The unique role of dentistry in caring for patients with cancer:

Prevention, detection, surveillance and supportive care

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Carol Anne Murdoch-Kinch, DDS, PhD, FDS FRCS(Ed)
Dr. Walter H. Swartz Professor of Integrated Special Care Dentistry
Associate Dean for Academic Affairs

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Learning Objectives

1. Identify patients at risk for cancer, and oral complications of its treatment, including cancers of the head and neck, through appropriate history and physical examination
2. Recognize signs and symptoms of oral complications of cancer therapy, including newer targeted therapies
3. Understand how to safely and effectively provide dental treatment , before during and after cancer treatment.
4. Comply with guidelines for pain management for dental patients, including new rules for prescribers in the state of Michigan.

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- Part 1: Assessing risk for head and neck cancer-
- Part 2: Oral complications of cancer therapy, head and neck cancer; Oral supportive care
- Part 3. Oral complications of cancer therapy, non- head and neck cancer; Oral supportive care
- Part 4: Guidelines for pain management

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Key Concepts for Part I

- Early detection of oral and oropharyngeal cancer (OSCC) requires the dental team to assess risk and perform screening examination for all patients at initial and recall visits
- Review of steps of screening examination for head and neck cancer; role of brush biopsy in detection and diagnosis of OSCC
- Modifiable and non-modifiable risk factors for oral and oropharyngeal cancer
- HPV and OSCC- "breaking bad news"
- HPV tests- how should they be used?
- How to communicate with your patients about their HPV and OSCC cancer risk- common questions
- Using motivational interviewing techniques to communicate with your patient about oral cancer risk and behavior change- tobacco cessation, diet and alcohol

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High Risk Sites for Oral Cancer

- Posterior lateral and ventral surfaces of the tongue
- Floor of the mouth
- Soft palate
- Gingiva
- Buccal mucosa
- Labial mucosa
- Hard palate

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High Risk Sites for Oropharyngeal Cancer

- Cancers in these sites are often quite advanced, with spread to the neck, at the time of detection
  - ¾ Tonsil or soft palate
  - ~ ¼ Base of tongue

These are the sites most often associated with HPV

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ADA Policy on HPV Vaccination for Prevention of Oral HPV infection

- 50,000 new cases of OSCC in 2018
  - ~70% of oral and oropharyngeal cancers are associated with HPV (American Cancer Society)
- CDC, AAP-Boys and Girls should receive the HPV vaccine during adolescence
- Individuals < 26 years of age may benefit from HPV vaccine
  - Young men through age 21
  - Young women through age 26
- Individuals who did not receive the vaccine in adolescence, now FDA- approved for persons 27-45 to be vaccinated (2018)

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Assessing Risk and Screening for Oral and Oropharyngeal Cancer: Listen, Look and Feel

Listen:

Review health history. Identify risk factors for oral cancer.

Any signs or symptoms? Pain, difficulty swallowing, new spots, lumps or sores?

Look and feel: Screening examination

Systematically - *same* steps for *every* patient *every* time

1. Extraoral- examine skin of neck, face, ears, head, scalp
2. Extraoral- neck- palpate lymph nodes, muscles, thyroid
3. Extraoral- face and head- palpate lips, cheeks, TMJs, mandible
4. Intraoral- palpate and examine- lips, buccal mucosa, floor of mouth, tongue, palate, soft palate, gingiva
5. Intraoral- examine- soft palate, tonsils, oropharynx
6. Intraoral- look for asymmetry as patient extrudes tongue, says “aahh”, move tongue from side to side

- Instruments: gauze, mirror, light, gloved hands

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Assessing Risk and Screening for Oral and Oropharyngeal Cancer: Listen, Look and Feel

- Screening examination should be done on every patient at time of initial and recall visits
- Patients with a previous history of dysplasia or malignancy, may need to be followed more frequently
- To be done after review of medical history and risk assessment
- Significant findings may be followed by observation, brush biopsy, and/or scalpel biopsy, depending on degree of suspicion for malignancy or additional need for definitive biopsy

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Risks for Oral and Oropharyngeal Cancer

- Tobacco use
- Alcohol
- UV light (lip)
- Immunosuppression
- Previous head and neck cancer
- History of radiation therapy to head and neck
  - e.g. HIV/AIDS
  - Post- transplant- solid organs; HSCT
  - Autoimmune diseases
  - Systemic corticosteroids
- HPV infection
- Male gender
- Age
- Diet- low in fruits and vegetables
- Rare familial cancer syndromes
  - Li-Fraumeni syndrome
  - Fanconi anemia
  - Dyskeratosis congenita

Erythroplakia = Red Plaque

- Erythroplakia is a red lesion not otherwise diagnosed. Red lesions can be caused by processes such as infection, trauma and inflammatory diseases.
- An erythroplakia with no known cause/diagnosis is more likely to undergo malignant transformation than a white lesion
- Speckled erythroplakia is a combination of leukoplakia and erythroplakia
  - 5I% of cases will show invasive carcinoma on biopsy

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Clinical Appearance of Oral Cancer

- Leukoplakia:
  - Bornstein M, Benquerel M, Magnin P, Peier E, Busser D. Oral leukoplakia. A retrospective study of clinical and histologic data. Schweiz Monatsschr Zahnmed. 2004;114(7):680-6 (52 lesions)
    - 62% NO dysplasia
    - 26% Mild dysplasia
    - 6% Moderate dysplasia
    - 6% Carcinoma In-situ
- Erythroplakia:
  - Shafer W, Waldron C. Erythroplakia of the oral cavity. Cancer 36(3) 1021-28, 1975. (65 lesions)
    - 51% invasive CA
    - 40% CA in situ
    - 9% mild to moderate dysplasia

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Differential Diagnosis of Red, White or Mixed Lesions

- If trauma is suspected, re-evaluate after 2 weeks. If lesion persists, further evaluation is necessary.
- Most red or white lesions, such as lichen planus, should be assessed by biopsy.
- There is no way to be absolutely certain that these lesions are not cancer, so biopsy is necessary.

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An Abnormality is Detected on Clinical Examination- What Do You Do?

- For highly suspicious lesions, biopsy is indicated
- To establish a definitive diagnosis, biopsy is indicated
- For cases of white lesions, which are not highly suspicious for cancer, but for which there is no definitive diagnosis, an oral brush biopsy can serve as a useful screening tool to rule out malignant change

Our goal is the early detection of oral cancer!

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Oral Brush Biopsy

- A non-painful technique that allows early detection of oral cancer in lesions that appear benign clinically, and would not otherwise be "biopsied".
- It is easy and quick to perform, and
- It is a covered benefit by many dental and medical insurance carriers.

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Oral Brush Biopsy

In this procedure the dentist samples a white lesion by collecting a full thickness of mucosal epithelial cells, places them on a slide and performs a fixation step and then forwards the slide to a laboratory for examination and diagnosis. This is a useful screening test to help detect oral cancer at an early stage.

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Limitations

- It does not render a diagnosis. Negative and atypical results require follow-up biopsy.
- It is not appropriate for lesions that do not display surface epithelial changes (e.g. lumps)
- Cost may be a concern for patients without dental or medical insurance.

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Prepare the Slides for Processing

- Open the package of fixative and flood the slide.
- Allow the slide to sit undisturbed until the fixative has dried.
- Send the sample to Oral Scan Laboratories for analysis.

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Oral Brush Biopsy

- This test is especially useful for those lesions that are abnormal in appearance but for whom the dentist is unsure whether a conventional biopsy is really warranted.
- It also may be useful for patients who are reluctant to have a surgical procedure performed. Additional information is obtained that can help the patient and dentist decide whether such an invasive procedure is needed.

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When you find an abnormality, what do you do?

The specific indications for a scalpel or punch biopsy rather than a brush biopsy would include

- ✓ obvious cancer,
- ✓ a highly suspicious lesion or
- ✓ a lesion in a person at high risk for whom a definitive diagnosis is needed as soon as possible.

The brush biopsy is better used for evaluation of lesions of unknown significance or behavior.

