

Incidence of Adverse Oral Outcomes in Cancer Patients

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Financial Disclosure

- I have no significant relationships to disclose



GOAL OF CHEMOTHERAPY

- Interfere with cell division
- Narrow toxicities
 - Short Term: Nausea, Vomiting, Alopecia, Myelosuppression, Renal failure, Hypersensitivity, Stomatitis
 - Long Term: Leukemia, Cardiomyopathy, Pulmonary Fibrosis, Peripheral Neuropathy, Hemolytic-Uremic Syndrome, Sterility
- Strong correlation between dose and cure rates



GOAL OF RADIOTHERAPY

- Goal deliver tumoricidal dose and spare normal tissue
- Tumoricidal dose:
 - Lymphomas: 4000-4500 rads
 - Solid Tumors: 5000-7000
- Tissues of rapid cell renewal most vulnerable
 - Skin, Bone Marrow, GI mucosa



Oral Complications of Cancer Therapy

- Acute Complications
 - Mucositis
 - Oral Pain
 - Microbial Infections
 - Xerostomia
 - Dysgeusia



Mucositis

- Etiology
 - Direct stomatotoxic effects of chemo and/or radiotherapy
 - Role of neutropenia?
 - Role of oral colonization?



Mucositis

- Clinical Appearance
 - Erythema to ulceration
- Differential Diagnosis
 - Viral
 - Fungal
 - Traumatic
 - Autoimmune: Recurrent Aphthae
- Clinical Assessment
 - WHO Oral Mucositis Scale



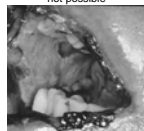
WHO ORAL MUCOSITIS SCALE

- Rates overall status
- Combines mucosal appearance, symptoms, functions
 - Grade 0: no changes
 - Grade 1: soreness/erythema
 - Grade 2: " + ulceration / solid foods
 - Grade 3: " " / liquid diet
 - Grade 4: " " / oral
alimentation not possible



WHO ORAL MUCOSITIS SCALE

- Grade 0: No changes
- Grade 1: Soreness/erythema
- Grade 2: + ulceration / solid foods
- Grade 3: / liquid diet
- Grade 4: / alimentation not possible



GUIDELINES

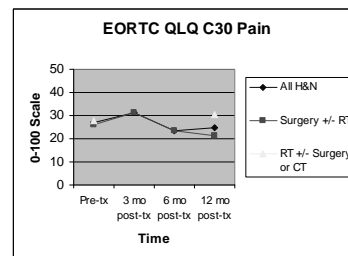
- Oral Mucositis Incidence

- HDC + HSCT
 - Oral mucositis incidence near 100% for any grade
 - 30-50% Grade 3 and 4 oral mucositis without TBI
 - >60% Grade 3 and 4 oral mucositis with TBI
- RT for head and neck cancer
 - Near 100%
- Standard chemotherapy regimens
 - non-Hodgkin lymphoma and breast cancer (standard doxorubicin and -taxane based therapies with grade 3 and 4 mucositis: 3-10%)



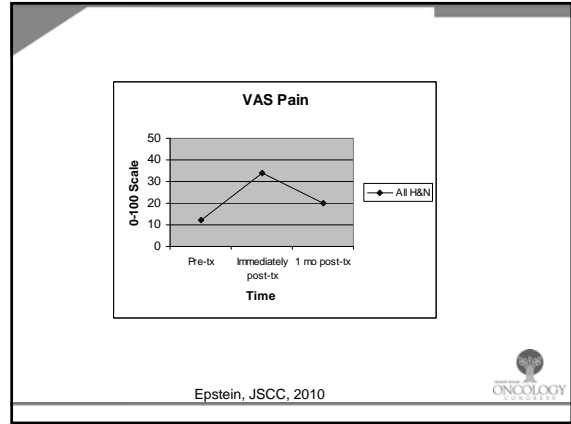
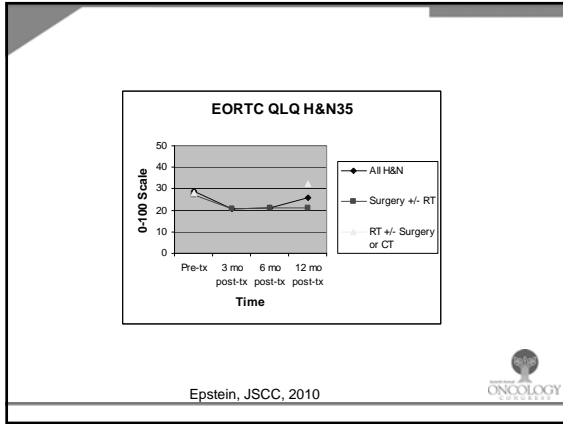
Oral Pain

- Etiology
 - Acute mucosal tissue injury
 - Role of inflammatory or infectious mediators?
- Clinical Assessment
 - EORTC QLQC30
 - EORTC Head and Neck
 - University of Washington Quality of Life questionnaire
 - VAS
 - Study specific questionnaires: Epstein Addendum, French Schaub, Hospital Anxiety and Depression Scale [HADS], Oral Mucositis Daily Questionnaire [OMDQ]).



