

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



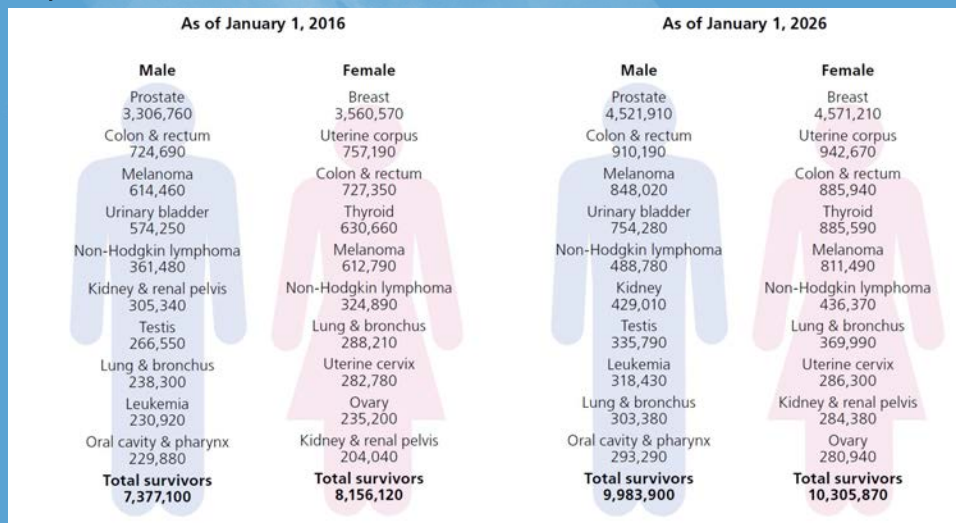
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Learning objectives

- 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



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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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S O A P NOTE

Subjective <ul style="list-style-type: none">• Chief concern• History of present illness• Past medical/surgical history• Social history/family history• Medications/allergies	Assessment <ul style="list-style-type: none">• Diagnosis/working diagnosis
Objective <ul style="list-style-type: none">• Vitals• General appearance• Extraoral exam• Intraoral exam	Imaging/studies/tests/procedure
	Plan <ul style="list-style-type: none">• 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?

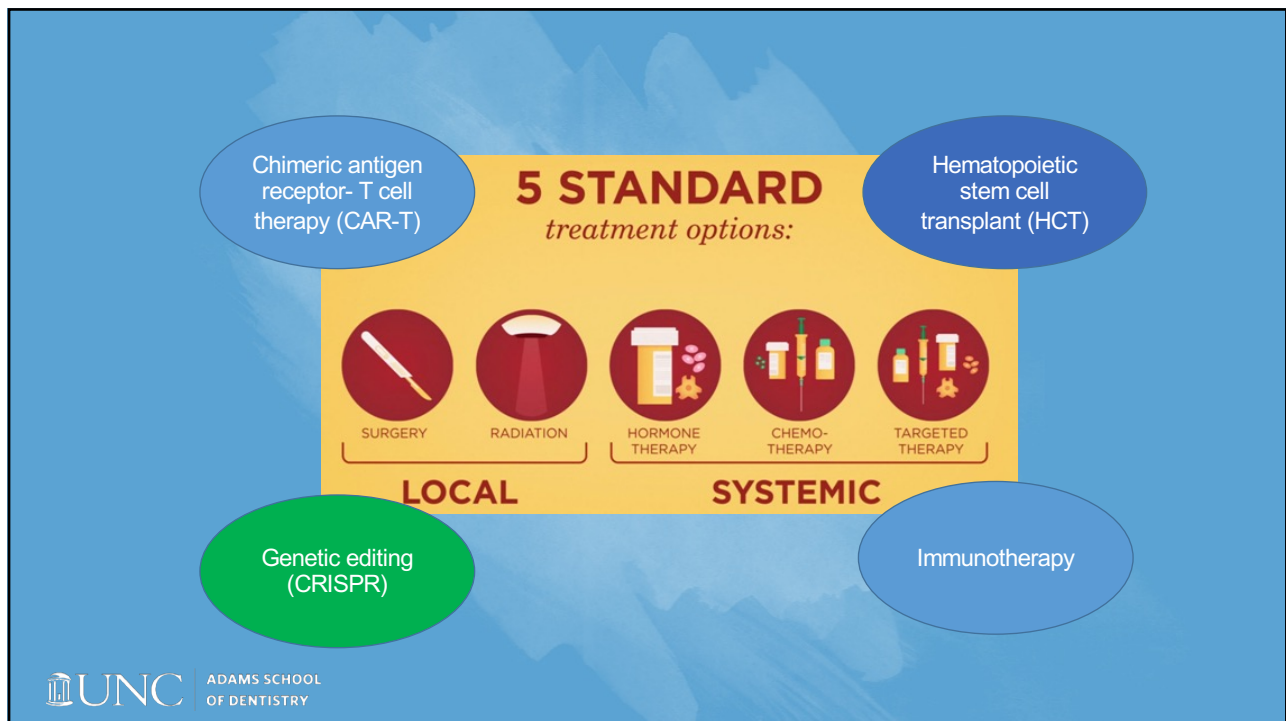
Incisional biopsy returns positive for cancer... What next?