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Oral CDx Results

Classification is based on cellular morphologic features

- Negative – No cellular abnormalities
- Positive – Definitive cellular evidence of epithelial dysplasia or carcinoma
- Atypical – Abnormal cellular changes warranting further investigation

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Sciubba JJ and Larian B. Gen Dent Nov/Dec 2018

- *Oral squamous cell carcinoma: early detection and improved 5-year survival in 102 patients.*
- Retrospective study
  - 102 patients (55% make and 45% female)
  - Ages: 27-87 years
  - > 50% had NEVER used tobacco
    - 8% of those asked- consumed>21 alcohol drinks/week
  - ~70% of all lesions first evaluated with a brush biopsy by a general dentist; remainder by ENT or Dental specialist

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Summary

1. Clinical oral cancer screening examination can aid in earlier detection of oral cancer, with impact on mortality
2. Dentists are better than physicians in detecting oral cancer at an earlier stage
3. Lesions that are highly suspicious for cancer MUST be biopsied

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Tailoring evaluation, assessment and counseling to the individual patient:

1. Evaluate the patient's risk for oral and oropharyngeal cancer- health history, interview

2. Provide information about risk for oral and oropharyngeal cancer

3. Identify which of these risks are **relevant to this patient – physical findings and risk factors**
"A teachable moment"

4. Are any of these risk factors **modifiable behaviors**? If so, use motivational interviewing techniques to assist the patient to change behavior

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Plan ahead

- Difficult conversation- plan what you will say ahead of time
  - Paper by Fahkry and D' Souza- talking points
- Simple language- at the patient's level
- Slow down
- Written and verbal
- Pictures, brochures, other resources available online- See www.ada.org/cancer
- Opportunity for the patient to ask questions
- Confirm understanding

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HPV and Oral Cancer

- Diagnosis of HPV-OSCC imparts upon the patient a ***cancer diagnosis*** and the diagnosis of a ***sexually transmitted infection***.
- Few resources exist to answer patients' questions
  - Why? How? When?
- Complex psycho -social impacts of this diagnosis; effects on relationships
- ***Evidence-based guidelines for screening and prevention of HPV- associated OSCC are currently lacking***

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General Dentist- When Will YOU Use this Information?

- Will you ever be the one to break the bad news about cancer and HPV status? Maybe not.
- You have the longstanding relationship with your patient- TRUST- may come to you for answers and advice
- When assessing risk and screening for cancer
- Answering patient questions about HPV testing, health promotion and disease prevention
- When loved ones receive a diagnosis- patient questions

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Discussing tumor HPV status in OSCC-patients with a new diagnosis

- There are no formal recommendations for when and how to discuss HPV test results with patients; Testing of the tissue is part of the NCCN standard of care because HPV status may lead to different treatment approaches and prognosis
- The significance of HPV infection and the reasons for testing should be explained BEFORE the tumor is tested for HPV

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Discussing tumor HPV status in OSCC-patients with a new diagnosis

- When providing test results:
  - Summarize why the test was done and provide a context for a positive result in a neutral non-stigmatizing manner
  - Reinforce the high prevalence of HPV in the population; transient nature of most infections
  - Acknowledge concerns about potential of transmission to partners
  - PRINT as well as VERBAL communication
  - Lay terminology; pictures, stories, anecdotes
  - SLOW DOWN
  - "Teach back"- have the patient tell you what they understand
  - Recent study by Inglehart et al showed many patients have gaps in knowledge, trust their doctors, but DON'T ASK

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Reactions to HPV-positive test

- How did this happen?
- Are oral HPV and HPV-positive H/N cancers caused by oral sex?
- When did I get this?
- Does a diagnosis of HPV-OSCC indicate past or present promiscuity?
- Will I transmit this infection to others?
- Is my spouse/partner at increased risk of this cancer?
- What should they do?
- Will I always have this HPV infection?
- What does being HPV-positive mean about my disease?
- Does current or past tobacco use affect oral HPV infection and HPV-OSCC?
- Can the HPV vaccines help?

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What is HPV?

- Very common
- Sexually transmitted infection that can infect the oropharynx (tonsils and back of throat), anus and genitals
- There are many types of HPV. HPV can cause cancer, warts or have no effect
- Over 20 million Americans have some type of genital or oral HPV infection
- In some people oral HPV leads to an HPV-OSCC many years later

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How did I get an oral HPV infection?

- HPV is transmitted to your mouth by oral sex. It may also be possible to get oral HPV by other ways.
- Performing oral sex and having many oral sex partners can increase your chances of an oral HPV infection
- Having an oral HPV infection does not mean your partner was/is unfaithful and does not suggest promiscuity
- Many people with HPV-OSCC have had a few oral sex partners in their life

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Who has oral HPV infection?

- Many people will likely be exposed to oral HPV in their life
- Around 1% of men and 3.6% of women in the US have HPV in their mouths and HPV infection is more commonly found with older age
- Most people clear the infections on their own in a year or two, but in some people with HPV infections persists

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Can I transmit oral HPV infection to others?

- Family and friends:
  - Oral HPV is not casually transmitted by sharing drinks or kissing on the cheek
  - We do not know if open mouth kissing can transmit HPV
- Partners of people with HPV-OSCC
  - You have likely already shared whatever infections you have
  - You do not need to change your sexual behavior
  - Female partners should have regular cervical Pap screening
- New sexual partners in the future:
  - Many patients with HPV-OSCC no longer have HPV detectable in their mouth after treatment, while others do
  - With new partners, discuss protection methods (e.g. Condom and barrier protection)

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When did I get this infection?

- We do not know the time from first oral HPV infection to cancer but it takes many years
- We know that some people have infection 15 years or more before cancer

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What does having HPV in my tumor mean?

- Oropharyngeal cancer patients with HPV in their tumor live longer, on average, than people without HPV
- However patients who currently smoke tobacco or have smoked in the past, do not live as long as patients who never smoked
- Patients who are current smokers should consider quitting

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Will the HPV vaccine help me?

- The HPV vaccine helps people from getting new HPV infections
- The vaccine will not help you clear an infection you already have
- The vaccine is recommended for people 9-26 years old, and has recently been FDA approved for people up to age 47.

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Will my spouse/partner also get HPV-OSCC?

- The risk of HPV-OSCC may be slightly higher among spouses of HPV-OSCC but this cancer remains rare among spouses
- There are no recommended screening tests for HPV-OSCC

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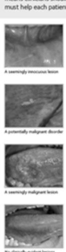
Evidence-Based Clinical Practice Guideline for the Evaluation of Potentially Malignant Disorders in the Oral Cavity: A Report of the American Dental Association

The expert panel suggests that clinicians* should obtain an updated medical, social and dental history and perform an intraoral and extraoral conventional visual and tactile examination† in all adult patients (no quality of evidence rating and no strength of recommendation assigned).

The GRADE Interpretation of the Strength of Recommendations listed below is intended for clinicians. A **Strong Recommendation** means most individuals should receive the intervention. A **Conditional Recommendation** means clinicians should recognize that different choices will be appropriate for individual patients and that clinicians must help each patient arrive at a management decision consistent with his or her values and preferences.

GRADE Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect.
Low	Our confidence in the effect estimate is limited.
Very Low	We have very little confidence in the effect estimate.


A seemingly innocuous lesion
A potentially malignant disorder
A seemingly malignant lesion
No clinically evident lesions or other symptoms

Expert Panel Recommendation	Quality of the Evidence	Strength of Recommendation
The panel suggests that for adult patients with a clinically evident oral mucosal lesion with an unknown clinical diagnosis considered to be **seemingly innocuous** or nonsuspicious of malignancy, or other symptoms‡, clinicians* should follow up periodically with the patient to determine the need for further evaluation. If the lesion has not resolved and the clinical diagnosis of a potentially malignant disorder cannot be ruled out, then clinicians* should perform a biopsy of the lesion or refer the patient to a specialist§.	Low	Conditional
The panel suggests that for adult patients with a clinically evident oral mucosal lesion considered to be suspicious of a **potentially malignant** or **malignant disorder**, or other symptoms‡, clinicians* should perform a biopsy of the lesion or provide immediate referral to a specialist§.	Low	Conditional
The panel does not recommend cytologic adjuncts for the evaluation of potentially malignant disorders among adult patients with clinically evident, seemingly innocuous or suspicious lesions. Should a patient decline the clinician's* recommendation for performing a biopsy of the lesion or referral to a specialist§, the clinician can use a cytologic adjunct to provide additional lesion assessment. • A positive or atypical cytologic test result reinforces the need for a biopsy or referral. • A negative cytologic test result indicates the need for periodic follow-up of the patient. If the clinician* detects persistence or progression of the lesion, immediately performing a biopsy of the lesion or referral to a specialist§ is indicated.	Low	Conditional
The panel does not recommend autofluorescence, tissue reflectance, or vital staining adjuncts for the evaluation of potentially malignant disorders among adult patients with clinically evident, seemingly innocuous or suspicious lesions.	Low to Very Low	Conditional
The panel suggests that for adult patients with **no clinically evident lesions** or symptoms‡, no further action is necessary at that time.	Low	Conditional
The panel does not recommend commercially available salivary adjuncts for the evaluation of potentially malignant disorders among adult patients with or without clinically evident, seemingly innocuous or suspicious lesions and their use should be considered only in the context of research.	Low	Conditional

* "Clinician" refers to the target audience for this guideline, but only those trained to perform biopsies (that is, dentists) should do so.
† "Examination" refers to initial, routine, or emergency visits.
‡ "Symptoms" could include globus sensation, unexplained ear pain or oropharyngeal pain, and hoarseness.
§ "Specialist" refers to clinicians with advanced training in oral and maxillofacial surgery, oral and maxillofacial pathology, oral medicine, periodontology, and otolaryngology – head and neck surgery.