Epstein, JSCC, 2010





Microbial Infection - Bacterial

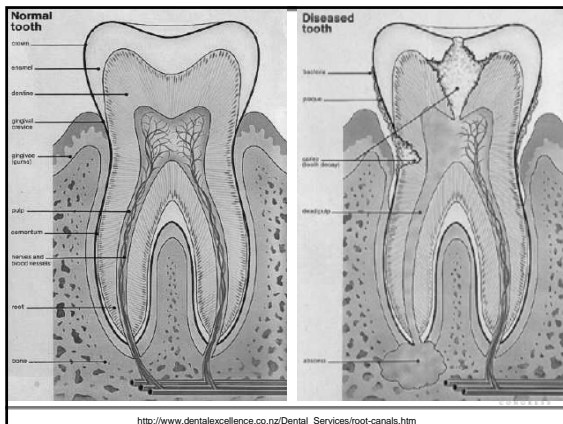
- Etiology
 - Dental and periodontal disease are bacterially mediated
 - Mucosal colonization of atypical oral flora occurs in hospitalized and outpatient cancer patients
 - Oral mucosal bacterial infections << fungal and viral infections
 - Bacteremia from mucositis
 - Bacteremia from periapical disease (caries) vs. gingival/periodontal crevice?
- Clinical Assessment
 - Dental and periodontal examination
 - Mucosal changes

ONCOLOGY

Microbial Infection - Bacterial


- Increased incidence of Strep Viridans bacteremia during past 10-15 years
- Risk factors: Severe neutropenia, oral mucositis, high-dose Ara C, antimicrobial prophylaxis
- S. mitis as most common isolate

ONCOLOGY



Microbial Infection - Bacterial

- Pericoronitis
 - 7% (3/43)¹
 - 5% (2/44)²
- Severe Gingivitis
 - 19% (8/43)¹
 - 58% (22/38)³
 - 14% (6/44)²
- Dental infection/abscess
 - 4-19%^(4,5)



1) Fayle SA. Pediatr Dent. 1991 2) Batiga AM. J Indian Soc Pedod Prev Dent. 1995
3) Laine PG. Oral Oncol. Eur J Cancer. 1992 4) Niehaus, CS. Cancer Nurs. 1987. 5) Arduzzoni, A. Br J Cancer. 1996

ONCOLOGY


Mucositis from Bacterial Species

- **Systematic Review:** 13 prospective observational studies - 300 patients with 13 diagnoses
- Most common species:
 - Gram (-): Pseudomonas sp. and E. coli
 - Gram (+): Staph. sp. and Strep. sp.
- Outcome: No clear pattern for quantitative or qualitative changes, or association with mucositis
- Limitations
 - Varied patient populations, sample size, chemo.
 - Pediatric and adult, inpatient/outpatients, mucositis assessment, microbiology methodology and sites cultured

ONCOLOGY

Napenas JJ et al. Oral Surg Oral Med Oral Path. 2007

Alterations in Oral Flora Following Chemotherapy



Methods:

- Characterize oral bacterial flora before and after first cycle of intensive chemotherapy
 - Prospective cohort – Outpatients – Breast Ca
 - Oral bacterial sampling Day 0 and between 7-14
 - Culture-independent molecular techniques

ONCOLOGY

Napenas, J et al OOOOE, 2010

Alterations in Oral Flora Following Chemotherapy

- 9 patients
- 41 bacterial species
 - 9 species – pre and post-chemotherapy
 - 7 species - pre-chemotherapy only
 - 25 species - post-chemotherapy only
- Increased species diversity – 6
- Decreased species diversity – 2
- No changes in number of species – 1
- Conclusion: Appears to be a shift to a more complex oral bacterial profile on the buccal mucosa of breast cancer patients

