacking.

The results from RCTs on amifostine administered during radiation therapy were published before January 1, 2009, and thus were included in the 2010 systematic reviews (Data Supplement).[26,27] These studies indicate a significant benefit of amifostine treatment on patients' experience of

acute and late xerostomia, although the effect may be clinically minor[93-98] and possibly not associated with a significant difference in salivary flow rate compared with placebo.[99,100] One study assessed the use of intravenous administration of amifostine in patients treated with radioiodine showing a reduction of radiation-induced xerostomia and salivary gland dysfunction (scintigraphy).[101] In this systematic review, two RCTs[34,60] compared subcutaneous versus intravenous administration of amifostine and intravenous amifostine versus placebo, with no difference in grade 2 acute or late xerostomia between the two groups (Data Supplement). The acute toxicity of amifostine differed significantly between the two arms with regard to hypotension, skin rash, local pain at injection site,[34] vomiting, fatigue, and hypocalcemia.[60]

Two RCTs assessed the use of low-level laser therapy to prevent salivary gland hypofunction because of radiation therapy (Data Supplement). One RCT[67] (N = 60) compared low-level laser therapy (Indium-Gallium-Aluminum-Phosphorus [InGaAlP] diode laser) versus sham laser therapy in patients with head and neck cancer undergoing radiation therapy showed higher unstimulated whole saliva flow rate in the experimental group. Of note, this study was excluded from a recent systematic review on photobiomodulation therapy for cancer treatment–related salivary gland hypofunction because the physical parameter settings were not considered reproducible.[102] A second RCT[47] (N = 27) in patients with head and neck cancer undergoing chemoradiotherapy and treated with low-level laser therapy (InGaAlP diode laser, three times a week, on alternate days, for a total of 21 sessions) versus standard clinical care (periodontal and restorative treatment, and oral hygiene care) showed higher unstimulated whole saliva flow rate in the test group compared with the control group (clinical care only) at elected times up to 30 radiation therapy sessions.

Miscellaneous preventive interventions. The results from RCTs on the following interventions can be found in the Data Supplement: n-acetylcysteine oral rinse, traditional Chinese medicine–based herbal mouthwash, local clonidine, concurrent chemotherapy with nedaplatin, boost radiation therapy, hyperfractionated or hypofractionated radiation therapy, intra-arterial chemoradiation, minocycline, melatonin, nimotuzumab, zinc sulfate, propolis, viscosity-reducing mouth spray, TENS, parotid gland massage, thyme honey, and human epidermal growth factor.

Clinical Interpretation

Tissue-sparing radiation modalities. The Expert Panel endorses the use of radiation modalities that reduce the mean doses of radiation to the major salivary glands, where clinically indicated. In addition to sparing the parotid glands, reducing the mean doses to the other major glands (submandibular and sublingual glands), as well as reducing the mean dose to the noninvolved oral tissues (within which most minor salivary glands are dispersed), is expected to further improve xerostomia. Care must be taken to avoid underdosing clinically important target volumes. The ideal treatment modality and dose-limiting constraints continue to evolve with emerging evidence.

There is no clear threshold dose below which preservation of parotid gland function can be guaranteed; rather, there is a gradual decrease in normal tissue complication probability with decreasing mean dose. A radiation therapy planning constraint of 25-30 Gy to the parotid glands has been shown to correspond to 17%-26% complication probability at 1 year after radiation therapy, whereas at 40 Gy mean dose, a 50% probability of parotid gland flow reduction to $< 25\%$ of the preradiation therapy parotid flow rate was shown.[103] In many centers, currently dose delivery to the parotid glands is capped at a mean of 26 Gy when possible. Regarding the submandibular glands, studies have shown that unstimulated and stimulated submandibular salivary flow rates decreased exponentially as mean doses increased up to 39 Gy threshold and then plateaued to near-zero saliva flow rates at higher doses.[104]

Xerostomia may be assessed using patient-reported outcome measures or observer-rated scales such as the Radiation Therapy Oncology Group xerostomia toxicity scale. It is important to note that the majority of included studies assessed xerostomia using an observer-rated scale. There is evidence that observers underestimate patient-reported xerostomia.[105,106]

