Update in Symptom management : New era in Oral mucositis care

Asst. Prof. Pratanporn Arirachakaran , DDS, PhD

Paranee Phongnopakoon, RN, MSN, APN

ORAL MUCOSITIS DEFINITION

" A complication of some cancer therapies in which the lining of the digestive system becomes inflamed. Often seen as sores in the mouth. "

- Cancer patients have a high risk of oral complications for a number of reasons:
- Chemotherapy and radiation therapy slow or stop the growth of new cells.
- Radiation therapy may directly damage and break down oral tissue, salivary glands, and bone.
- Chemotherapy and radiation therapy upset the healthy balance of bacteria in the mouth.
- Chemotherapy and radiation therapy may cause changes in the lining of the mouth and the salivary glands. These changes may lead to mouth sores, infections, and tooth decay.

National Cancer Institute,US

RISK OF MUCOSITIS INDUCTION

- Myeloablative (Bone Marrow-suppressing) Chemotherapy Is Associated With 60%–100%,
- Combination of Radiotherapy and Chemotherapy With a Risk of Almost 100%
- Patients' Age and Gender.
- Smoking, Excessive Alcohol Use,
- Daily, Repetitive Radiation Treatment, Radiation Source, Dose Intensity, Cumulative Dose,
- Type of Chemotherapeutic Agents and the Volume Of Irradiated Mucosa.

" Chemotherapy-induced OM Usually Begins Within The 1st Week After The Initiation Of Treatment And The Peak Is In The 2nd Week. Radiation-induced Mucositis Typically Develops After About 10 Days, At A Cumulative Dose Of About 15 Gy And Usually Peaks Full Severity At A Dose Of 30 Gy ."

Gholizadeh N, Sheykhbahaei N, Sadrzadeh-Afshar MS. New Treatment Approaches of Oral Mucositis: A Review of Literature. Adv Hum Biol 2016;6:66-72

CANCER TREATMENT INDUCED ORAL MUCOSITIS

- Oral mucositis can :
  - Range in degree from mild changes in sensation to severe oral pain
  - Infection and ulcerative bleeding lesions
  - Experience anorexia
  - Dehydration
  - Weight loss, and malnutrition because of difficulty eating and drinking

TYPES OF REVIEWED STUDIES ON THE ORAL COMPLICATIONS OF CHEMOTHERAPY PUBLISHED IN THE LITERATURE (2002-2012).

	PUBMED		COCHRANE		SCOPUS		TOTAL		TYPE OF STUDY					
DISORDER	**N**	**n**	**N**	**n**	**N**	**n**	**N**	**n***	**Tri-al**	**Co-hort**	**Case-control**	**Cross-sectional**	**Case series**	**Revi-sion**
ORAL COMPLICATIONS	23	12	4	1	89	28	116	47	15	6	4	5	4	13
ORAL MUCOSITIS	202	127	36	25	93	25	331	116	51	12	4	7	2	40
DENTAL DEVELOPMENT	15	5	0	0	48	6	63	6	0	0	5	1	0	0
DYSGEUSIA	19	6	3	3	22	8	44	12	3	4	0	0	1	4
TASTE ALTERATIONS	3	3	3	3	1	0	7	5	1	1	0	1	0	2
SALIVA	40	9	8	1	26	4	74	13	1	2	4	1	1	4
CANDIDIASIS	26	12	35	4	18	8	79	28	7	4	1	2	1	13
PERIODONTAL DISEASE, GINGIVITIS, CARIES, VIRAL INFECTIONS	162	30	22	0	30	4	214	27	1	11	2	5	4	4
BRONJ	72	53	18	2	275	60	365	79	9	7	3	2	14	44
TOTAL	**562**	**257**	**129**	**39**	**602**	**143**	**1293**	**333**	**88**	**47**	**23**	**24**	**27**	**124**

Begonya Chaveli-López, J Clin Exp Dent. 2014 Feb; 6(1): p81–90.