ONCOLOGY

Microbial Infection - Bacterial

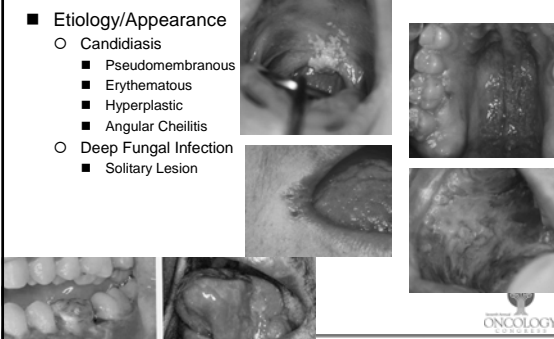
Oral Hygiene and Gingival Indices as Risk for Bacteremia

- Methods:
 - 98 healthy subjects
 - Multiple blood cultures before, during and following tooth brushing
- Results:
 - 32% incidence bacteremia with tooth brushing
 - 3.8 and 4.4 fold increased risk of bacteremia with mean calculus and plaque scores ≥ 2
 - Generalized bleeding with brushing associated with an 8-fold increased risk of bacteremia

ONCOLOGY

Microbial Infection - Fungal

- Etiology/Appearance
 - Candidiasis
 - Pseudomembranous
 - Erythematous
 - Hyperplastic
 - Angular Cheilitis
 - Deep Fungal Infection
 - Solitary Lesion



ONCOLOGY

Microbial Infection - Fungal

- Differential diagnosis
 - Trauma
 - Mucositis
 - Epithelial Dysplasia
 - Squamous Cell Carcinoma
 - Metastasis
 - Mesenchymal-type benign tumor
- Clinical Assessment
 - Appearance
 - Smear
 - Culture
 - Biopsy- deep fungal



Weighted prevalence of clinical oral fungal infection by cancer therapy

Cancer Therapy	Number of Studies	Total Number of Subjects	Prevalence Pre-Treatment	Prevalence During Treatment	Prevalence Post-Treatment
All treatments	Eleven	480	7.5%	39.1 % (0.08) [21.0 – 57.2]	32.6% (0.09) [0 - 100]
CT only	Five	212	NA	38.0% (0.13) [1.2 - 74.7]	NA
RT only	Six	262	7.5%	37.4% (0.16) [0 – 88.4]	32.6% (0.09) [0 – 100]
CT + RT	One	6	NA	66.7%	NA



Weighted prevalence of oral fungal colonization by cancer therapy

Cancer Therapy	Number of Studies	Total # of Pts.	Prevalence Pre-Treatment	Prevalence During Treatment	Prevalence post treatment
All Treatments	Seven	267	48.2% [22.3 – 74.1]	72.2% [59.5 – 84.8]	70.1% [57.8 – 82.3]
CT only	Four	157	47.3 [0 - 100]	72.8% [0 - 100]	69.3%
RT only	Three	110	50.0 [0 - 100]	74.5% [34.1- 100]	71.4%
CT + RT	Zero	0	NA	NA	NA



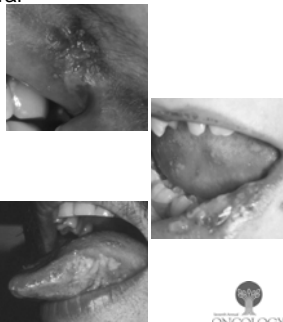
Weighted prevalence of colonization by candida species

Candida species	Number of Studies	Total # of Pts	Prevalence
<i>Candida albicans</i>	Five	174	46.2 % (0.13) [9.8 – 82.5]
<i>Candida tropicalis</i>	Three	122	16.6 % (0.07) [0 – 48.4]
<i>Candida glabrata</i>	Three	120	5.5 % (0.02) [0 – 12.8]
<i>Candida krusei</i>	Three	120	3.0% (0.02) [0 – 9.8]



Microbial Infection - Viral

- Etiology/Appearance
 - Herpes Simplex Virus-1
 - HSV-2
 - Other Herpesviruses
 - VZV
 - EBV
 - CMV



Microbial Infection - Viral

- Differential Diagnosis
 - Mucositis
 - Trauma
 - Fungal
 - Allergy
 - Vesiculoerosive
- Clinical Assessment
 - Appearance
 - Smear
 - Culture
 - Biopsy



