Oral complications associated with cancer therapy: a multi-disciplinary approach to oral oncology

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Disclosures

I do not have any financial or intellectual disclosures to make pertaining to the contents of this presentation

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Learning objectives

- Familiarize with short and long-term complications associated with cancer
- Practical approaches to management of these oral complications
- Role of multi-disciplinary care
- Emerging therapies and clinical trials in oral oncology

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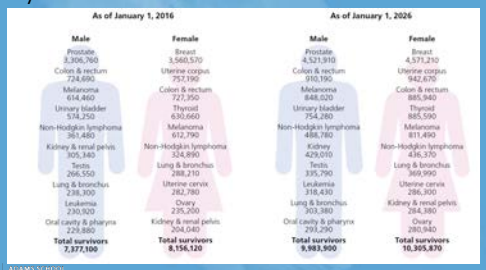
Reality check: cancer survivors are on the rise



American Cancer Society. Survivorship. Factbook. 2016-2017

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A 72 y.o female with a history of hypertension and anxiety presents to your office to establish routine care…

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Curtesy: BWH/ DFCI Oral Medicine

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S O A P NOTE

Subjective
- Chief concern
- History of present illness
- Past medical/surgical history
- Social history/family history
- Medications/allergies

Objective
- Vitals
- General appearance
- Extraoral exam
- Intraoral exam

Assessment
- Diagnosis/working diagnosis

Imaging/studies/tests/procedure

Plan
- Order
- Prescriptions
- Instructions
- Next visit

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Biopsy revealed: myeloid sarcoma of the R maxillary gingiva

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Incisional biopsy returns positive for cancer… What next?

1. You are part of the healthcare team
2. Documentation
   a) Organize all pertinent progress/exam notes
   b) Gather all radiographs, biopsy report, and images
   c) Correspond findings to primary care physician (PCP)
   d) Secure e-mail > fax
3. Familiarize with regional cancer centers
   a) Inquire on waiting times
   b) Required referral and documentation
   c) Key contact personnel
   d) Frequency of managing oral cancer?

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Incisional biopsy returns positive for cancer… What next?

4. Conveying the diagnosis
   a) In-person > phone call (unless patient is unable to commute)
   b) Educate and empathize
   c) Dedicate uninterrupted time
5. Offer to coordinate care
   a) Setting up referral to cancer center
   b) Involving family and support
   c) Work collaboratively to facilitate timely referral
6. Send documentation to cancer center
   a) Introduce yourself and make yourself available to the provider
   b) Consistent communication

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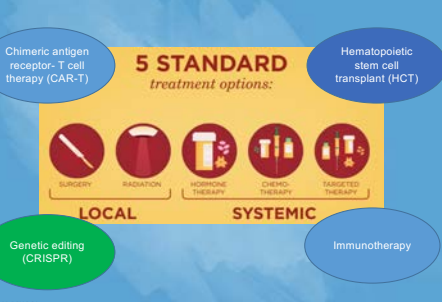

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Pre-treatment oral/dental evaluation

- RATIONALE
  - To minimize the risk of oral infections during cancer treatment
- PROTOCOL
  - Remove source of trauma, acute infection, or teeth with guarded prognosis.
- TIMING
  - As early as possible prior to cancer treatment
- BENEFITS
  - Optimal cancer treatment, reduced oral pain, reduced hospitalization costs
- CONSEQUENCES IF UNTREATED
  - Suboptimal cancer care, poor quality of life, increased hospitalization costs

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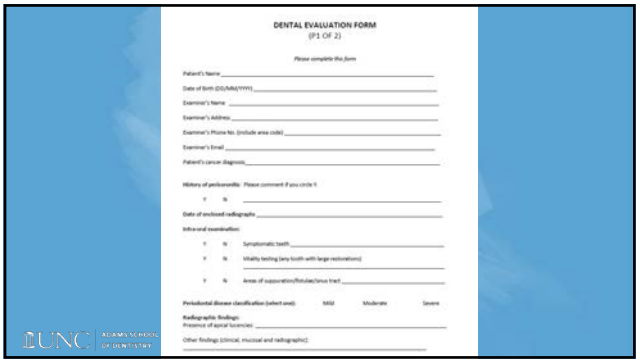
DENTAL EVALUATION FORM
(P1 OF 2)