CHEMOTHERAPY RELATED ORAL MUCOSITIS

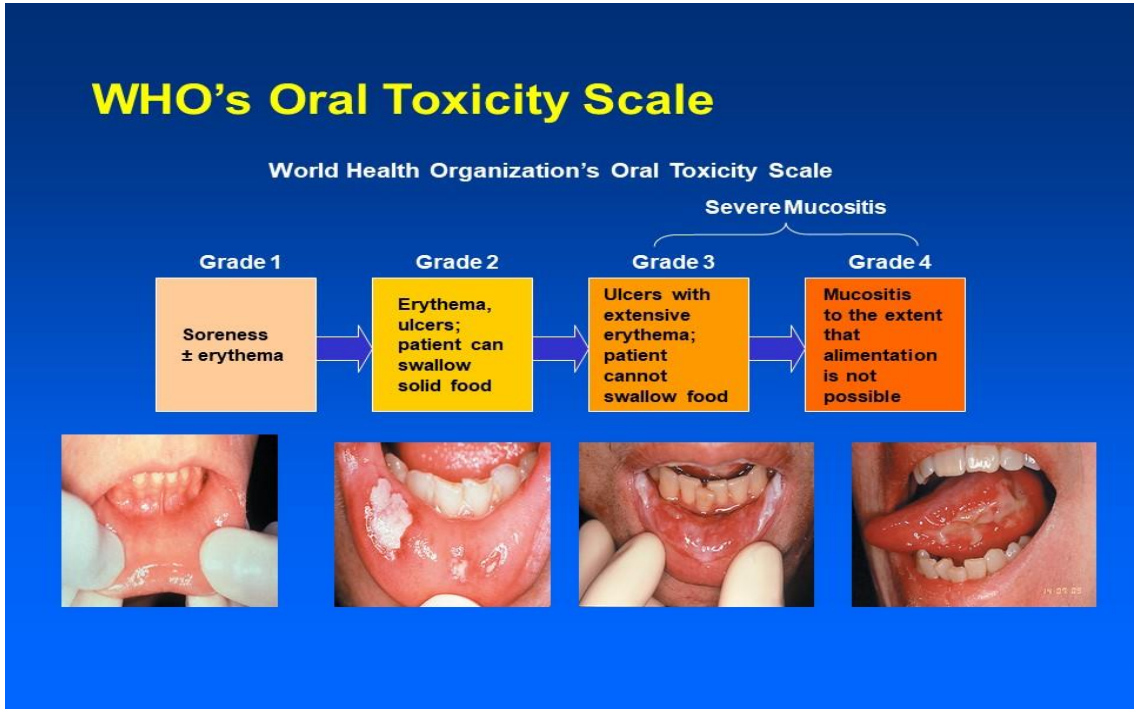
Alkylating agents	Antitumor antibiotics	Antimetabolites
Busulfan	Actinomycin D	Cytosine arabinoside
Cyclophosphamide	Amsacrine	5-fluorouracil*
Mechlorethamine	Bleomycin	Hydroxyurea
Procarbazine	Mithramycin C	Methotrexate*
Thiotepa	Mitomycin	6-mercaptopurine
		6-thioguanine

Vinca alkaloids	Anthracyclines	Taxanes	Others
Vinblastine*	Daunorubicin	Docetaxel	Etoposide*
Vincristine	Doxorubicin*	Paclitaxel	Teniposide
Vinorelbine	Epirubicin		Nitrogenated mustards

Begonya Chaveli-López, J Clin Exp Dent. 2014 Feb; 6(1): p81–90.