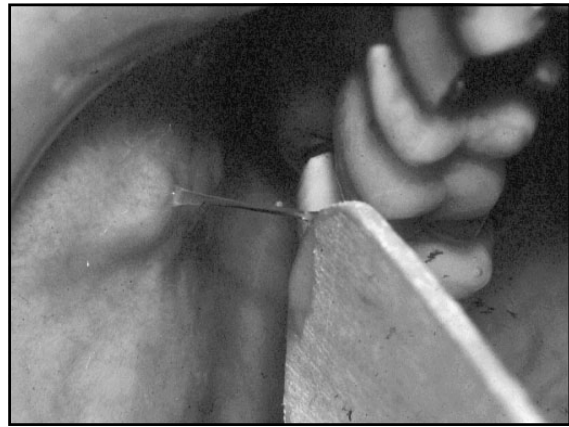
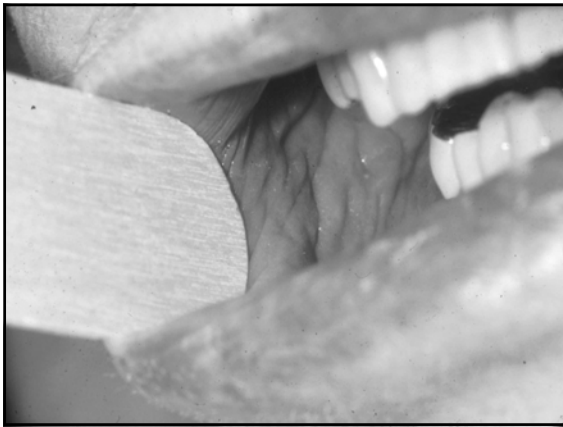
Oral Microbial Infection - Viral

- Chemotherapy
 - The prevalence of oral HSV infection was 49.8% in patients with oral ulcerations
 - The prevalence was found to be lower when percentage was calculated relative to the patient population independently of the presence of oral ulcerations – 33.8%
- Radiotherapy
 - 0-43.2% in 2 studies (both with adjunctive CT)



Xerostomia

- Definition: Xerostomia vs. Salivary Hypofunction
- Etiology
 - RT and CT- direct toxic effect with salivary tissue
 - Xerostomia medication side effects
- Assessment
 - Subjective complaint
 - VAS, RTOG/EORTC, EORTC QLQ-C30
 - Objective tests
 - Salivary flow
 - Tissue dryness



Production of Saliva

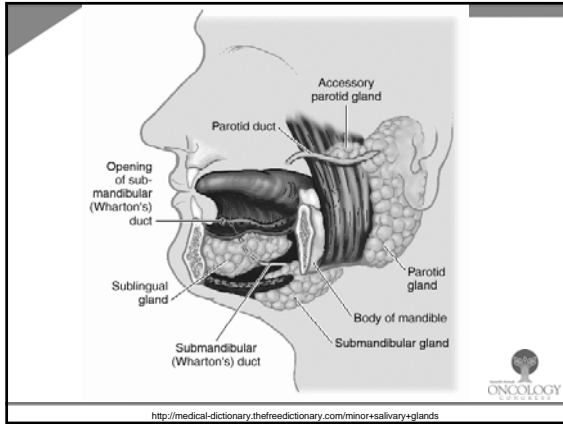
- Healthy adult produces 1.5 L of saliva in 24 hours.
- 3 major pairs of salivary glands
 - parotid
 - submandibular
 - sublingual
- Minor salivary glands
 - approximately 750
 - not located in the gingiva or anterior hard palate



Production of saliva

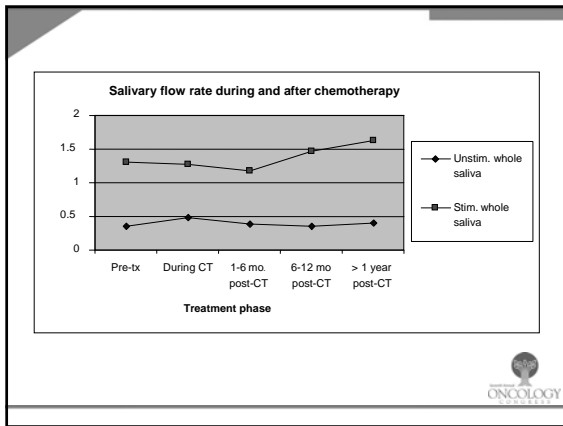
- Percentage of saliva production
 - Parotid 45%
 - Submandibular 45%
 - Sublingual 5%
 - Minor salivary glands 5%
- The sublingual and minor salivary glands produce the majority of mucous secretions.