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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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 pericoronitis: 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					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
20					
21					
22					
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

<h3>Early effects</h3> <ul style="list-style-type: none"> • Mucositis • Infection • Taste dysfunction • Dysphagia • Sialadenitis • Xerostomia • Acute graft-versus-host disease 	<h3>Late effects</h3> <ul style="list-style-type: none"> • 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

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: Benzylamine 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.

Low-level laser therapy in oral mucositis

- | | | |
|-----|----|---|
| PBM | I | <ul style="list-style-type: none"> • The panel recommends the use of intraoral <i>PBM</i> 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 | <ul style="list-style-type: none"> • The panel recommends the use of intraoral <i>PBM</i> 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 | <ul style="list-style-type: none"> • The panel recommends the use of intraoral <i>PBM</i> 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. |
| | | <ul style="list-style-type: none"> • For all PBM guidelines, it is recommended that the specific PTPs of the selected protocol will be followed for optimal therapy. |

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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)

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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



Radiographic features: ONJ/ORN

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



Management: ONJ/ORN

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



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.

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

<p>Acute GVHD</p> <ul style="list-style-type: none"> • High dose systemic prednisone (mg/kg) • Topical steroids <ul style="list-style-type: none"> • 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 	<p>Chronic GVHD</p> <ul style="list-style-type: none"> • Treat only if symptomatic (ulcers, erythema, dry mouth) <ul style="list-style-type: none"> • Ulcers and erythema <ul style="list-style-type: none"> • Same topical approach for acute GVHD • Intralesional steroid therapy • Dry mouth <ul style="list-style-type: none"> • Salivary stimulants • Saliva substitutes • Pharmacologic sialogogue therapy • Mouth tightness <ul style="list-style-type: none"> • Physical therapy • Pentoxifylline (weak evidence) • Photobiomodulation (weak evidence)
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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

- $\leq 0.5 - 0.7$ mL/min

Unstimulated salivary flow

- ≤ 0.1 mL/min

Normal function

Stimulated salivary flow

- $1.5 - 2.0$ mL/min

Unstimulated salivary flow

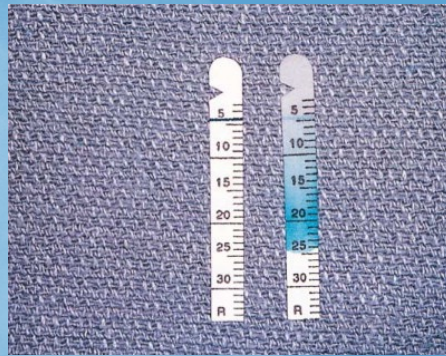
- $0.3 - 0.4$ mL/min

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Modified Schirmer Test (MST)