Please complete this form

Patient's Name: _____

Date of Birth (DD/MM/YYYY): _____

Examiner's Name: _____

Examiner's Address: _____

Examiner's Phone No. (include area code): _____

Examiner's Email: _____

Patient's cancer diagnosis: _____

History of periodontitis: Please comment if you circle Y

Y N _____

Date of enclosed radiographs: _____

Intra-oral examination:

Y N Symptomatic teeth: _____

Y N Vitality testing (any tooth with large restorations) _____

Y N Areas of suppuration/fistulae/sinus tract: _____

Periodontal disease classification (select one): Mild Moderate Severe

Radiographic findings:
Presence of apical lucencies: _____

Other findings (clinical, mucosal and radiographic):
_____

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DENTAL EVALUATION FORM (P2 OF 2)

DENTAL TREATMENT PLAN

Tooth	Caries	Severe Periodontal disease	Partial Soft tissue Impacted	Other	Completed Treatment
1					
2					
3					
4					
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6					
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12					
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14					
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23					
24					
25					
26					
27					
28					
29					
30					
31					
32					
Other					

☐ Prophylaxis completed (date): _____

☐ Scaling root planning completed (if applicable): _____

Other comments: _____

_____

Signature of examiner/Date

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KEY TO SUCCESSFUL TREATMENT IS COMMUNICATION WITH THE CARE TEAM

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Oral effects of cancer treatment

Early effects
- Mucositis
- Infection
- Taste dysfunction
- Dysphagia
- Sialadenitis
- Xerostomia
- Acute graft-versus-host disease

Late effects
- Dental caries
- Xerostomia
- Osteonecrosis
- Taste dysfunction
- Muscle fibrosis
- Infections
- Chronic graft-versus-host disease

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Mucositis

- >75% patients in head and neck chemoradiation therapy
- Cytotoxic injury to mucosa
- Onset: 2-3 weeks from chemoradiation (CRT)
- Resolves 2-3 weeks post-CRT
- Incremental cost: $5000-30,000 among patients receiving RT

Linda S Elting. JNCI Monographs. 2019: 53
https://doi.org/10.1093/jncimonographs/lgz010
Elad, S. Cancer. 2020: 126: 4423– 4431

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WHO mucositis grading

Grade	Description
0 (none)	None
I (mild)	Oral soreness, erythema
II (moderate)	Oral erythema, ulcers, solid diet tolerated
III (severe)	Oral ulcers, liquid diet only
IV (life-threatening)	Oral alimentation impossible

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Mucositis: management approaches

- ***Mucositis Management***
- Bland rinses:0.9% saline solution.
- Sodium bicarbonate solution.
- 0.9% saline/sodium bicarbonate solution.
- Topical anesthetics:Lidocaine: viscous, ointments, sprays.
- Benzocaine: sprays, gels.
- 0.5% or 1.0% dyclonine hydrochloride (HCl).
- Diphenhydramine solution.
- Mucosal coating agents:Amphojel.
- Kaopectate.
- Hydroxypropyl methylcellulose film-forming agents (e.g., Zilactin).
- Gelclair (approved by the U.S. Food and Drug Administration [FDA] as a device).
- Analgesics:Benzydamine HCl topical rinse (not approved in the United States).
- Opioid drugs: oral, intravenous (e.g., bolus, continuous infusion, patient-controlled analgesia [PCA]), patches, transmucosal.
- Growth factor (keratinocyte growth factor-1):Palifermin (approved by the FDA in December 2004 to decrease the incidence and duration of severe oral mucositis in patients undergoing high-dose chemotherapy with or without radiation therapy followed by bone marrow transplant for hematologic cancers).

PDQ® Supportive and Palliative Care Editorial Board. PDQ Oral Complications of Chemotherapy and Head/Neck Radiation. Bethesda, MD: National Cancer Institute. Updated 12/16/2016.