New radiation delivery techniques and modalities are being developed that may allow further reduction in the radiation dose delivery to target volumes. Whether this will result in additional clinical benefit as manifested by decreased incidence, duration, or severity of salivary gland hypofunction or xerostomia is unknown. There is no evidence in the literature on the efficacy of these new radiation techniques and modalities and, for ethical considerations, it is unlikely that a randomized trial with salivary gland function as the primary outcome will be undertaken to confirm their benefits. We further note the critical importance for the detection of true clinical and biologic outcomes of appropriate patient selection as well as anatomic site of the tumor relative to design of RCTs directed to novel tissue-sparing radiation modalities. Assessment will be based on the principle that to limit toxicities in radiation therapy, the mean dose to organs at risk such as the salivary glands has to be as low as reasonably achievable (ALARA) without compromising the prescribed dose to the tumor. Within patient treatment, radiation dose comparison plans are necessary to select the best sparing technique.

Preventive acupuncture. The use of acupuncture during radiation therapy may be considered where the service is available to reduce xerostomia. There is no evidence that acupuncture during radiation therapy will increase salivary flow rates.

Muscarinic agonist stimulation (bethanechol) during radiation therapy. The available data support the potential effectiveness of bethanechol; however, the Expert Panel recommends a careful discussion with the patient regarding potential benefits and likely side effects (dizziness, lightheadedness, nausea, abdominal pain, increased urination or sweating, flushing, and headache). Factors such as the expected radiation dose to the salivary glands and patient compliance should be taken into consideration.

Vitamin E and antioxidants. Randomized data in the head and neck cancer population demonstrated an adverse impact of antioxidant therapy on cancer-related outcomes. Patients should be counseled against use of supplemental antioxidants during head and neck cancer therapy. The evidence base provides enough data to recommend against the use of antioxidants.[89-91]

Submandibular gland transfer. The available data support the use of submandibular gland transfer in clinically appropriate cases (personalized medicine) where this clinical service is available and two-dimensional and three-dimensional radiotherapy is used. There are no data on the use of submandibular gland transfer with contemporary tissue-sparing modalities.

Patients with lymph node metastasis, patients who had undergone previous neck surgery, and patients whose treatment plan will not include surgery are not considered suitable candidates. The limited evidence available suggests that submandibular gland transfer does not affect the recurrence rate in cervical lymph nodes.

Oral pilocarpine, amifostine, and low-level laser therapy. Evidence remains insufficient for a recommendation for or against pilocarpine during radiation therapy for head and neck cancer.

Although amifostine has been approved by the US Food and Drug Administration in 1999 to reduce xerostomia in patients undergoing postoperative radiation therapy for head and neck cancer, its subcutaneous or intravenous administration is not commonly used because of its potential side effects and there is no evidence on the interaction and efficacy with newer parotid-sparing radiation modalities.

The Expert Panel does not support the use of low-level laser therapy in patients undergoing radiation therapy, noting that the two RCTs available in the literature do not include patient-reported outcome measures and therefore it is unclear whether this treatment will be clinically significant. The exact mechanisms responsible for low-level laser therapy effects on salivary gland tissue remain poorly understood. Furthermore, each RCT uses different modalities and doses resulting in treatment heterogeneity that confounds translation to clinical practice.

Clinical Question 2

What is the efficacy of available pharmacologic and nonpharmacologic interventions for the management of salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies?

Recommendation 2.1. Topical mucosal lubricants or saliva substitutes (agents directed at ameliorating xerostomia and other salivary gland hypofunction-related symptoms) may be offered to improve xerostomia induced by nonsurgical cancer therapies (type: evidence-based; evidence quality: intermediate; strength of recommendation: strong).

Recommendation 2.2. Gustatory and masticatory salivary reflex stimulation by sugar-free lozenges, acidic (nonerosive and sugar-free special preparation if dentate patients) candies, or sugar-free, nonacidic chewing gum may be offered to produce transitory increased saliva flow rate and transitory relief from xerostomia by stimulating residual capacity of salivary gland tissue (type: evidence-based; evidence quality: intermediate; strength of recommendation: moderate).