ASSESSMENT SCALE

World Health Organization (WHO)-Oral Mucositis

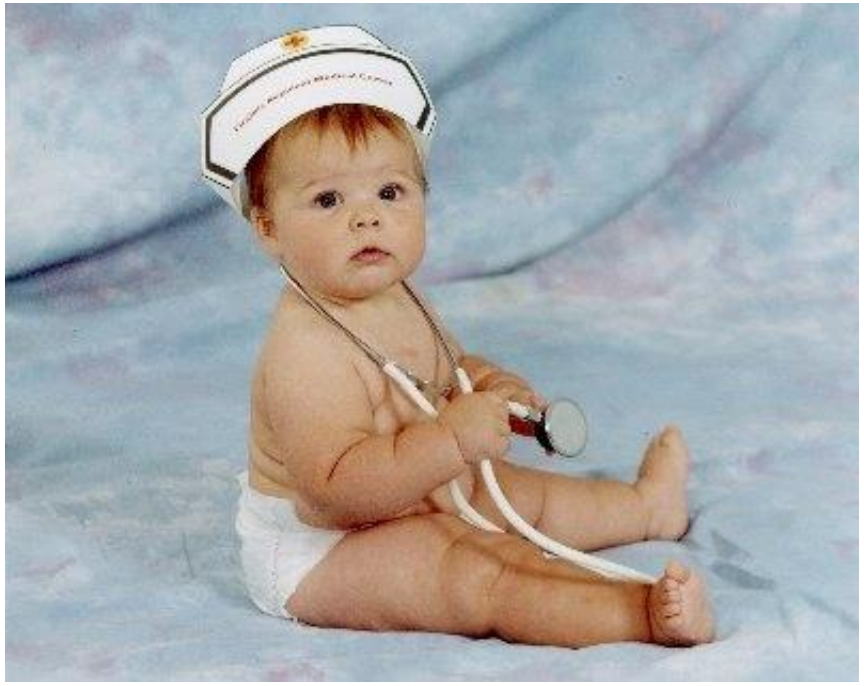


National Cancer Institute Common Toxicity Criteria (NCI-CTC)-Oral Mucositis

Grade	0	1	2	3	4	5
Clinical (version 3.0)	Normal	Erythema	Patchy ulcerations or pseudomembranes	Confluent ulcerations or pseudomembranes; bleeding with minor trauma	Issue necrosis; significant spontaneous bleeding; life-threatening consequences	Death
Functional (version 3.0)	No symptoms	Minimal symptoms, normal diet; minimal respiratory symptoms but not interfering with function	Symptomatic but can eat and swallow modified diet; respiratory symptoms interfering with unction but not interfering with ADL	Symptomatic and unable to adequately aliment or hydrate orally; respiratory symptoms interfering with ADL	Symptoms associated with life-threatening consequences	Death
Version 4.0		Asymptomatic or mild symptoms; intervention not indicated	Moderate pain; no interfering with oral intake; modified diet indicated	Severe pain; interfering with oral intake	Life-threatening consequences; urgent intervention indicated	Death

SUMMARY

QUESTION ??



EVIDENCE-BASED MANAGEMENT STRATEGIES FOR ORAL COMPLICATION FROM CANCER TREATMENT

- Management recommendation and guideline classification was based on criteria of the American Society of Clinical Oncology rating the level of evidence and grade of recommendation.
- The definition, prevalence and management strategies based on the literature are presented for the following oral complications:
  - Bisphosphonate Osteonecrosis (BON)
  - Dysgeusia
  - Oral Fungal Infection
  - Oral Viral Infection
  - Dental Disease
  - Osteoradionecrosis (ORN)
  - Trismus
  - Oral Pain
  - Xerostomia

GUIDELINE RECOMMENDED

Case discussion

CASE 1

- Thai male, 56 yrs.
- Diagnostic : Nasopharyngeal cancer , Pathology = Undeferential carcinoma
- Underlying : DM,HT,HD
- Rx : Chemotherapy (CMT) concurrent Radiation therapy (RT)
- Chemotherapy regimen plan
  - Platinum alone q 3 wks. Cc RT x 3 cycles
  - PF (Platinum + 5 FU) q 3 wks. x 3 cycles
- RT
  - 33 F.

TREATMENT

- CMT
  - 23-03-2016 Start 1st cycle with Plat 155 mg. Til 02-05-2017 x 3 cycles.
  - 09-11-2016 Start 4th cycle with Plat 120 mg. 5-FU 1500 mg. x 3 cycles.