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Low-level laser therapy in oral mucositis

PBM	I	• The panel recommends the use of intraoral *PBM* therapy using low-level laser therapy for the prevention of OM in adult patients receiving HSCT conditioned with high-dose CT, with or without TBI, using one of the selected protocols listed in Table 2.
	II	• The panel recommends the use of intraoral *PBM* therapy using low-level laser therapy for prevention of OM in adults receiving RT to the H&N (without CT) (Table 2); safety considerations unique to patients with oral cancer should be considered.
	I	• The panel recommends the use of intraoral *PBM* therapy using low-level laser therapy for the prevention of OM in adults receiving RT-CT for H&N cancer (Table 2); safety considerations unique to patients with oral cancer should be considered.
		• For all PBM guidelines, it is recommended that the specific PTPs of the selected protocol will be followed for optimal therapy.

Elad, S. Cancer. 2020: 126: 4423– 4431

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VOICE trial: oral mucositis intervention trial at UNC

- Phase IIB/III, double blinded, multi-center trial
- Use of topical clonidine (adhesive) during chemoradiation therapy for oropharyngeal cancer patients
- Primary endpoint: reduction of incidence of severe (grade 3 or higher oral mucositis)
- Estimated open to recruitment at UNC in Q4 2022
- PI: Shazib (Oral Medicine) and Sheth (Medical Oncology)

https://clinicaltrials.gov/ct2/show/NCT04648020

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Jaw osteonecrosis/MRONJ/ORN

- Persistent non-healing bone exposure in the setting of radiation therapy or anti-resorptive therapy
- Head and neck radiation >60 Gy
- Bisphosphonates, RANK-L inhibitors, VEGF inhibitors, TKIs

Yarom N. J Clin Oncol. 2019 Sep 1;37(25):2270-2290. PMID: 31329513.

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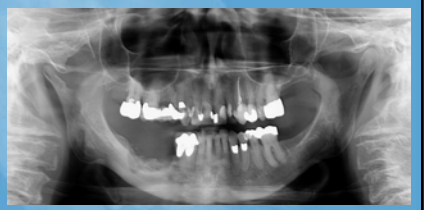
Radiographic features: ONJ/ORN

- Persistent extraction socket
- Altered bone trabeculation
- Thickened lamina dura
- Mixed radiolucent changes



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Management: ONJ/ORN

- PREVENTION
  - Dental clearance prior to anti-resorptive therapy/ head and neck radiation therapy
- Chlorhexidine rinses
- Sequestrectomy
- Systemic antibiotics
- Resection/reconstruction

Yarom N. J Clin Oncol. 2019 Sep 1;37(25):2270-2290. PMID: 31329513.

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Ongoing trials in BMT

Agent	Benefit/efficacy	Reference
Hyperbaric Oxygen (HBO)	Not clear benefit	Cochrane Database Syst Rev. 2016 Feb 26;2(2):CD008455.PMID: 26919630
Pentoxifylline + tocopherol (PENTACOL)	Larger studies are warranted	Int J Radiat Oncol Biol Phys. 2011 Jul 1;80(3):832-9. PMID: 20638190.
Teriparatide	Larger studies warranted	Journal of Clinical Oncology 2020 38:26, 2971-2980
Low level laser therapy (PBM)	Larger studies warranted	Lasers in medical science, 31(6), 1261–1272.

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Graft-versus-host disease

- 35-80% of allogeneic stem cell transplant patients
- Donor T-cell driven immune-reaction; loss of T-regs
- Acute GVHD
  - Within 100 days of transplant
  - Aggressive mucosal/skin hemorrhage
- Chronic GVHD
  - After 100 days
  - Lichenoid/ sclerodermatous

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Management approaches for GVHD

Acute GVHD
- High dose systemic prednisone (mg/kg)
- Topical steroids
  - Dexamethasone 0.1 mg/ml solution
  - Compounded 0.1% clobetasol solution
  - Budesonide 0.3 mg/ml solution
  - Tacrolimus 0.1% solution
  - Clobetasol 0.05% gel
  - Tacrolimus 0.1% ointment

Chronic GVHD
- Treat only if symptomatic (ulcers, erythema, dry mouth)
  - Ulcers and erythema
    - Same topical approach for acute GVHD
    - Intralesional steroid therapy
  - Dry mouth
    - Salivary stimulants
    - Saliva substitutes
    - Pharmacologic sialogogue therapy
  - Mouth tightness
    - Physical therapy
    - Pentoxifylline (weak evidence)
    - Photobiomodulation (weak evidence)

PDQ® Supportive and Palliative Care Editorial Board. PDQ Oral Complications of Chemotherapy and Head/Neck Radiation. Bethesda, MD: National Cancer Institute. Updated 12/16/2016.