ADA. Center for Evidence-Based Dentistry™

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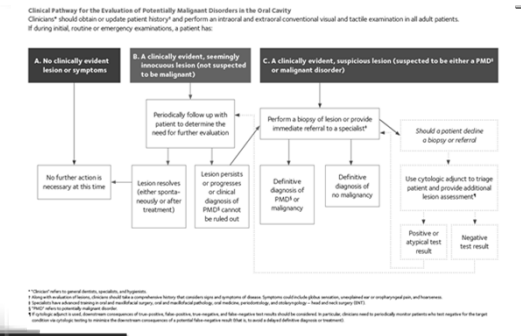
Evidence-Based Clinical Practice Guideline for the Evaluation of Potentially Malignant Disorders in the Oral Cavity: A Report of the American Dental Association



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Key Concepts

- Early detection of oral and oropharyngeal cancer requires the dental team to assess risk and perform screening examination for all patients at initial and recall visits
- Review of steps of screening examination for head and neck cancer; oral brush biopsy
- Modifiable and non-modifiable risk factors for oral and OP cancer (OSCC)
- HPV and OSCC- breaking bad news- cancer and STI
- HPV tests- how should they be used?
- How to communicate with your patients about their HPV and OSCC cancer risk- common questions
- Using motivational interviewing techniques to communicate with your patient about oral cancer risk and behavior change- tobacco cessation, diet and alcohol

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Learning Objectives

1. Plan dental treatment prior to the start of cancer therapy to preserve oral function and reduce risk for dental caries, tooth loss, trismus, osteoradionecrosis and other complications
2. Communicate effectively with the radiation oncologist/radiation therapist about coordination of dental treatment with the overall treatment plan
3. Provide oral supportive care for patients undergoing head and neck radiotherapy, during and after treatment
4. Select and prescribe dental products and devices to assist patients treated for head and neck cancer, including fluorides, sialogogues and saliva substitutes

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Key Concepts for Part II

- Primary treatment for **oral cancer** is surgery; radiation therapy is often an adjunctive therapy
- Patients with **oropharyngeal or tonsil cancer** are almost always treated with radiation therapy as curative treatment, with or without chemotherapy
- IMRT/IMPT allows for **sparing of normal tissues** including salivary glands; however some damage will still occur
- Patients treated with head and neck radiation therapy need thorough dental evaluation, treatment, and prevention started before the beginning of RT.

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Key Concepts for Part II

- Dentist and dental hygienist need to work with the rest of the healthcare team (radiation oncologist, head and neck/oral and maxillofacial surgeon, medical oncologist, speech pathologist) to achieve optimal outcomes- **interprofessional care**
- Dental extractions should be completed **at least 2 weeks** before the start of RT
- Dental extractions and dental disease are associated with greatly increased risk of osteoradionecrosis; **lifetime risk** for the patient
- Xerostomia is the most common short term and long term complication of head and neck radiation therapy
- Caries prevention for head and neck RT: Daily high potency topical fluoride, lifelong; stimulate the saliva; more frequent dental recalls

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Scope of the Problem

- ~ 51,000 new cases of oral cavity and oropharyngeal cancer diagnosed in US in 2018; ~10,000 deaths
  - ~70% of oral and oropharyngeal cancers are associated with HPV (American Cancer Society)
  - Majority are oral squamous cell carcinomas
  - ~62% have regional or distant spread at the time of diagnosis
  - **Five year survival** for all stages combined: ~ 60%
  - Stage, location, and HPV status determine treatment
  - **Most patients will receive head and neck radiotherapy, +/- Chemotherapy as primary curative or adjunct therapy**

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Head and Neck Cancer: Cancer Therapies

- Head and neck radiation.
- Chemotherapy.
- Head and neck surgeries.

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Goals of Dental Management

- Pre-radiation therapy/surgery:
  - Eliminate potential sources of infection
  - Start preventive protocol- topical fluoride
  - Provide patient education about short and long term complications of cancer therapy
- During radiotherapy:
  - Provide supportive care for oral mucosits
  - Provide treatment of oral candidiasis
  - Manage xerostomia
  - Prevent trismus
- Long term- post- treatment:
  - Manage xerostomia
  - Prevent and minimize trismus
  - Prevent and treat dental caries
  - Prevent post-radiation osteonecrosis (ORN)
  - Detect tumor recurrence/new primary tumors

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Oral/Craniofacial Complications of Head and Neck Radiation Therapy

Acute

- Xerostomia and Salivary Hypofunction
- Oral Mucositis and Oral Pain
- Tooth Sensitivity
- Taste Loss
- Oral Candidiasis
- Dysphagia
- Re-activation of Herpes Simplex
- Radiation Dermatitis

Chronic

- Xerostomia and Salivary Hypofunction
- Oral Candidiasis
- Dental Caries, Erosion
- Trismus
- Taste Loss
- Accelerated Periodontal Disease
- Osteoradionecrosis
- Hypothyroidism

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Radiation Therapy Complications

Risk of and Intensity of Complications are related to:

- **Total radiation dose**
  - larger doses result in more complications.
- **Fraction rate**
  - fractions greater than 200cGy/day result in more complications.
- **Site of radiation**

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Oral Mucositis

- Incidence:
  - Radiotherapy ~ 100%
  - Chemotherapy 30-75%
  - BMT up to 90%
- Develops 7-14 days after start of radiotherapy; may last for 5-7 weeks following end of RT with gradual healing
- Varies according to dose, fractions, backscatter from metal restorations
- Infection by Candida or HSV- persistent, severe
- Can lead to sepsis
- Regular epithelial regeneration is impaired due to inability of basal layer cells to replicate
- If not managed, the pain can be severe enough to discourage continuance of therapy----less favorable outcomes

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1. Inflammatory/vascular phase
   - Release of cytokines from the epithelium, vascular dilation
   - IL-1 –increased subepithelial vascularity
   - TNF-α – tissue damage

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2. Epithelial phase
   - **Drugs affecting S phase**
   - Epithelial basal cell damage
   - Reduced epithelial renewal, atrophy and ulceration – begins 4-5 days after administration of the agent
   - Oral mucosa is red- reduced thickness, and increased vascularity
   - Functional trauma leads to ulceration

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3. Ulcerative/bacteriologic phase
   - PAIN!
   - ~ 1 week after administration of agent (Chemotherapy)
   - Usually coincides with neutropenia too
   - Lowest neutrophil counts usually ~ 14 days after administration of agent, 3-4 days after peak mucositis
   - Localized full thickness erosions, covered by fibrinous exudate
   - Secondary bacterial colonization (Gram negative, endotoxins released); cytokines released from connective tissue cells (IL=1, TNF) – more tissue injury

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4. Healing phase
   - Renewal of epithelium proliferation and differentiation
   - Normalization of the WBC,
   - Re-establishment of normal commensal oral flora
   - Anything that negatively impacts on normal wound healing will affect this phase – eg. malnutrition

Oral Mucositis-Pain!

- Depends on degree of damage and elaboration of inflammation and pain mediators
- Worse with poor OH, tobacco, xerostomia, low neutrophil counts
- Non-keratinized tissues at greatest risk
- Oncology Team manages the pain aggressively
  - Narcotic analgesics
  - Topical rinses

Grading Mucositis

NCI-CTC: National Cancer Institute Common Toxicity Criteria scale

1. Erythema of the mucosa
2. Patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)
3. Confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)
4. Necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion

Mucositis Management

- Oncology Team
  - Topical agents
  - Systemic agents
- Dentist
  - Oral environment improvement- look again at teeth, prostheses, oral hygiene, smoking, foods, etc.

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Multinational Association for Supportive Care in Cancer/ International Society for Oral Oncology (MASCC/ISOO)

Clinical Practice Guidelines for the Management of Oral Mucositis secondary to Cancer Therapy. Cancer 2014

- **Recommendations in Favor of an Intervention:**
  - Benzydamine mouthwash be used to prevent oral mucositis in patients with head and neck cancer receiving moderate dose radiation therapy (up to 50 Gy) without concomitant chemotherapy.

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- **Suggestions in Favor of an Intervention:**
  - **Oral care protocols be used to prevent oral mucositis in all age groups and all cancer treatments**
    - **Toothbrushing, flossing , mouthrinses**
  - LLLT (wavelength~623.8nm)- to prevent OM in patients receiving radiation therapy without chemotherapy
  - 2% morphine mouthwash may be effective in treating pain in patients receiving chemoradiation
  - 0.5% doxepin mouthwash may be effective in treating pain from OM
  - Systemic zinc supplements administered orally may be of benefit to prevent OM in oral cancer patients receiving radiation or chemoradiation
- **Suggestions against an Intervention:**
  - Use of chlorhexidine mouthrinse to prevent OM

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Mucositis-topical agents

- Topical anesthetics (dyclonine, lidocaine, doxepin, benzydamine)
  - May have adverse effects if absorbed systemically
  - Cream/gel better than liquid
  - Lacking evidence of effectiveness
- Gelclair- bioadherent gel, polyvinylpyrrolidone and sodium hyaluronate.