- RT

Region Treated	Radiation Energy	Tumor Dose	From-to	Daily Dose
NPC mass / Node+ve	IMRT	7,095 cGy / 33 F	21 Mar.,2016- 4 May,2016	215 cGy/d
Microscopic area	IMRT	6,600 cGy / 33 F	21 Mar.,2016- 4 May,2016	200 cGy/d
High risk nodes / Low risk nodes	IMRT	5,940 / 5,445 cGy / 33 F	21 Mar.,2016- 4 May,2016	180 / 165 cGy/d

CLINICAL MANAGEMENT OF ORAL MUCOSITIS 2014

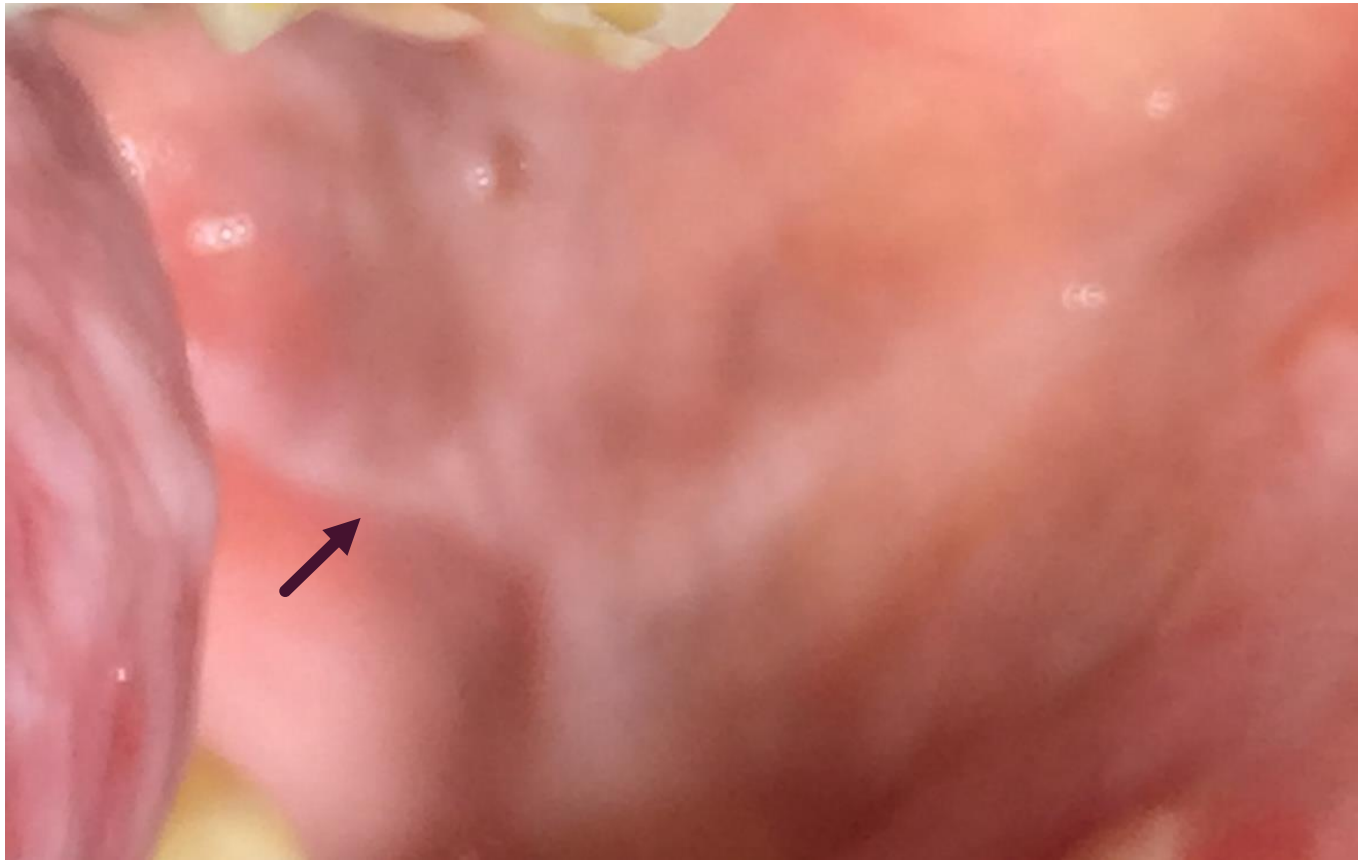
1. Basic oral care
2. Nutritional support
3. Oral decontamination
4. Palliation of dry mouth
5. Pain control
6. Management of oral bleeding
7. Therapeutic interventions for oral mucositis