Mean MST at 3-minutes for normal flow:
 $29.5 \text{ mm} \pm 4.3 \text{ mm}$

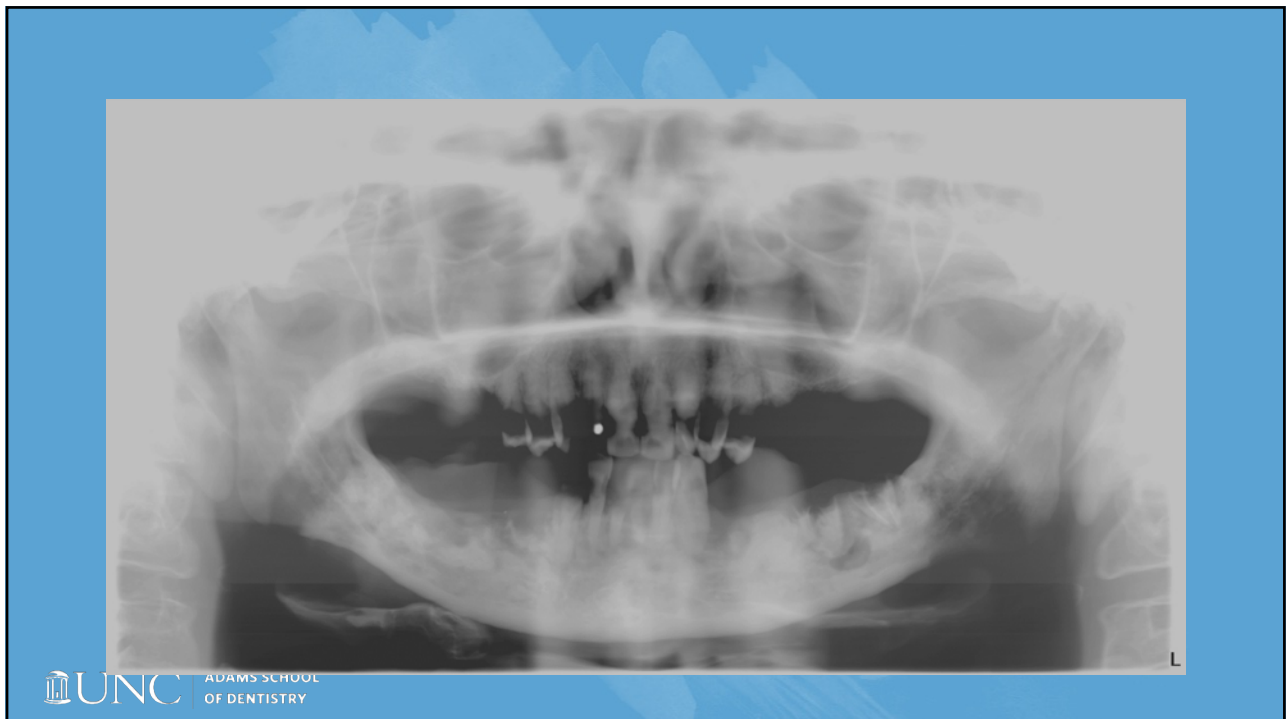


Mean MST at 3-minutes for hypofunction:
 $6.9 \text{ mm} \pm 2.6 \text{ mm}$

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Management

<p>Pharmacologic</p> <ul style="list-style-type: none"> • Pilocarpine 5 mg PO TID • Cevimeline 30 mg PO TID • Bethanecol 50 mg PO TID 	<p>Non-pharmacologic</p> <ul style="list-style-type: none"> • Salivary stimulants • Mouth moisturizers • Sodium fluoride 1.1%
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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

- Recrudescence 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

Management



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Bacterial infections

- Gingivitis
- Periodontitis
- Pericoronitis
- Pulpitis
- Periapical infection

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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