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Mucositis-prevention

- Optimize oral hygiene
- Prostheses should be well-fitting and clean; teeth well restored and minimal sharpness
- Avoid irritants: tobacco, ETOH, foods which are spicy, minty, rough, hot

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Radiation guards for mucositis prevention

- Prevents backscatter of radiation off metallic restorations
- Position tissue and oral structures where desired in a daily repeatable position
- Described in literature, however hard evidence of efficacy is lacking; our experience at UM-supports their use (unpublished)

SCHOOL OF DENTISTRY

Oropharyngeal Candidiasis

- Up to 27% of patients undergoing radiotherapy
- Pseudomembranous and erythematous types
- Clotrimazole may be more effective than Nystatin
  - Caution- high sucrose content
- Fluconazole 100 mg per day for 10 days or 200 mg per day for 5 days- clinical recovery
- Resistant , non-albicans candidiasis also possible in this population
  - Infectious disease consult

SCHOOL OF DENTISTRY

Xerostomia and Salivary Gland Hypofunction

- Leads to increased risk for oral fungal infections, dental caries, and tooth loss
- Affects sleep, swallowing, taste, speech
  - This increased risk of oral disease is related to oral microflora changes as well as changes in composition and volume of saliva, and interactions between salivary constituents and oral microbes
- Xerostomia impacts on oral comfort, function and quality of life

SCHOOL OF DENTISTRY

Xerostomia – In Other Words

- My mouth feels dry, rough, sticky
- I feel like there's a film on my teeth
- Feels slimy
- **My mouth burns**
- My tongue feels swollen, too big for my mouth
- I can't speak properly; I slur my speech
- **I have a bad taste in my mouth**
- My mouth hurts, sensitive to spicy food, citrus, ketchup…etc

SCHOOL OF DENTISTRY

How Much Saliva is Enough?

- **How Much Saliva is in the Mouth** depends on the balance between production, amount swallowed and amount lost to evaporation
- Thin film of saliva is needed over all of the mucosa, especially the palate, to prevent a feeling of dry mouth
- **Mucous** saliva produced by the minor salivary glands in the labial and buccal mucosa, soft palate; as well as the submandibular glands
- **Serous** saliva is produced by the parotid glands; most important during mastication, speaking, swallowing

How Much Saliva is Enough?

Whole Saliva Flow Rates

- Stimulated
  - Normal 1-2 ml/min
  - Abnormal <0.5 ml/min
- Resting
  - Normal 0.3-0.4 ml/min
  - Abnormal < 0.1 ml/min

Strategies to Prevent RT-Induced Xerostomia

- Amifostine
- Conformal Radiotherapy Techniques:
  - Salivary Gland-Sparing Intensity Modulated Radiation Therapy
  - Intensity Modulated Proton Beam Therapy
- Submandibular Gland Transfer Surgery
- Administration of Pilocarpine During Radiation Therapy

Strategies to Increase Salivary Flow After RT

- Sialogogues- pilocarpine and cevimeline
- Mechanical Stimulation –sugarless gum, candy
- Citric Acid Stimulation –Salix tablets

SCHOOL OF DENTISTRY

Treat the Xerostomia

- Sip water or ice chips all day
- Saliva substitutes, esp. at bedtime.
- Humidifier in bedroom
- Glycerin or lanolin on lips "Lanollele" or "Lansinoh"
- Avoid caffeine
- Avoid tobacco and alcohol
- Switch to bland oral products-
  - Dry mouth toothpaste, mouthrinses, or children's toothpaste with fluoride

SCHOOL OF DENTISTRY

Gustatory Stimulation Caution during Radiotherapy- Mucositis

- Chewing sugarless gum- careful with TMD/OM
  - Xylitol to help prevent caries?
- Numoisyn lozenges (malic acid and sorbitol)
  - *Align Pharmaceuticals USA*
  - Prescription needed
- Salivasure lozenges
  - *Scandinavian Pharmaceuticals-* shop online
- Xylimelts lozenges
  - *Amazon.com*

SCHOOL OF DENTISTRY

What Else?

- Novel devices under development- Saliwell
  - (not yet FDA-approved)
  - Custom-made appliance for mandibular arch- electrode stimulates the submandibular gland- GenNarino™
  - SaliPen™- insert under tongue

- Acupuncture
- TENS stimulation of the salivary glands
- Massage of the salivary glands
- Improved denture occlusion (if wears CUD/CLD)
- On the horizon- Gene therapy/Tissue engineering for radiation-induced salivary gland hypofunction

SCHOOL OF DENTISTRY

Dental Caries

- Shift in oral microflora after radiotherapy- acidogenic cariogenic flora
- Caries can develop rapidly; as early as 3 months post-RT
- All surfaces at risk, even those most resistant to caries

- Prevention: Daily high potency topical fluoride;
- Oral hygiene practice, Diet counseling

SCHOOL OF DENTISTRY

Potent Daily Topical Fluorides

- Best
  - 1 .1 %Neutral sodium or stannous fluoride gel in vinyl custom fluoride carriers
  - Use for 10 minutes once daily, at bedtime
  - Thera-Fluor-N gel drops; Prevident gel
- Next best
  - 5000 ppm Na F dentifrice, use instead of regular toothpaste once daily
    - Eg. Prevident 5000, OmniiCare,
- What about fluoride varnish applications
  - (every 3 months)?

SCHOOL OF DENTISTRY

Daily Topical Fluoride

- Several small clinical trials of different fluoride regimens have been done in the past: in order to prevent dental caries, patient must use daily fluoride, preferably 1.1% NaF gel in trays
- Meticulous oral hygiene
- Studies have shown that frequent (every 4-6 months) dental recall **improves compliance** with the fluoride regimen and decreases risk of dental caries

SCHOOL OF DENTISTRY

Do patients use the carriers?

- Epstein et al. (1995) studied compliance in use of fluoride gel in carriers in irradiated patients via survey
  - **67%** of those with regular follow-up and reinforcement used fluoride in carriers
  - Without regular follow up, **only 28%** used carriers

SCHOOL OF DENTISTRY

Periodontal Disease

- Direct radiation effects on periodontium
- Risks include accelerated periodontal bone loss AND osteoradionecrosis
- Prevention: Optimal oral hygiene, periodontal therapy as needed, Periodontal surgery is possible for selected cases

SCHOOL OF DENTISTRY

Osteoradionecrosis (ORN)

- Failure of bone healing after head and neck radiation therapy
- Usually occurs 6 months-5 years after radiation; Lifelong risk
- Risk factors:
  - Treatment dependent: radiation dose, volume, brachytherapy, surgery, infection, concomitant chemotherapy, and
  - Patient-dependent factors : age, co-morbidities
  - Oral/dental disease, biopsy, bone proximity to tumor site, excessive tobacco and alcohol consumption
- Greatest risk: Mandible.
- 50 Gy/65%, 70Gy/95%

M SCHOOL OF DENTISTRY

Osteoradionecrosis (ORN)

- Hypovascular, hypocellular, hypoxic bone
- Poor healing capacity
- Can be triggered by surgery or infection
  - E.g. dental extractions, periodontal infection, poorly fitting dentures
- Can occur spontaneously
- Greatest risk: Mandible.
  50 Gy/65%, 70Gy/95%.
- Lifelong risk

M SCHOOL OF DENTISTRY

Prevention of ORN

- All extractions before radiotherapy (ideally at least 2 weeks prior to start of RT)
- Avoid extractions/surgery during and after RT
- If extractions necessary in irradiated bone, atraumatic technique or RCT
- PREVENT CARIES and PERIODONTAL DISEASE !
  - Lifelong Daily 1.1% NaF gel or toothpaste, start before RT
  - Frequent recall- reinforce preventive plan, early detection of caries
- Mucosal guards
- Patient education

M SCHOOL OF DENTISTRY

Prevention of ORN

- Perform all extractions before radiotherapy
- Avoid extractions/surgery during and after RT
- If extractions necessary in irradiated bone, atraumatic technique or RCT
- PREVENT CARIES and PERIODONTAL DISEASE !

Trismus

- Radiation- induced tissue damage in muscles of mastication, especially lateral pterygoids, TMJ
  - Fibrosis, reduced range of motion
  - Reduced oral hygiene, increased caries
- Prevention- Jaw exercises! Physical therapy.