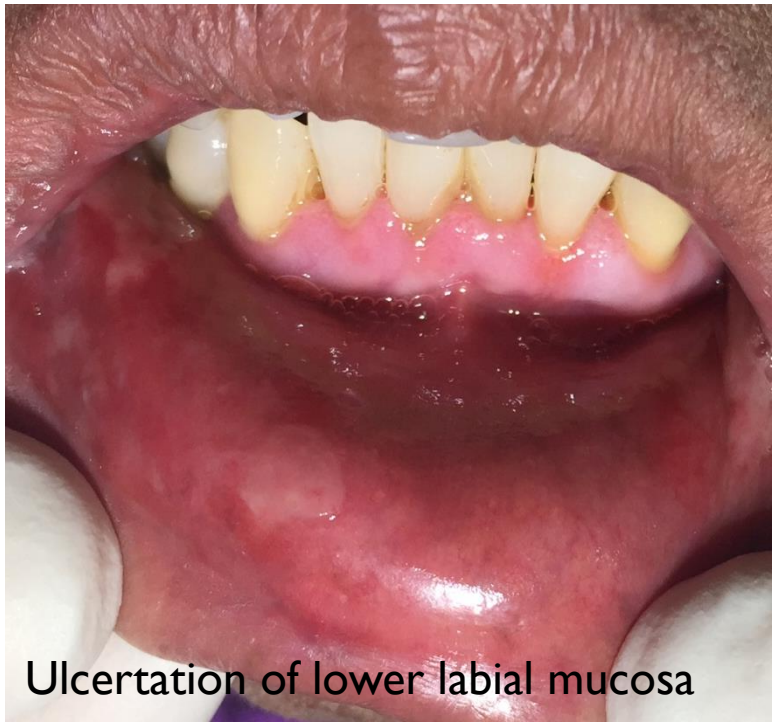
The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) 2014

Week	day	Symptom During CT & RT	Treatment	
			Laser	supportive
1 **	D1-5	None	None	
2	D 9	Gr 2 OM at lower lip and soft palate left and right, vestibule 36-37	LLLT	
3	D11	Gr 2 OM at lower lip and retromolar area	LLLT	
	D13	Posterior of right lateral side of tongue and lower lip	LLLT	Nyst, Lidocaine, kamistad
	D15	Epithelialization of previous ulcerated area (Gr 1 OM)	LLLT	
4	D18		LLLT	
5**		OM soft palate above uvula, lower labial mucosa, sore throat	LLLT	Ulcefate, xylocaine, dry mouth gel
6		Improving of OM	LLLT	
7		Improving of OM	LLLT	
8		OM at oropharyngeal mucosa, right buccal mucosa, right lateral tongue Viral infection at lower right lip		Solcoseryl vilerm