Recommendation 2.3. Oral pilocarpine, and cevimeline where available, may be offered postradiation therapy in patients with head and neck cancer for transitory improvement of xerostomia and salivary gland hypofunction by stimulating residual capacity of salivary gland tissue. However, improvement of salivary gland hypofunction may be limited (type: evidence-based; evidence quality: high; strength of recommendation: strong).

Recommendation 2.4. Acupuncture may be offered after radiation therapy in patients with head and neck cancer for improvement of xerostomia (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 2.5. Transcutaneous electrostimulation or acupuncture-like transcutaneous electrostimulation of the salivary glands may be offered after radiation therapy in patients with head and neck cancer for improvement of salivary gland hypofunction and xerostomia (type: evidence-based; evidence quality: low; strength of recommendation: weak).

Recommendation 2.6. Evidence remains insufficient for a recommendation for or against the use of the following interventions for improvement of salivary gland hypofunction and xerostomia: Extract of ginger and mesenchymal stem cell (MSC) therapy.

Literature Review and Analysis

Topical mucosal lubricants or saliva substitutes. Four RCTs assessed the use of topical mucosal lubricants or saliva substitutes for patients with salivary gland hypofunction or xerostomia because of radiation therapy (Data Supplement).

One RCT[30] (N = 62) evaluated the efficacy of a herbal compound containing *Malva sylvestris* and *Alcea digitata*

compared with artificial saliva to improve xerostomia in patients with head and neck cancer, showing no significant difference between tests and controls except for one time point (4 weeks).

A second RCT[32] (N = 45) developed a novel oily formulation for potential use as a saliva substitute for the treatment of xerostomia and compared it in a crossover trial to a standard carboxymethylcellulose saliva substitute and showed no short-term clinical benefit in the experimental group. A third RCT[64] (N = 52) compared an oral moisturizing jelly to a topical saliva gel showing that the continuous use of saliva substitutes for at least a month improved signs and symptoms of salivary gland hypofunction and xerostomia with a mild benefit for the topical saliva gel. The fourth RCT[83] (N = 50) compared a novel saliva substitute gel to a commercially available carboxymethylcellulose-based saliva substitute, showing better results in terms of short-term xerostomia severity in the control group compared with the test group.

Earlier studies, included in the 2010 systematic reviews[26,27] and even before 1990, generally indicated that salivary substitutes were more effective than a placebo in providing short-term relief from xerostomia (Data Supplement).[107-114]

Gustatory and masticatory stimulation. One RCT[56] (N = 91) compared the daily use of sugar-free chewing gum to standard care (water, saliva substitutes, or stimulants already part of daily routine) in patients with radiation-induced xerostomia after treatment for head and neck cancer, showing a significant improvement of short-term xerostomia in the experimental group compared with the control group (Data Supplement).

However, an additional RCT,[115] included in the 2010 systematic reviews,[26,27] reported that an oral antimicrobial lozenge administered to prevent mucositis did not influence xerostomia during radiation therapy (Data Supplement).

Muscarinic agonist stimulation after radiation therapy. The results from RCTs[112,116-123] on pilocarpine administered in patients with radiotherapy-induced xerostomia were included in the 2010 systematic reviews (Data Supplement).[26,27] Available studies suggest that oral pilocarpine is more effective than a placebo in alleviating symptoms of radiation-induced xerostomia with increased unstimulated and stimulated whole salivary flow rates. An earlier study, included in the 2010 systematic review, showed that cevimeline can be effective to improve xerostomia and increase unstimulated whole saliva flow rate with mild to moderate side effects.[124]

Therapeutic acupuncture. One RCT (N = 145) compared two group sessions of oral care education to eight acupuncture sessions in patients with radiation-induced xerostomia showing no change in either unstimulated or stimulated whole saliva flow rates, but improved long-term xerostomia in the acupuncture group compared with the control group[76] (Data Supplement).

Transcutaneous electrostimulation or acupuncture-like transcutaneous electrostimulation. Three RCTs assessed the use of transcutaneous electrostimulation or acupuncture-like transcutaneous electrostimulation in patients with salivary gland hypofunction or xerostomia induced by radiation therapy (Data Supplement). One RCT[40] (N = 68) evaluated the efficacy of TENS on hyposalivation compared with a control group receiving standard care (no intervention) and found a statistically significant long-term improvement in stimulated whole saliva flow rate in the experimental group compared with the control group. A second RCT[85] (N = 148) compared acupuncture-like transcutaneous stimulation (ALTENS) with pilocarpine for relieving radiation-induced xerostomia in patients with head and neck cancer showing no significant difference between the two groups. The third RCT[53] (N = 30) compared two different schedules for ALTENS treatment (four-times weekly for 6 weeks versus a twice-weekly schedule for 12 weeks) showing no significant difference between the two schedules.