Radiation Therapy and Dental Treatment Planning

- Patients receiving radiation therapy (RT) for head and neck cancer require **dental evaluation and elimination of potential sources of infection**, prior to RT
- Current dental guidelines for patients pre-RT are aggressive because dental infection or oral surgery can cause significant morbidity and even mortality as a consequence of osteoradionecrosis (Little JW, Falace DA, et al, 2012; Murdoch-Kinch and Zwetchkenbaum, MDA Journal 2012)

Goals of Dental Treatment: Pre-treatment Goals

1. Eliminate potential sources of infection
2. Counsel patient about short-term and long-term complications of cancer therapy
3. Provide preventive care

- ✓ Limited time to provide dental treatment
- ✓ Risk of ORN in irradiated bone with dental extractions or untreated infection
- ✓ Increased risk of dental caries in patient whose radiation field includes salivary glands

SCHOOL OF DENTISTRY

Pretreatment Considerations

- Pertinent consultations
- Comprehensive dental assessment
- Eliminate sources of intraoral trauma and infection.
- Obtain casts of dentition
- Provide the patient with information about the impact of treatment on oral health.
- **Patient motivation to maintain their teeth and comply with recommended treatment.**

SCHOOL OF DENTISTRY

Data provided by Radiation Oncology to the Dentist

- Cancer type, stage and prognosis.
- Treatment regimen- Conventional RT, IMRT, Chemotherapy?
- Radiotherapy: Dosage, location and duration of treatment.
- Chemotherapy: Number of treatment cycles and agents to be administered, route of administration.
- Current CBC with differential.
- Anticipated start of therapy.

SCHOOL OF DENTISTRY

Data provided by the Dentist to the Oncologist

- Dental treatment plan including periodontal status, teeth requiring restorations, teeth requiring endodontic treatment and teeth requiring extractions.
- Time necessary to complete dental treatment.
- Other urgent care requirements.
- Unresolved oral issues that may significantly affect patient comfort during therapy.
- Anticipated oral complications.

SCHOOL OF DENTISTRY

Before Radiation Therapy

- Determine prognosis of carious and periodontally involved teeth
- Determine patient's motivation to keep /maintain teeth
- Disease Control
  - Restore carious teeth, and replace fractured restorations
  - Remove calculus
  - Adjust ill -fitting prostheses
  - Perform any necessary extractions
- Prevention
  - Prescribe daily high potency topical fluoride
  - Mucosal guards to reduce mucositis
  - Oral hygiene instruction and dietary counseling

SCHOOL OF DENTISTRY

Dental Examination

- Past and current medical history. Includes history of HSV, HPV and VZV.
- Past surgical history.
- Medications.
- Allergies.
- Past dental history.
- Past social history.
- Clinical Evaluation. Includes comprehensive Intra and Extraoral examinations.
- Periodontal Evaluation.
- Dental Evaluation.
- Radiographic Evaluation

SCHOOL OF DENTISTRY

Oral Surgery, Pre-RT

- **Extractions**:
  - Non-restorable teeth,
  - Third molars not completely covered with bone,
  - Periodontally involved teeth,
  - Teeth with > Class I mobility,
  - Teeth with furcation involvement,
  - apically involved teeth within the radiation field and
  - teeth requiring extensive restorative treatment.
  - Sound teeth may be extracted due to poor patient motivation or compliance. Teeth at greatest risk are **mandibular molars.**

SCHOOL OF DENTISTRY

Oral Surgery, Pre-RT

• Pre-prosthetic surgery.

Timing: 2-3 weeks prior to RT and 3-10 days prior to chemotherapy.

SCHOOL OF DENTISTRY

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During and After Radiation Therapy

- Avoid dental treatment if possible during RT
- May assist with treatment of Candidiasis, mucositis
  - Usually handled by the oncology team

SCHOOL OF DENTISTRY

Extractions Post-RT: What to do?

- Determine how much radiation and where: contact radiation therapists to obtain record
- Consider taking out one or two teeth at a time
- Atraumatic technique
- Alternative: endodontic therapy and submersion/coronal reshaping

SCHOOL OF DENTISTRY

Dentures post-RT

- Looked at those already edentulous prior to diagnosis
- Average time to delivery 8.9 months, half were within 6 months.
- No osteoradionecrosis
- Those with telangiectasias of mandibular mucosa were not successful (indicative of large amount of radiation to the mandibular mucosa.)
  - Beumer et al, 1976

SCHOOL OF DENTISTRY

Prosthodontic procedures: Examination

- Look for scarring, fibrosis, salivary function, trismus.
- Severe mucosa changes may indicate dentures may be contraindicated.
- Examine for undercuts
- Discuss prognosis with patient

SCHOOL OF DENTISTRY

Prosthodontic procedures: Impressions

- Border mold carefully, avoiding overextension.
- Be aware of alterations in the vestibules or FOM anatomy
- Considering placing vaseline on dry mucosa
  - ZOE impression paste may burn
- Digital scans now possible- may offer an advantage

SCHOOL OF DENTISTRY

Before Radiation Therapy

- Current dental guidelines for patients pre-RT are aggressive because dental infection or oral surgery can cause significant morbidity and even mortality as a consequence of osteoradionecrosis
- Patients receiving radiation therapy (RT) for head and neck cancer require dental evaluation and elimination of potential sources of infection**,** prior to RT; Extract teeth with questionable prognosis
  - Restore other teeth, and replace fractured restorations
  - Remove calculus
  - Adjust ill -fitting prostheses

SCHOOL OF DENTISTRY

During and After Radiation Therapy

- Avoid dental treatment if possible during RT
- Manage Trismus-
- Frequent Recall-
  - reinforce prevention,
  - early detection of disease,
  - cancer surveillance

SCHOOL OF DENTISTRY

Goals of Dental Management

- Pre-radiation therapy/surgery:
  - Eliminate potential sources of infection
  - Start preventive protocol- topical fluoride
  - Provide patient education about short and long term complications of cancer therapy
- During radiotherapy:
  - Provide supportive care for oral mucositis
  - Provide treatment of oral candidiasis
  - Manage xerostomia
  - Prevent trismus
- Long term- post- treatment:
  - Manage xerostomia
  - Prevent and minimize trismus
  - Prevent and treat dental caries
  - Prevent post-radiation osteonecrosis (ORN)
  - Detect tumor recurrence/new primary tumors

SCHOOL OF DENTISTRY

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SCHOOL OF DENTISTRY

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Key Concepts Part III

- Before cancer treatment- eliminate potential oral sources of infection; oral preventive care
  - Patients undergoing cancer treatment
    - Myelosuppressive chemotherapy; radiation therapy, hormonal therapy, immunotherapy, hematopoietic stem cell transplant (HSCT)
    - Risks during therapy: infection, bleeding, other specific complications of their cancer, treatment
  - After HSCT, specific complications:
    - Chronic graft versus host disease
    - Xerostomia, oral lichenoid lesions, dental caries
    - MRONJ in patients on anti-resorptive medications- maintain oral health, avoid surgery
- During cancer treatment; support oral care; treat active infections
- Supportive care for long term survivors of cancer
  - Surveillance for new malignancies (including OSCC!), immunosuppression
  - Management of chronic complications of cancer, therapy

SCHOOL OF DENTISTRY

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Treatment of Cancer

- Hormone Therapy-breast cancer
  - Tamoxifen
  - Aromatase inhibitors
- Radiation Therapy
- Surgery
- Anti-neoplastic Chemotherapy
- Targeted Therapies: Precision Oncology
  - Targeted biological therapies; immune checkpoint inhibitors
  - nivolumab-Keytruda®; pembrolizumab-Opdivo®
- Adjunctive agents –bisphosphonates
  - Metastatic carcinoma (breast, prostate)
  - Multiple myeloma

SCHOOL OF DENTISTRY

Cancer

- Dental management of patients before chemotherapy
  - Eliminate potential sources of infection – could be life threatening during myelosuppression
  - Indications for extraction – pocket depths > 6mm, excessive mobility, purulence, periapical inflammation, non-restorable tooth, patient not motivated, tooth is associated with inflammatory, infectious or malignant disease

SCHOOL OF DENTISTRY

Pretreatment Considerations

- Rule out oral disease that may exacerbate during cancer therapy or recovery.
- Provide a baseline for monitoring effects of Cancer Treatment.
- Detect Metastatic lesions.
- Develop strategies to deal with post Cancer Treatment side effects.

  eg. GVHD, MRONJ, Xerostomia, ORN, Surgery, etc.