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Salivary gland dysfunction

Pathogenesis
- Loss of acinar cells
- Ductal epithelium alteration
- Fatty degeneration

Source of damage
- Radiation
- Chemotherapy
- Conditioning for HSCT
- Chronic GVHD

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Salivary gland dysfunction

Clinical features
- Altered speech
- Difficulty swallowing
- Dental caries
- Taste changes
- Infections
- Burning sensation

Reversible damage
- Parotid < 26 Gy
- Submandibular <39 Gy

Irreversible damage
- > 60 Gy
- >80% H&N radiation pts

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Saliva flow measurement

Hypofunction

Stimulated salivary flow
- ≤0.5– 0.7 mL/min

Unstimulated salivary flow
- ≤0.1 mL/min

Normal function

Stimulated salivary flow
- 1.5 – 2.0 mL/min

Unstimulated salivary flow
- 0.3 – 0.4 mL/min

Villa. Ther Clin Risk Manag. 2014 Dec 22;11:45-51.

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Modified Schirmer Test (MST)

Mean MST at 3-minutes for normal flow: 29.5 mm ± 4.3 mm

Mean MST at 3-minutes for hypofunction: 6.9 mm ± 2.6 mm

Woo. J Am Dent Assoc. 2005 Feb;136(2):164-70

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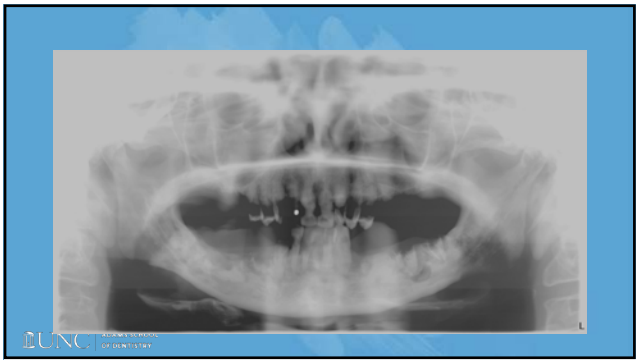

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Management

Pharmacologic
- Pilocarpine 5 mg PO TID
- Cevimeline 30 mg PO TID
- Bethanecol 50 mg PO TID

Non-pharmacologic
- Salivary stimulants
- Mouth moisturizers
- Sodium fluoride 1.1%

AAOM Clinical Practice Statement. OOOO 2016;122(3):

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Oral infections

- Viral, bacterial, fungal
- Higher risk with myeloablative condition/ SCT
  - ANC less than 1,000/mm3
- Challenging to clinically diagnose
- Insert image

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Viral infections

- Recrudescent HSV
  - Shedding viral particles
  - Hard to distinguish from oral mucositis in severely immunosuppressed patients
  - Culture/swab highly diagnostic
- CMV
  - Solitary deep ulcer
  - Does not shed/culture swabbing not helpful
  - Blood serology for CMV anti-IGM, IgG, PCR
- EBV
  - Post-transplant lymphoproliferative disorder
  - Does not shed/culture swabbing not helpful
  - Blood serology for CMV anti-IGM, IgG, PCR

Management

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Fungal infections

- Candida
  - Pseudomembranous
  - Erythematous
  - Oral cytology (hyphae)
- Non-candida
  - Deep penetrating ulcers
  - Solitary
  - Seen in immunosuppressed patients
  - Tissue biopsy advised

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Bacterial infections

- Gingivitis
- Periodontitis
- Pericoronitis
- Pulpitis
- Periapical infection

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Oral effects of cancer treatment

Early effects
- Mucositis
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- Sialadenitis
- Xerostomia
- Acute graft-versus-host disease

Late effects
- Dental caries
- Xerostomia
- Osteonecrosis
- Taste dysfunction
- Muscle fibrosis
- Infections
- Chronic graft-versus-host disease

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Oral immune-related adverse events irAEs

- Under-reported in literature
- Seen secondary to PD-1i/PDL-1 or CTLA-4i
- Median onset (PD-1i)
  - Four infusions (range: 1-16)
- Median duration (PD1i)
- 95 days (range: 7-284)

- Clinical features
  - Oral lichenoid reaction/mucositis
  - Erythema multiforme
  - Re-activation of GVHD
  - Xerostomia/hyposalivation
  - Oral crohn disease
  - Vesiculubullous conditions

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Shazib et al. Oral immune-related adverse events associated with PD-1 inhibitor therapy: A case series. Oral Dis. 2020 Mar;26(2):325-333.