Xerostomia - Prevalence

- TBI/CT with HSCT
 - Weighted prevalence during treatment: 40.2%
- Cancer CT
 - Weighted prevalence during treatment: 49.9%



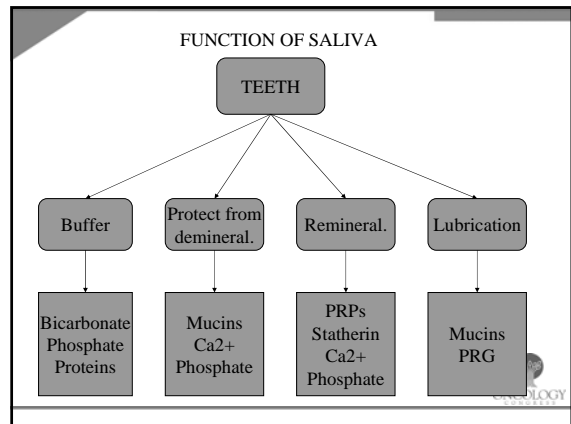
Xerostomia - Radiotherapy

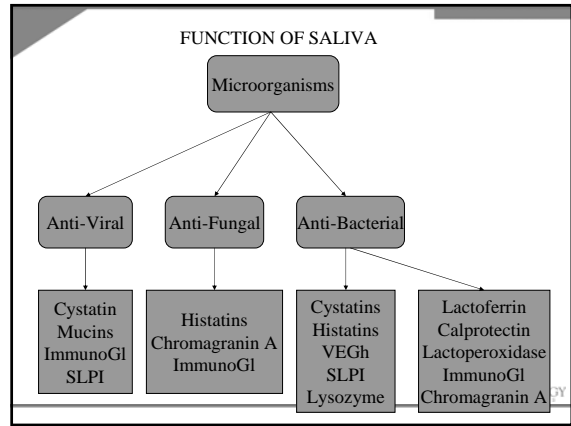
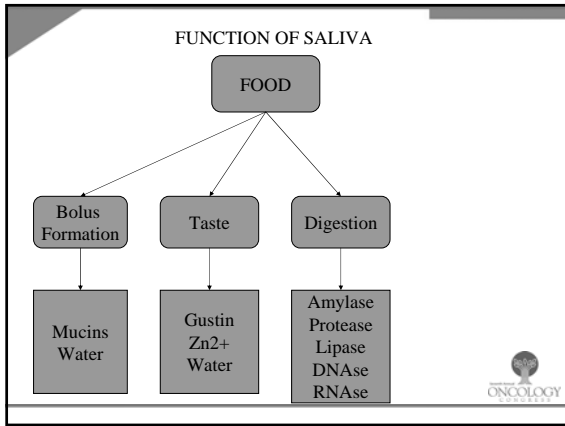
- Weighted Prevalence - During RT
 - All RT – 92%
 - Conventional RT – 80%
 - IMRT – 100%

Radioactive Iodine Therapy

- The weighted prevalence of xerostomia
 - 0.5% (0-7.7) before treatment
 - 33.6% (0-75) - 37.8% (15.8-59.8) at 1-2 years after treatment
- Salivary Flow
 - reduced by 27%-41% and 27%-36%, four months to 20 years after radioactive iodine treatment.
 - Another study found no difference at 8 years post-tx.

Jensen SB et al. JSuppCareCA 2010, 18(8)

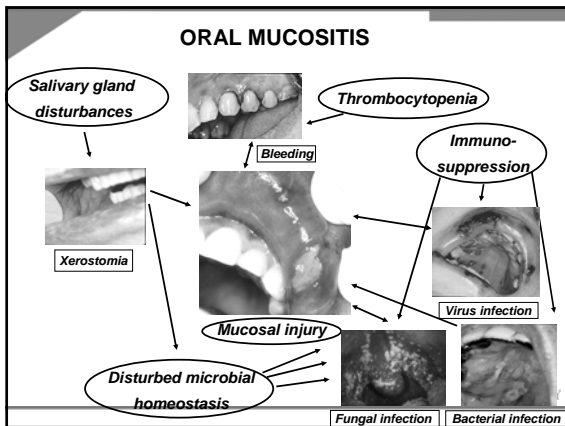




- ### Dysgeusia
- Etiology
 - Damage to sensory receptor cells
 - Turnover rate taste bud - 10 days
 - Olfactory - 7 days
 - Abnormal neuronal activities
 - Decreased salivary function
 - Microbial infection
 - Medication side effect
 - Smell defect
 - Clinical Assessment
 - Subjective
 - Assess five basic tastes: sweetness, bitterness, sourness, saltiness and umami (the savoriness of protein-rich foods)
 - Patient report
 - VAS, QOL scales
-

Weighted Prevalence of Dysgeusia During Cancer Therapy

	Number of Studies	Mean Prevalence	95% Conf. Interval
During Cancer Therapy			
Chemotherapy Only	5	56.3%	15.0 – 97.6
Radiotherapy Only	5	66.5%	26.8 – 100.0
Radiotherapy and Chemotherapy	3	76.0%	0.0 – 100.0



Questions?