SCHOOL OF DENTISTRY

Post -Cancer Treatment and Management

- Regular dental recalls
- Surveillance for cancer recurrence, complications of cancer therapy
- Manage xerostomia if present
- Prevent dental caries and periodontal disease, especially important for patients who have had bisphosphonate therapy

SCHOOL OF DENTISTRY

- Extraction Guidelines
  - Minimal trauma, at least 5 days before chemo for maxilla or at least 7 days before chemo for mandible
  - Trim bone at wound margins
  - Obtain primary closure
  - Avoid intra-alveolar hemostatic agents
  - Transfuse if platelets< 50,000
  - Delay if wbc is < 2000 or ANC < 1000 or expected to be within this level within 10 days; if MUST extract can use prophylactic cephalosporin
    - Consider RCT as an alternative

SCHOOL OF DENTISTRY

Complications associated with myelosuppressive chemotherapy

- Mucositis – up to 40% of patients
  - Usually between 7th and 14th day after chemo, coincides with low wbc count
  - Treatment: Maintain mucosal integrity and oral hygiene
    - Bland mouthrinses –salt and soda water
    - Topical anesthetic rinse
    - Antimicrobial rinses
    - Anti-inflammatory agents such as dexamethasone
    - Hydration and nutrition
    - Oral lubricants
  - Remove prostheses – don't wear until healed

SCHOOL OF DENTISTRY

Grading mucositis

NCI-CTC: National Cancer Institute Common Toxicity Criteria Scale

1. Erythema of the mucosa
2. Patchy pseudomembranous reaction (patches generally ≤ 1.5 cm in diameter and non-contiguous)
3. Confluent pseudomembranous reaction (contiguous patches generally > 1.5 cm in diameter)
4. Necrosis or deep ulceration; may include bleeding not induced by minor trauma or abrasion

SCHOOL OF DENTISTRY

- Secondary infections
  - If wbc falls below 2000 cells/mm^3
  - Most frequent infection: Candidiasis
    - Pain, burning, taste alterations, intolerance to foods
    - During chemo most often pseudomembranous
    - Other types also seen – erythematous
    - Treat with nystatin suspension or clotrimazole troches
    - Prophylactic for those with frequent infections – Ketoconazole, fluconazole, itriconazole

SCHOOL OF DENTISTRY

  - Bacterial and viral infections
    - Shift in oral flora to gram-negative organisms –Pseudomonas, Klebsiella, Proteus, E. coli
    - May cause ulcer – should culture – send for sensitivity testing
    - Typical features of swelling, redness etc may be masked by low wbc's
  - Recurrent herpes simplex virus infections
    - Lesions tend to be larger and take longer to heal than normal
    - Acyclovir, valacyclovir and famciclovir as prophylaxis

SCHOOL OF DENTISTRY

- Bleeding
  - Thrombocytopenia may result from chemo
    - Gingival bleeding, submucosal hemorrhage as a result of minor trauma, esp if platelets < 50,000
    - Palatal petechiae, gingival oozing, purpura along lateral tongue
    - When platelets low pt should avoid brushing, use softer device; chlorhexidine in water

SCHOOL OF DENTISTRY

- Neural and Chemosensory Changes
  - Chemotherapy can cause bitter tastes, unpleasant odors and aversion to foods
  - Neurotoxocity can cause pain, toothache
    - Vinblastine and vincristine

SCHOOL OF DENTISTRY

Indwelling catheters – "ports"

- SBE prophylaxis before invasive dental procedures ?
  - Not covered by AHA guidelines
  - Medical consult with oncologist
- Before dental treatment
  - Know wbc count, platelet count
  - Routine dental procedures can be done if granulocyte count >2000/mm3, platelets> 50,000/mm and patient feels ok-usually ~ 17 days after chemo

SCHOOL OF DENTISTRY

- Urgent care
  - If platelets<50,000 need med consult – may need platelets
  - Topical therapy -pressure, thrombin, microfibrillar collagen, and splints
  - If granulocyte count<2000
    - Med consult
    - Antibiotic prophylaxis – no evidence but recommended: Pen v 500 mg at least one hour before, and continue for three days after

SCHOOL OF DENTISTRY

Medication-related Osteonecrosis of the Jaw- MRONJ

- Adverse effect of treatment with denosumab or bisphosphonates
- Risk is dependent on treatment exposure
  - >90% of cases occur in patients with cancer and bone metastases taking high doses to prevent skeletal-related events

SCHOOL OF DENTISTRY

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MRONJ

- Cumulative incidence in patients with malignancy exposed to BPs:
  - 0.8-12%
  - If have dentoalveolar surgery risk increases at least 7 times
  - Mandible: maxilla = 2:1
  - Thin mucosa increased risk (e.g. Tori)
  - Concomitant inflammatory disease increase risk at least 7 times
  - Genetic predisposition- SNPs in cyt p450-2C gene
- Cumulative incidence in patients taking oral BPs:
  - 0.01-0.6%
  - Associated with duration > 3 years

SCHOOL OF DENTISTRY

Bisphosphonates

Non-nitrogenous
- Non-*N*-containing bisphosphonates:
- Etidronate (Didronel®) - 1 (potency relative to that of etidronate)
- Clodronate (Bonefos®, Loron®) - 10
- Tiludronate (Skelid®) - 10

Nitrogenous
- *N*-containing bisphosphonates:
- Pamidronate (APD, Aredia®) - 100
- Neridronate- 100
- Olpadronate- 500
- Alendronate(Fosamax®) - 500
- Ibandronate(Bondronat®) - 1000
- Risedronate (Actonel®) - 2000
- Zoldronate(Zometa®) - 10000

SCHOOL OF DENTISTRY

Denosumab (Xgeva, Prolia)

- Monoclonal antibody; targets the receptor activator of nuclear factor kappa B ligand (RANKL)
- Used to prevent skeletal related events in adults with advanced malignancies involving bone
  - Breast, prostate, multiple myeloma
- Lower doses used to treat osteoporosis

SCHOOL OF DENTISTRY

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MRONJ

- Defined by presence of all the following:
  - Current or previous treatment with BPs or denosumab or anti-angiogenic therapy
  - An area of exposed jawbone or bone that can be probed through at least on intraoral or extraoral fistula that has persisted for more than 8 weeks
  - No history of radiation therapy to jaw or obvious metastatic disease to the jaw

SCHOOL OF DENTISTRY

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STAGE	1	2	3
Staging Criteria	Exposed bone Asymptomatic	Exposed bone Associated pain Adjacent/regional soft tissue inflammatory swelling or infection	As Stage 2 + at least one of - pathologic fracture - extra-oral fistula - oro-antral fistula - Radiographic evidence of osteolysis extending to inferior border of mandible or floor of maxillary sinus
Treatment	Conservative therapy-OHI Consider surgery to remove necrotic bone Treat active dental disease Topical antibiotic rinses	As Stage 1, and Surgery to remove necrotic bone Systemic antibiotics to treat infection Treat symptoms if patient declines surgery	As Stage 2, and Surgery to remove necrotic bone In extended cases, consider jaw resection and reconstruction Systemic antibiotics to treat infection

SCHOOL OF DENTISTRY

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Current AAOMS Guidelines (2014)

- Treatment and Management Recommendations
- Prevention: Before Start Therapy
  - Comprehensive examination, radiographs
  - Eliminate sources of potential sources of infection
  - Periodontal therapy – pocket elimination
  - Extract indicated teeth
  - Restore caries, replace defective restorations
  - Evaluate fit and function of prostheses
  - Prophylaxis and OHI
  - Educate about signs of ONJ
  - Frequent follow-up care

SCHOOL OF DENTISTRY

Management of Patients with MRONJ

- Routine restorative care
- Scaling and prophylaxis with atraumatic technique, gentle soft tissue management
- Avoid dental extractions if possible, unless mobility >3
- Atraumatic extraction technique; weekly follow-up for first month, then monthly until sockets completely healed
- Carious teeth – endo; prepare as overdenture abutments, cut off at gingiva

SCHOOL OF DENTISTRY

Management of MRONJ

- Treat the area of ONJ:
  - Eliminate sharp edges of bone
  - Superficial debridement
  - Antibiotics if evidence of infection
  - Chlorhexidine mouthrinse, 3-4 times per day
  - Soft vinyl appliances?
  - Reline of poor fitting prostheses
  - Odontogenic infections : treat aggressively with antibiotics
  - No scientific evidence to support the discontinuation of bisphosphonate therapy to promote healing
  - Coordination of care: Dentist and Oncologist
  - More research is needed – long term clinical trials

SCHOOL OF DENTISTRY

Precision Oncology

- mTOR inhibitors
  - Mammalian target of rapamycin-inhibitors
  - Used to treat renal cell carcinoma, mantle cell lymphoma
    - Everolimus, Temsirolimus
- Immune checkpoint inhibitors
  - **Programmed cell death inhibitors (PD-1)**
  - Used to treat melanoma, nonsmall cell lung cancer
    - ivolumab, pembrolizumab
  - **Programmed cell death ligand inhibitors (PDL-1)**
  - Used to treat metastatic nonsmall cell lung cancer
    - atezolizumab
  - Cytotoxic- T cell antigen 4 inhibitors
    - ipilimumab

SCHOOL OF DENTISTRY

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Precision Oncology

- Multi-targeted tyrosinase kinase inhibitors (TKI)
  - Block several tyrosinase kinase pathways in human cancers
    - VEGFR, EGFR, HER2, PDGFR ….
    - Angiogenesis inhibitors
      - Sunitinib for metastatic renal cell carcinoma, advanced GIST, metastatic neuroendocrine tumor
      - Sorafenib for hepatocellular carcinoma, renal cell carcinoma, thyroid carcinoma
      - Axitinib for renal cell carcinoma
      - Cabozantinib for hepatocellular carcinoma, metastatic renal cell carcinoma, medullary thyroid cancer
    - BCR-ABL inhibitors
      - Imatinib for CML, ALL, GIST, myelodysplasia
    - HER inhibitors
      - Lapatinib for HER2+ breast cancer
      - Afatinib for nonsmall lung cancer