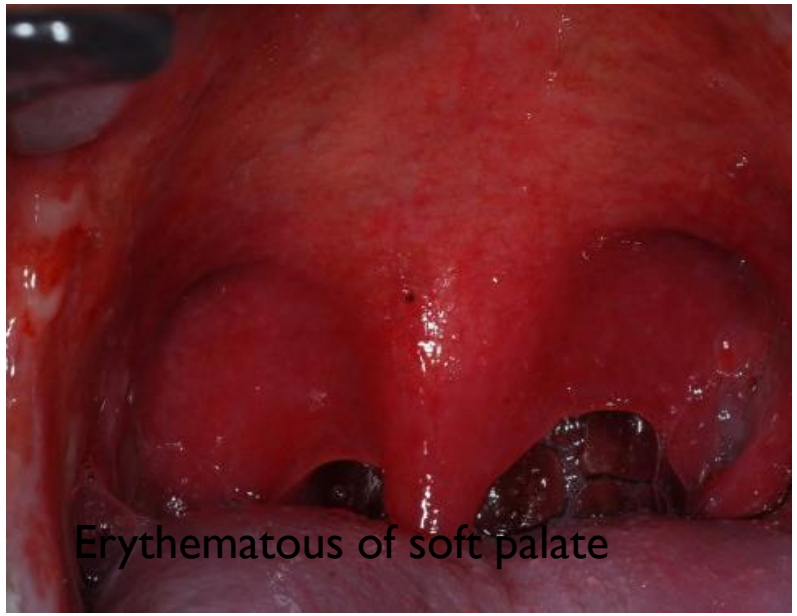
FIRST SIGN

- The first clinical signs of mucositis occur at the end of the 1st week of a conventional 7- week radiation protocol (daily dose of 2 Gy, 5 times a week)
- Erythema as the first reaction
- [white discoloration of the oral mucosa: an expression of hyperkeratinization as the first symptom] followed by or in combination with erythema