Miscellaneous therapeutic interventions. The results from RCTs on the following interventions can be found in the Data Supplement:

Extract of ginger, MSC therapy, and low-level laser therapy.[48,73,75]

Clinical Interpretation

Topical mucosal lubricants or saliva substitutes. Oral mucosal lubricants or saliva substitutes are mainly useful in patients who do not respond to pharmacologic, gustatory, or masticatory stimulation. Moreover, it is worthwhile to try different saliva substitutes as patient preference may play a role in the compliance and effect of this treatment.[107-114]

Gustatory and masticatory stimulation of the salivary reflex. The Expert Panel supports the use of sugar-free and nonacidic chewing gum to stimulate saliva flow rate in patients with residual salivary gland secretory function. Long-term benefits are uncertain. Chewing gum should be mildly flavored, as patients with sensitive oral mucosa might not tolerate a strong flavor. Sugar-free gum is important, given the increased risk of caries because of salivary gland hypofunction.

The use of gustatory and masticatory salivary reflex stimulation has been sparsely addressed within the field of salivary gland hypofunction and xerostomia as sequelae of cancer therapies. Texture and taste should be tested in different cancer treatment populations since patient preferences and tolerability for the stimulatory product may differ depending on level of saliva production and the sensitivity of the oral mucosa.

Muscarinic agonist stimulation after radiation therapy. No new evidence was identified by the updates of the systematic review and therefore the recommendation remains unchanged since the 2010 systematic reviews (Data

Supplement).[26,27] The Expert Panel recommends the use of oral pilocarpine and oral cevimeline where available following radiation therapy in patients with head and neck cancer for improvement of xerostomia. The improvement of salivary gland hypofunction may be limited. Adverse effects of mild to moderate severity can be expected for pilocarpine (sweating, headache, increased urinary frequency, dyspepsia, lacrimation, and nausea) and cevimeline (sweating and dyspepsia). The Expert Panel notes that cevimeline is only available in selected countries, including the United States, Canada, Japan, and Taiwan.

Therapeutic acupuncture. Acupuncture may be offered to patients with radiation-induced xerostomia, where this service is available. Evidence is limited to only one study. Some patients might experience a reduction in xerostomia without an improvement in salivary flow rate. The evidence is limited by the lack of a true control in clinical studies.

Transcutaneous electrostimulation or acupuncture-like transcutaneous electrostimulation. The Expert Panel supports the use of TENS as a noninvasive treatment with a low toxicity profile where this facility is widely available. Further studies in a multicenter trial setting might be helpful to clarify the mechanism of action and confirm its efficacy.

DISCUSSION

The literature collectively highlights the clinical importance of salivary gland hypofunction and xerostomia in patients undergoing nonsurgical cancer therapies. Salivary gland hypofunction can lead to short- and long-term adverse outcomes including but not limited to (1) oral mucosal opportunistic infection,[2] (2) dysgeusia with associated dietary alterations, (3) increased cariogenic risk,[6,125] and (4) dysphagia.[126] The symptom of xerostomia may further contribute to compromised quality of life in these patients, particularly if moderate or severe.[127] In aggregate, the two conditions can have significant adverse clinical and financial impact including a range of oral complications that are expensive to treat.[128]

The oral sequelae of salivary gland hypofunction and the combination of severe dental pulpal or periodontal disease,[5,129,130] or ill-fitting dentures that traumatize oral mucosa, can lead to increased risk for osteoradionecrosis of the jaw in patients with cancer therapy–induced salivary gland hypofunction.[3,131-133]