SCHOOL OF DENTISTRY

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Precision Oncology

- Monoclonal antibodies
  - Bevacizumab- for breast cancer, nonsmall cell lung cancer, ovarian cancer, glioblastoma, cervical cancer
  - Cetuximab- for colorectal cancer, **head and neck carcinoma**

SCHOOL OF DENTISTRY

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Precision Oncology

- Immune checkpoint inhibitors
  - Oral manifestations in ~10% of patients taking on agent
  - Mucosal changes most common:
    - Lichenoid reactions
    - Gingival erythema, sloughing
  - Dry mouth ~5%

SCHOOL OF DENTISTRY

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Precision Oncology

- Tyrosine Kinase Inhibitors
  - Adverse events associated with these drugs:
    - Fatigue/asthemia, anorexia/loss of appetite, hand-foot skin reaction, stomatitis, dysgeusia, diarrhea/abdominal pain, hypothyroidism, hypertension and myelosuppression
  - With TKIs, the "stomatitis" includes
    - Oral mucosal sensitivity (burning associated with hot spicy acidic foods and drinks)
    - Normal appearing oral mucosa
    - Dysgeusia/hypogeusia

SCHOOL OF DENTISTRY

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Summary

Most Common Oral Side Effects of Targeted Therapies

Agent	Side effect
MTOR inhibitors: *Everolimus, temsirolimus*	Stomatitis
Multi-targeted inhibitors of VEGF and PDGF: *Sunitinib, Axitinib*	Stomatitis, benign migratory glossitis, MRONJ
EGFR inhibitors *Cetuximab, Bevacizumab*	Mucositis
BRAF inhibitors	Hyperkeratotic lesions
Imatinib	Pigmentary changes, lichenoid reactions
PD-I monoclonal antibodies: *ivolumab, pembrolizumab*	Xerostomia, dysgeusia, lichenoid lesions
From Vigarios E, Epstein JB, Sibaud V. Supp Care Cancer 2017 25:1713-1739	

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- Every year 50,000-60,000 hematologic stem cell transplants are performed worldwide
  - 20,000 allogenic; nearly half to treat acute leukemia
  - 35,000 autologous; multiple myeloma and NHL
- Used as curative therapy for hematologic disease, other solid cancers, some inborn errors of metabolism and autoimmune disorders
- HSCT also used to rescue bone marrow after myeloablative chemo or radiation therapy

SCHOOL OF DENTISTRY

Types of HSCT

- Bone marrow transplant
  - Marrow harvested from posterior iliac crest after administration of GSF
- Peripheral blood stem cell transplant
  - Preferred source for harvesting stem cells in adults
  - Earlier engraftment and recovery of granulocytes and platelets than BMT
  - Reduced early infection and shorter hospitalization
  - Higher incidence of cGVHD
- Umbilical cord blood (UBC)
  - Pediatric transplants
  - Slower engraftment and increased graft failure
  - Limited number of cells from single umbilical cord

SCHOOL OF DENTISTRY

Types of HSCT

- Autologous HCT
  - Marrow reconstitution
  - Curative for chemosensitive malignancies such as NHL and Hodgkin's
  - Multiple myeloma- tandem HCT, (combined autologous HCT plus nonmyeloablative allogenic HCT)
- Allogeneic HCT
  - Preferred treatment for leukemia –GVL
  - Matching HLA type
  - Immunosuppressive regimens are required in allogenic HSCT even when grafts are from genotypically identical donors

Conditioning Regimens

- Myeloablative therapy
  - Eradicated malignant cells
  - Prior to allogenic HCT, induce immunosuppression to induce engraftment
  - Total body irradiation (TBI) plus cyclophosphamide was standard
    - Toxicity – now uses radiation-free regimens
  - Now- reduced intensity conditioning and non-myeloablative regimens
    - Immunosuppressive, to enable engraftment
    - Rely on graft to eradicate cancer
    - Less toxicities short term, but more complications long term

Donor Lymphocyte Infusion

- Induce remission in early stage relaepse CML, after allogenic HCT
- Moderately effective for relapses of AML
- Rarely effective in relapsed ALL
- Moderately effective in MM
- Complications –acute and chronic GVHD
- Graft rejection or successful conversion to full donor type

Complications Affecting the Oral Cavity

- Mucositis
- Infection
- Oral bleeding
- Graft-versus-host disease
- Salivary changes, dry mouth
- Taste alterations
- Second malignancies
- Osteoporosis and bone necrosis

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Mucositis

- Induced by radiation therapy and/or chemotherapy
- Mucosal damage –mild inflammation to extensive ulceration
- Myeloablative HCT –usually affects non-keratinized mucosa
- Peaks 6-12 days post transplant, begins to resolve day 14-19
- OM is most debilitating acute complication, can cause life threatening infection
- 74%-100%
- Conditioning regimen, genetics, being overweight increase risk of OM
- Differential diagnosis includes reactivation of Herpes simplex

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Infection

- Frequent complication of HCT
- Risk factors- underlying malignant disease, other medical issues, presence of chronic or latent infections, type of transplant, source of stem cells antimicrobials, mucosal barrier loss, GVHD
- Uncomplicated recovery starts with healing of mucosal tissues and recovery of granulocytes and NK cells~ 2 weeks after myeloablative conditioning
- Oral microflora is a major source of oral infection, especially in presence of mucositis!
- Must treat existing oral infection, reduce the oral microbial load, maintain good oral hygiene after HCT
- Candidiasis, aspergillosis, Late infection with CMV
- Dental infections –can become an source of systemic infection in neutropenic patients
- Local signs and symptoms of infection are reduced-hard to diagnoses

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Oral Bleeding

- Can occur during profound thrombocytopenia due to active disease in patients with acaute leukemia pr secondary to chemotherapy
- Platelets > 40,000 –rare oral bleeding
- Platelts < 10,000 spontaneous oral hemorrhage
- HSV infection significantly increases bleeding risk

Graft versus Host Disease

- Major cause of morbidity and mortality in allogenic HCT
- Reaction of donor-derived immunocompetent cells against recipient's tissues
- Clear distinction between aGVHD and cGVHD based on time of occurrence is no longer valid in era of RIC transplantation
- Defined now based on clinical features

- Acute GVHD
  - Apoptosis and necrosis of the skin, GI tract, and liver
  - Skin rashes, diarrhea, nausea and vomiting, and jaundice
  - Painful erythematous, ulcerative and desquamative oral lesions

- Chronic GVHD
  - ~ 50% of allogenic HCT develop cGVHD
  - Can affect skin, GI tract, eyes, lungs, gential tract, and liver
  - Inflammatory and fibrotic process
  - Oral lesions in 70% of PBSCT and 53% of BMT recipients with cGVHD
  - Lichenoid changes with varying degrees of erythema, white striae and plaques, ulceration, hyposalivation mucoceles, gingival atrophy tooth hypersensitivity and sclerosis of oral mucosa with limited mouth opening
  - Increased infection risk –candidiasis and caries

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Salivary Changes

- Decreased salivary flow and xerostomia are common after HCT
- Second most distressing symptom at discharge fro transplant, and 1 year after HCT
- Superficial mucoceles can be found on the soft palate in many patients

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Taste alterations

- Dysgeusia, hypogeusia and ageusia
- Cyclosporine and tacrolimus may induce taste changes
  - Metallic, salty, sweet, sour or bitter; or no taste
- Lasts for days to months but usually recovers
- Can affect nutrition
- Significant effect on quality of life

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Second Malignancies

- Previous exposure to chemo/radiotherapy, alterations in immune function, GVHD and GVHD therapy all increase risk
- Lymphproliferative disorders, hematologic malignancies (early) and solid tumors (late)
- Solid tumors_ most often squamous cell carcinoma
  - Can occur in oral skin sites previously affected by GVHD
  - Lon term follow-up needed to detect cancers in early stage

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Osteoporosis and Bone Necrosis

- Conditioning regimens, especially radiation can induce endocrine function abormalities
- Long term corticosteroid therapy can lead to osteoporosis which may affect alveolar bone and TMJ
- HCT patients may have received bisphosphonates which may lead to musculoskeletal pain and ONJ

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Oral Supportive Care

- Pre-conditioning phase
- Early post-HCT: neutropenic phase/ engraftment
- Late post-HCT: immune reconsitution phase
- Long term follow-up

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Oral Supportive Care

- Main goals of oral/dental management are to prevent infections during periods of neutropenia, and to reduce oral side effects associated with HCT

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Pre-conditioning Phase

- Oral dental evaluation (clinical and radiographic)
- Reduce oral bacterial load
- Eliminate foci of infection
- Eliminate sources of trauma
- Educate patient and family
- Consider cryotherapy and Palifermin in myeloablative HCT
- Consider prophylaxis for strep, viral and fungal infection