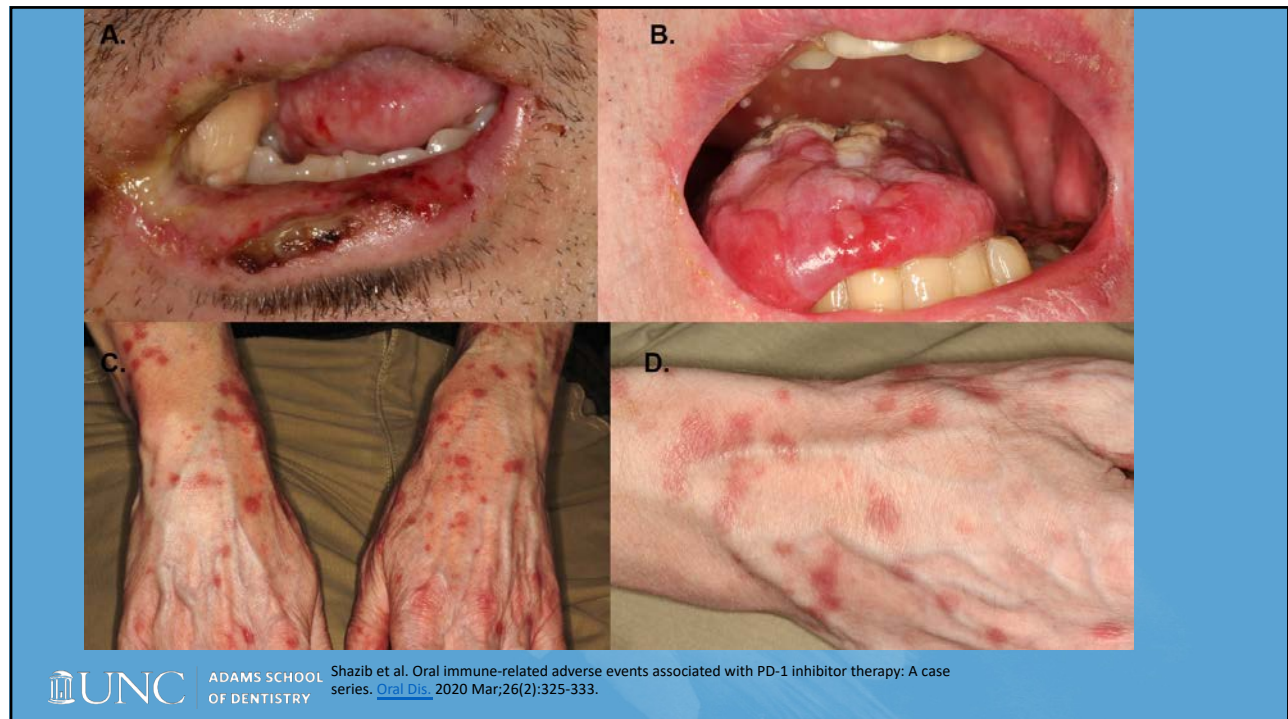
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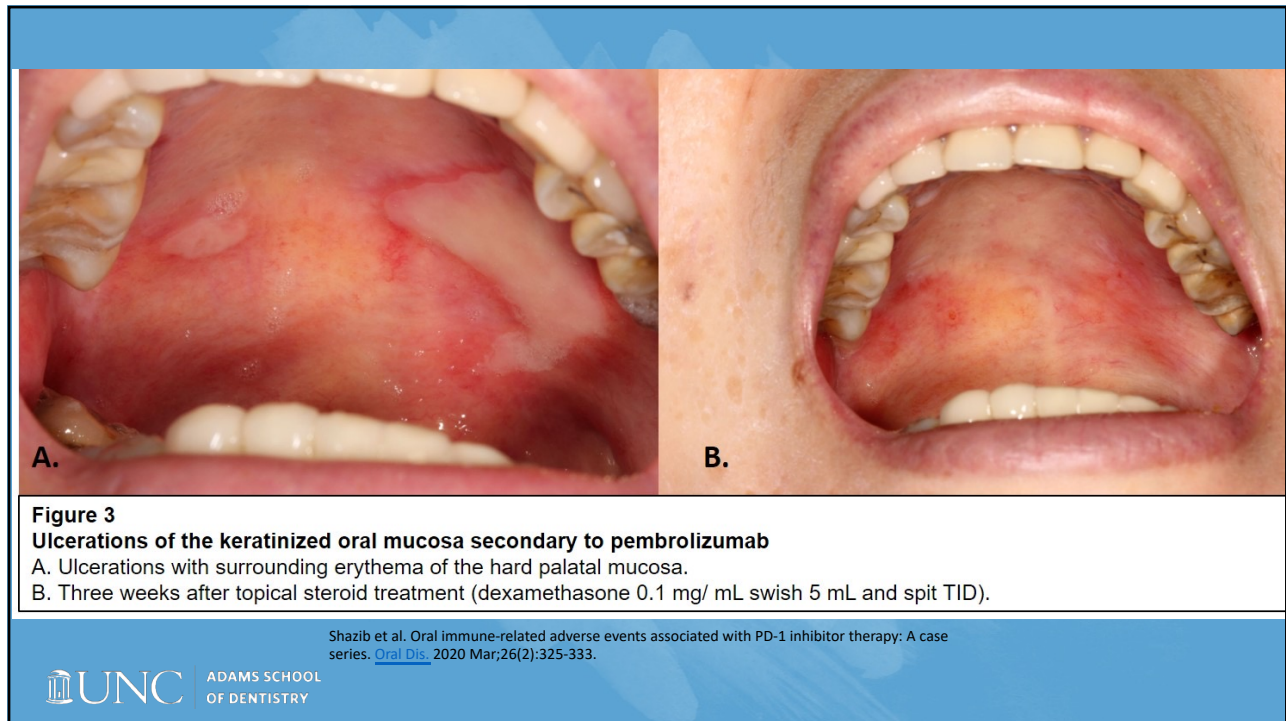
Oral immune-related adverse events irAEs

- 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
 - Vesiculobullous conditions

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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/MANAGEMENT WITH ONCOLOGY TEAM**



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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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