PATIENT AND CLINICIAN COMMUNICATION

The nonsurgical management of cancer may include chemotherapy, other systemic antineoplastic therapies, radiation therapy, or a combination of modalities. Care is delivered by multidisciplinary teams, which may include oral medicine specialists, ear, nose, and throat physicians, maxillofacial and plastic surgeons, oncologists, radiologists, pathologists, speech and language therapists, oncopsychologists, maxillofacial prosthodontic specialists, cancer nurse specialists, dietitians, general dental practitioners, and dental therapists. It is therefore vital to ensure good communication among the oncology multidisciplinary team, the dental team, and the patient throughout the entire journey. To reduce interruption of cancer treatment, optimize symptom management, and improve quality of life, clinicians should discuss with patients the importance of optimization of oral health before, during, and after cancer therapy.[134,135]

Patients should be informed of the essential protective role of saliva against tooth decay and sensitivity. Patients should be educated about the potential impact of nonsurgical treatment on salivary gland function. Specifically, patients with head and neck cancer undergoing radiation therapy may experience xerostomia and hyposalivation beginning the first weeks of radiation therapy. Upon completion of therapy, patients may experience a gradual improvement in salivary gland hypofunction and xerostomia. The degree of recovery is dependent on the extent and total radiation dose to the salivary glands. Most patients are unfortunately left with some degree of permanent salivary gland hypofunction and xerostomia.

Patients should be informed that xerostomia and salivary gland hypofunction has a profound acute and long-term impact on a wide range of health outcomes. Salivary gland hypofunction can make mastication and swallowing more difficult. This may result in dietary adaptations that result in poor diet quality and increased risk of aspiration. Patients may have trouble speaking for protracted periods, resulting in social and work-related limitations. Xerostomia may also be a barrier to exercise and may lead to sleep disruption. Patients may complain of difficulty wearing dentures. Although an implant-supported denture could be considered, dental implant treatment planning needs to be carefully assessed in relation to radiation dosimetry to the mandible and maxilla.[136,137]

Supportive and preventive oral health measures should be promoted to reduce the risk of side effects from oncologic treatment. Although there is no curative intervention, the clinician should be confident in discussing with the patient fluoride prescription in dentate individuals and topical management that may ameliorate xerostomia and its related complaints. For further management, a referral to a specialist Oral Medicine Unit or a dentist trained in the specific care these patients need should be considered. Attention should be paid to potential adverse impacts of xerostomia and salivary gland hypofunction with referral to appropriate ancillary services when indicated.

For general recommendations and strategies by which to optimize patient-clinician communication, see Patient-Clinician Communication: ASCO Consensus Guideline.[138]

HEALTH DISPARITIES

Although ASCO and MASCC/ISOO clinical practice guidelines represent expert recommendations on the best practices in

disease management to provide the highest level of cancer care, it is important to note that access to oral health care in general and medically necessary oral care in the context of cancer treatment vary across countries and health care systems, and many patients may have limited access to medical care. There are multiple, complex factors associated with oral health disparities.[139] For example, there are a number of social determinants that contribute to which patients have access to oral health care in general and medically necessary oral care in the context of cancer treatment in particular. These determinants include the patient's socioeconomic status and degree of health literacy, as well as access to oral health care information and interprofessional oncology protocols that incorporate the management of oral complications of cancer treatment. Despite the importance of addressing the burden of oral disease at the population level and that of the individual patient, important gaps remain in the oral management of the oncology patient.[140]

Racial and ethnic disparities in health care contribute significantly to limited access to medical and dental care in the United States. Patients with cancer who are members of racial or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other Americans.[141-143] Many other patients lack access to care because of their geographic location and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest level of cancer care to these vulnerable populations.

COST IMPLICATIONS

Cost implications for patients with cancer vary across countries and health care systems that in turn influence shared decision making between clinicians and patients. Increasingly, in some countries, individuals with cancer are required to pay a larger proportion of their treatment costs through deductibles and coinsurance.[144,145] Higher patient out-of-pocket costs have been shown to be a barrier to initiating and adhering to recommended cancer treatments.[146,147]

Discussion of cost can be an important part of shared decision making.[148] Clinicians should discuss with patients the use of less expensive alternatives when it is practical and feasible for treatment of the patient's disease and there are two or more treatment options that are comparable in terms of benefits and harms.[148]