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Early post-HCT: neutropenic

- Good OH; chlorhexidine may be indicated for plaque reduction and management of fungal infection
- Keep oral tissues and lips moist
- Avoid trauma (appliances, prostheses, hard hot spicy food)
- Assess mucositis and pain, mange pain
- Assess oral cavity for infection, culture suspect lesions
- Assess for bleeding
- Consider sugarless gum, salivary substitutes or sialogogues for xerostomia

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Late post-HCT ; Immune reconstitution phase

- Assess oral cavity for infection and culture suspect lesions
- Assess oral cavity for GVHD in allogenic HCT
- See patients with GVHD regularly
- See patients with cGVHD regularly; treat locally
- Reinforce OHI
- Perform invasive dental procedures after consult with hematologist
- Treat xerostomia, topical fluorides, remin products
- Be aware of oral lesions associated with tumor relapse

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Long term Follow-up

- Monitor oral cavity for oral complications (GVHD, hyposalivation, infections, caries and periodontal risk, second malignancies
- Be aware of oral lesions associated with tumor relapse
- Be aware of jaw osteonecrosis for patients on bisphosphonates
- Assess pediatric HCT patients for effects on craniofacial growth

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Oral cGVHD Treatment (Oncologist, Hospital Dentist)

- Oral mucosal lesions:
  - – Topical corticosteroids –
    - Dexamethasone liquid 0.5 mg/5 ml; 5 ml swish and spit or swallow q.i.d. prn
    - Fluocinonide gel 0.05%
    - Clobetasol gel 0.05%
    - Tacrolimus liquid or ointment 3% or 10% apply tid
    - Cyclosporine suspension
    - Azathioprine

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Oral cGVHD Treatment

- Salivary Hypofunction
  - Evoxac or Salagen
  - OTC saliva substitutes
  - Numoisyn buffered citric acid lozenges
  - Chew sugarless gum, with xylitol
  - Water or aloe-based lip balm
- Caries Risk
  - Topical fluorides -1.1% NaF
  - Chlorhexidine
  - MI paste
  - Nutritional counselling

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Oral cGVHD Treatment

- Oral mucosal pain
  - Magic mouthwash
    - 2% viscous lidocaine, Benadryl suspension, Maalox, +/- Nystatin suspension +/- Dexamethasone
  - 2% viscous lidocaine swish and spit
  - Systemic analgesics –work with team
  - Gelclair mouthrinse

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The Opioid Epidemic and Dentistry

- In 2015 ~12.5 million people misused prescription opioids; opioid ODs caused 33,091 deaths in 2015 alone
- Dentists wrote 6.4% of all opioid prescriptions in the US in 2012
  - Rate of opioid prescriptions in dental patients increased from 130.58 /1000 in 2010 to 147.44/1000 in 2015
  - ~68% during surgical dental visits; ~31% in non-surgical dental visits
  - Largest increase was in 11-18 year olds
- Quantity of opioids prescribed was 20
- The groups aged 11-18 and 19-25 received higher daily MME doses than did the other age groups
- Gupta N, Vujicic, Blatz A. Opioid prescribing practices from 2010 through 2015 among dentists in the United States JADA 2018:149(4):237-245.

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The Opioid Epidemic and Dentistry

- Recent study in JAMA –young people 13-30 who filled an opioid prescription immediately before or after they had wisdom teeth extracted were nearly 3 X as likely as their peers to still be filling opioid prescriptions weeks or months later.
  - Harbaugh CM, Nalliah RP, Hu HM, et al. Persistent opioid use after wisdom tooth extraction. JAMA 2018

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Evidence-based recommendations for managing acute dental pain

- NSAIDs with or without acetaminophen, offers the most favorable balance between benefits and harms, optimizing efficacy while minimizing acute adverse events

Moore PA, Ziegler KM, Lipman RD, Aminoshariae A, Carrasco-Labra A, Mariotti A. Benefits and harms associated with analgesic medication used in the management of acute dental pain. JADA 2018 149(4):256-265.

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- Efficacy data from high quality studies for analgesic agents available in the US
- Most effective analgesic/combination:

Ibuprofen 400 mg plus Acetaminophen 1000 mg

- NNTB= 1.5; 95% C.I. 1.4-1.7
- At least 50% maximum pain relief over 4-6 hours,
  - 72 % versus 6 % for placebo
- Mean or median time to remedication
  - 83 hours versus 1.7 hours for placebo

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What about Contraindications?

- Patients on anticoagulants/antithrombotic drugs?
  - Interact with aspirin, NSAIDs
  - Acetaminophen, opioid analgesic may be indicated, short term, lowest dose needed for the desired pain control
- Pregnant patient?
  - Late third trimester, NSAIDs contraindicated
  - Other considerations
- Liver disease? Renal disease?

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Guidelines for Managing Pain:
Summary of Selected Best Practices

Pre- procedure:

- Opioid prescriptions should not be written prior to completing a dental procedure
- Communicate conservative philosophy be emphasizing the efficacy and appropriateness of OTC medications' analgesic propertied
- Address dental pain through clinical intervention rather than opioid pain relief
- Refer patients to a free or low-cost dental program in the absence of insurance of financial constraints

SCHOOL OF DENTISTRY www.michigan.gov/documents/lara/Acute_Care_Opioid_Treatment_and_Prescribing_Recommendations_Dental_Final

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Guidelines for Managing Pain: Summary of Selected Best Practices

- Prescribing
  - The prescription drug monitoring program (PMDP) must be accessed prior to prescribing controlled substances scheduled 2-5, in compliance with Michigan law
  - Conduct full dental and medical history of the patient and include analysis of current medications
  - Identify any high-risk behaviors or diagnoses (previous substance use disorders, alcohol or tobacco use, psychiatric comorbidities including depression or anxiety)
  - Non-opioid therapies: acetaminophen, ibuprofen should be encouraged as the primary treatment
  - Non-pharmacologic therapies- acupuncture, mindful practice should be encouraged

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Prescription Drug and Opioid Abuse Commission (PDOAC)

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- For breakthrough or severe pain: short-acting opioids (hydrocodone, oxycodone) should be prescribed at the lowest effective dose for no more than 3-5 days
- Do not co-prescribe opioids with other sedatives or CNS depressants (e.g. benzodiazepines)
- Consider offering naloxone co-prescription to patients who may be at increased risk for OD, including those with a history of OD< substance use disorder, already prescribed benzodiazepines, and high doses of opioids (> 50 MME/Day)

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- For patients discharged with an opioid prescription
  - Discuss expectations regarding recovery and pain management goals with patient
  - Educate patient and parent/guardian regarding safe use of opioids, potential side effects, OD risks and developing dependence or addiction as required by Michigan law
  - Emphasize not using opioids with alcohol and other sedatives
  - Educate patient on tapering of opioids as dental/oral pain resolves
  - Refer to Michigan-Open.org for additional patient resources
  - Refer and provide resources for patients who have or are suspected to have a substance use disorder

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If you must prescribe an opioid analgesic…..

- Michigan Opioid Laws- Public Act 246 of 2017; Public Act 247 of 2017; Public Act 248 of 2017; Public Act 249 of 2017:
  - Mandated MAPs report
  - Minor's first controlled substance
  - Patient education
  - Seven-day prescription limit
  - Bona-fide patient-prescriber relationship

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- Beginning June 1, 2018 before prescribing or dispensing to a patient a controlled substance a quantity that exceeds a three-day supply, a licensed prescriber shall obtain and review a report concerning that patient from the Michigan Automated Prescription System.(MAPS) The prescriber must also be registered with MAPS

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- Beginning June 1, 2018 a prescriber shall comply with the following before issuing a new prescription for a controlled substance containing an opioid to a minor:
  - Discuss with the minor and the parent/guardian the potential risks of addiction and overdose associated with the controlled substance
  - Discuss the increased risk of addiction to a controlled substance to an individual suffering from both mental and substance use disorders
  - Discuss the danger of taking a controlled substance containing an opioid with a benzodiazepine, alcohol or another central nervous system depressant
  - Discuss any other information in the patient counseling information section of the label for the prescription

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- The signature of the minor's parent/guardian to consent to the minor's treatment is required on a "start talking consent form" which is to be filed in the minor's medical record

- Beginning June 1, 2018, before an opioid is prescribed to a patient, a prescriber shall provide the following information:
  - Dangers of opioid addiction
  - How to dispose of an expired, unused or unwanted controlled substance
  - Delivery of a controlled substance is a felony under Michigan law
  - If patient is pregnant or female of reproductive age the short and long term effects of exposing a fetus to an opioid, including neonatal abstinence syndrome
  - Obtain signature of patient in a start talking consent form, kept in patient's medical record
- Beginning March 21, 2018- must have a bona fide prescriber-provider relationship with the patient

References

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- www.michigan.gov/documents/lara/LARA_DHHS_Opioid_Laws_FAQ_05-02-2018_622175_7
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