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Shazib et al. Oral immune-related adverse events associated with PD-1 inhibitor therapy: A case series. Oral Dis. 2020 Mar;26(2):325-333.

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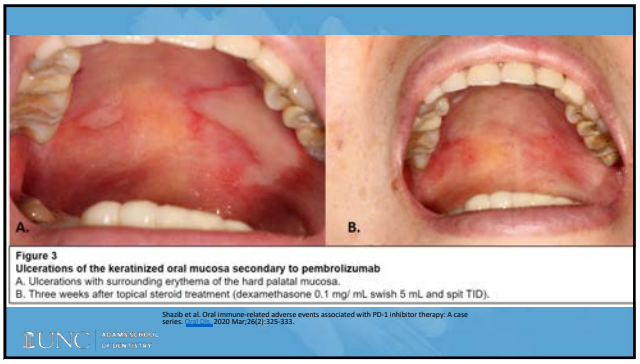
A.
B.
Figure 3
Ulcerations of the keratinized oral mucosa secondary to pembrolizumab
A. Ulcerations with surrounding erythema of the hard palatal mucosa.
B. Three weeks after topical steroid treatment (dexamethasone 0.1 mg/ mL swish 5 mL and spit TID).
Shazib et al. Oral immune-related adverse events associated with PD-1 inhibitor therapy: A case series. 2020 Mar;26(2):325-333.
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A.
B.
C.
D.
Figure 5
Acute GVHD reactivation secondary to pembrolizumab
A. Hemorrhagic ulcerations and crusting of the lips as well as erythema and ulcerations of the buccal mucosae.
B. Diffuse maculopapular rashes of the lower extremity.
C. Targetoid lesion of the palmar surface of the left hand.
D. Targetoid lesion of the palmar surface of the right and left hand.
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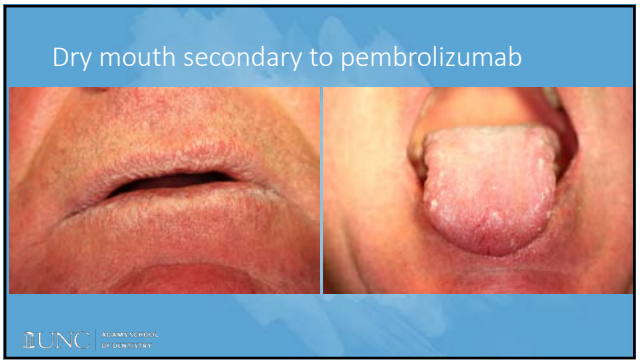
Dry mouth secondary to pembrolizumab
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Oral crohn-like features with nivolumab

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Management of oral irAEs

- GOAL
  Manage oral irAE without modifying ICI therapy for advanced cancer
- HOW?
  - Manage according to patient-reported symptoms (pain score/sensitivity score)
  - Topical therapies
    - Fluocinonide 0.05% gel? Clobetasol 0.05% gel?
    - Dexamethasone 0.1 mg/mL swish and spit or compounded clobetasol 0.05% swish and spit
  - Intralesional steroid therapy
  - Systemic corticosteroids (for severe/refractory cases)
  - Systemic immunomodulators (TNFis)
  - Dry mouth management (hydration, salivary stimulants, mouth moisturizers, sialagogues)
  - Observe/surveillance
- COMMUNICATE/COORDINATE FINDINGS/MANAGEMNT WITH ONCOLOGY TEAM

Support Care Cancer. 2017 Oct;25(10):3017-3030

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Summary

- Oral complications can complicate course of treatment and affect QOL
- Oral health evaluation prior to head and neck radiation, initiating bone modifying agents, and stem cell transplant will reduce dental complications (infections) during and after course of treatment.
- Recognize and consider multi-disciplinary approaches to managing acute and late oral effects of cancer treatment
- Ongoing efforts underway to improve management of oral complications (mucositis, MRONJ, GVHD)

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  - UNC School of Dentistry

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