Patient out-of-pocket costs may vary depending on insurance coverage, health care systems, and across countries. Coverage may originate in the medical or pharmacy benefit, which may have different cost-sharing arrangements. Patients should be aware that different products may be preferred or covered by their particular insurance plan. Even with the same insurance plan, the price may vary between different pharmacies. When discussing financial issues and concerns, patients should be made aware of any financial counseling services available to address this complex and heterogeneous landscape.[148]

As part of the guideline development process, we searched the literature for published cost-effectiveness analyses that might inform the relative value of available treatment options. However, no cost-effectiveness analyses were identified to inform clinical management of salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from October 9, 2020, through October 26, 2020. Response categories of "Agree as written," "Agree with suggested modifications," and "Disagree. See comments" were captured for each proposed recommendation, with nine written comments received. For 12 of the 15 recommendations, responses were either "Agree as written" or "Agree with suggested modifications." For the remaining three recommendations, up to two respondents disagreed and provided comments. In addition, a draft of the full guideline was shared with two external reviewers with content expertise. Rather than rating their agreement with each recommendation, the external reviewers were asked to provide broad commentary on all aspects of the manuscript. The reviewers provided important input regarding the wording of recommendations and the presentation and interpretation of the literature. Expert Panel members reviewed comments from all sources before the guideline was finalized. All changes were incorporated before review and approval by the ASCO Clinical Practice Guidelines Committee and the MASCC Guidelines Committee.

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN, posted on the ASCO and MASCC/ISOO websites, and submitted for publication in the *Journal of Clinical Oncology*.

LIMITATIONS AND FUTURE RESEARCH

This guideline focused on salivary gland hypofunction and/or xerostomia induced by nonsurgical cancer therapies. In this context, it is important to note that management of these conditions is only partially dependent on the underlying cause. It is more the actual residual unstimulated and stimulated whole saliva flow rate and the severity of xerostomia that should guide the clinician on how best to manage salivary gland hypofunction and xerostomia, and how best to prevent oral complications such as salivary gland hypofunction-related dental caries than the pathology underlying these symptoms. Perspectives from other populations, such as those with Sjögren's syndrome[149] or those experiencing medication-induced salivary gland hypofunction and xerostomia,[3,150] may provide additional useful information for clinicians as well. As cited in The Bottom Line box and the recommendations, selected recommendations are based upon expert opinion, versus a systematic review evidence base. This approach is designed to reflect current state-of-science across the collective set of recommendations.

Future areas for research should be considered in the context of (1) continued rapidly evolving radiation technology (eg, proton therapy and VMAT) and (2) length of time (eg, 1-5 years) needed to assess relationship of this technology to long-term adverse oral events such as salivary gland hypofunction or xerostomia, advanced dental disease, and osteoradionecrosis.

In addition, ethical considerations must continue to be paramount in study design and typically preclude implementation of RCTs comparing current and novel radiation therapy modalities. When the expected difference in toxicity resulting for an 'old' and new technology is large and a major effect on the quality of life can be predicted with large certainty, this does not agree with the principle of balanced uncertainty as an ethical prerequisite for RCTs.[151]

One example of how these collective dynamics can be successfully addressed is illustrated using a proton therapy model. Proton therapy has the benefit of a unique energy absorption profile. A spread-out Bragg peak results in a flat dose profile across the target volume with a rapid decrease to nearly zero dose distally from the target. This results in highly conformal dose depositions in the target with a strong dose reduction in the normal tissue depending on the localization of the tumor. However, proton therapy is much more expensive and may not always yield the expected optimization of the dose distribution. Therefore, an alternative method has been developed in case RCTs may not be ethically appropriate.[152] This model-based approach was developed for sparing of healthy tissues with an equivalent target dose to identify patients who are expected to benefit most from protons.[152] The feasibility of this approach was recently published.[153] This approach is currently being tested to select patients who benefit from proton therapy to reduce dose to the salivary glands. If shown to be feasible, such an approach could potentially be considered as an alternative for RCTs in this field. A phase II or III randomized trial (ClinicalTrials.gov identifier: NCT01893307, estimated study completion date: August 2024) is currently underway to compare late toxicities and progression-free survival between intensity-modulated photon therapy and intensity-modulated proton therapy for patients with advanced-stage oropharyngeal tumors.

Two additional future research directions also represent potential strategic advances in the field as well:

1. Radiosensitivity of parotid gland stem cells.

It was recently shown that not all parts of the parotid gland are equally radiosensitive because of an unequal distribution of the stem cells.[22] It was also observed that the radiation dose to the region of the salivary gland containing the stem or progenitor cells predicted the function of the salivary glands 1 year after radiation therapy. Finally, it has been shown that this region of the salivary gland could be spared during radiation therapy, thus reducing the risk of radiation-induced xerostomia.[22] This concept has to be incorporated in future RCTs and model-based selection of head and neck cancer patient studies.

2. Novel regenerative medicine technology

Novel regenerative medicine options may be used to spare, optimize, or restore salivary gland function after treatment. Innovative treatment approaches close to clinical use are adipose tissue–derived MSC[48] and adult salivary gland–derived stem cells.[154] Another option could be gene therapy using human aquaporin-1 gene transfer[155] or neurotrophic factor neurturin[156] optimizing saliva flow rate after radiation therapy or preventing radiation-induced salivary gland hypofunction, respectively.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/supportive-care-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Integration of Palliative Care into Standard Oncology Practice[157] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[158] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Medication-Related Osteonecrosis of the Jaw[131] (https://ascopubs.org/doi/full/10.1200/JCO.19.01186)

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EDITOR'S NOTE

This joint ASCO and Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology (MASCC/ISOO) Clinical Practice Guideline provides recommendations on the management of salivary gland hypofunction and xerostomia induced by nonsurgical cancer therapies, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/supportive-care-guidelines.

EQUAL CONTRIBUTION

V.M. and D.E.P. were Expert Panel Cochairs. V.M. and S.B.J. contributed equally to this work.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Salivary Gland Hypofunction and/or Xerostomia Induced by Nonsurgical Cancer Therapies: ISOO/MASCC/ASCO Guideline

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APPENDIX

TABLE A1. Salivary Gland Hypofunction and/or Xerostomia Induced by Nonsurgical Cancer Therapies: Multinational Association of Supportive Care in Cancer/International Society of Oral Oncology/ASCO Guideline Expert Panel Membership

Name	Affiliation and Institution	Role or Area of Expertise
Valeria Mercadante, BDS, PhD, cochair	Eastman Dental Institute, University College London, London, England	Oral medicine
Douglas E. Peterson, DMD, PhD, FDS RCSEd, cochair	School of Dental Medicine and Neag Comprehensive Cancer Center, UConn Health, Farmington, CT	Oral medicine
Siri Beier Jensen, DDS, PhD, steering group	Aarhus University, Aarhus, Denmark	Oral medicine
Jessica Bauman, MD	Fox Chase Cancer Center, Philadelphia, PA	Medical oncology
Michael T. Brennan, DDS, MHS	Atrium Health, Carolinas Medical Center, Charlotte, NC	Oral medicine
Robert P. Coppes, PhD	Department of Radiation Oncology, Department of Biomedical Sciences of Cells and Systems, University Medical Center Groningen, University of Groningen, Groningen, the Netherlands	Clinical radiation biology
Niels Jessen	Danish Cancer Society, Network for Patients with Head and Neck Cancer, Denmark	Patient advocate
Narinder K. Malhotra, MD	Meadville Medical Center, Meadville, PA	Medical oncology
Barbara Murphy, MD	Vanderbilt University, Nashville, TN	Head and neck oncology
David I. Rosenthal, MD	The University of Texas MD Anderson Cancer Center, Houston, TX	Radiation oncology
Deborah P. Saunders, BSc, DMD	North East Cancer Center, Health Sciences North, Northern Ontario School of Medicine, Sudbury, ON, Canada	Hospital Dentistry
Derek K. Smith, DDS, PhD, MPH	Vanderbilt University, Nashville, TN	Biostatistics
Arjan Vissink, DDS, MD, PhD	Department of Oral and Maxillofacial Surgery, University Medical Center Groningen and University of Groningen, Groningen, the Netherlands	Oral Medicine, Oral and Maxillofacial Surgery, Radiation Research
Jonn Wu, MD	British Columbia Cancer Agency, University of British Columbia, Vancouver, Canada	Head and Neck Radiation Oncology
Kari Bohlke, ScD	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)