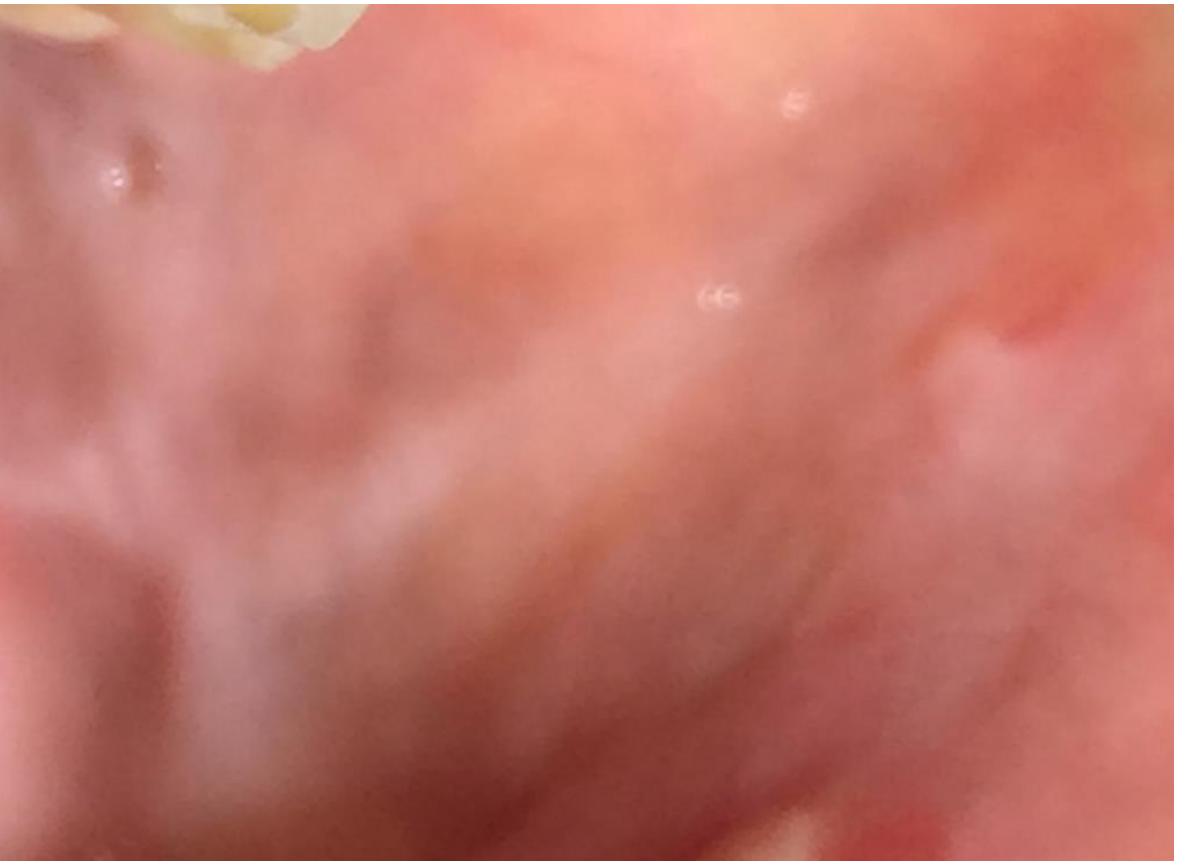
Ulcertation of lower labial mucosa



Erythematous of soft palate

Small ulceration and vesicles

EXPLANATION ON HYPERKERATOSIS



The lack of formation of new basal cells caused by radiotherapy leads to a gradual, linear decrease in cell numbers

If the cellularity of the mucosa drops below 70% of the normal level, the cell production rate from the surviving cells increases dramatically (whitish aspect of oral mucosa)

ERYTHEMA

As radiotherapy continues,

a steady state between mucosal cell killing and mucosal cell regeneration may occur and favor an acute reaction in the form of a prominent erythema

PAIN CONTROL

- *Short-term relief*
  - Topical anesthetic mouthrinse
  - 2% viscous lidocaine
  - Saline mouth rinses
  - Ice chips

- Coating agents
  - Sucralfate: commonly used , no significant decrease in the pain control
  - Topical agents, most patients with severe mucositis require systemic analgesics, often including opioids, for satisfactory pain relief

- Use of narcotic drug:
  - Transdermal fentanyl
  - Morphine mouth rinse
  - Doxepin mouth rinse

ORAL CAVITY CARE DURING CC

Mo	Day	symptom	Treatment	
			Laser	supportive
4 5 FU	D5	Gr 1 OM-- tip of tongue and left buccal mucosa burning sensation	LLLT	
	D 8	Gr 1 OM—anterior part of right and left buccal mucosa hyperkeratosis	LLLT	
	D12	Gr2 OM small ulceration at left side of lateral tongue	LLLT	
	D14	Gr 1 – pain on left side of tongue	LLLT	

ORAL CAVITY CARE DURING CC

Mo	day	symptom	Treatment	
			Laser	supportive
5 5 FU	D5	Gr 1 OM hyperkeratosis of anterior part of left and right buccal mucosa	LLLT	
	D 8	Gr 2- erythema at ventral of tongue, posterior part of lateral sides of tongue, Angle 0f lips, lateral part of oro-palatal arch	LLLT	
	D11	Gr 2- erythema at ventral of tongue, posterior part of lateral sides of tongue, Angle 0f lips, lateral part of oro-palatal arch	LLLT	
	D12	Improving of lesions	LLLT	

CASE 2

- Myanmar Female, 17 yrs.
- Diagnostic : Nasopharyngeal cancer , Pathology = Undeferential carcinoma
- Underlying : none
- Rx : Chemotherapy (CMT) concurrent Radiation therapy (RT)
- Chemotherapy regimen plan
  - Platinum alone q 1 wks. Cc RT x 6 cycles
  - PF (Platinum + 5 FU) q 3 wks. x 3 cycles
- RT
  - 33 F.

TREATMENT

- CMT
  - 26-11-2016 Start 1st cycle with Plat 120 mg. Til 02-05-2017 x 6 cycles.
  - 09-01-2017 Start 4th cycle with Plat 100 mg. 5-FU 1300 mg. x 2 cycles.

- RT

Region Treated	Radiation Energy	Tumor Dose	From-to	Daily Dose
GTV (gross fumor, enlarge nodes)	6	7,000 cGy ---------- 33 F	26/11/2015- 9/1/2016	212 cGy/d
high risk CTV (NP, nasal and PNS, upper cervical nodes)	6	5,940 cGy ---------- 33 F	26/11/2015- 9/1/2016	180 cGy/d

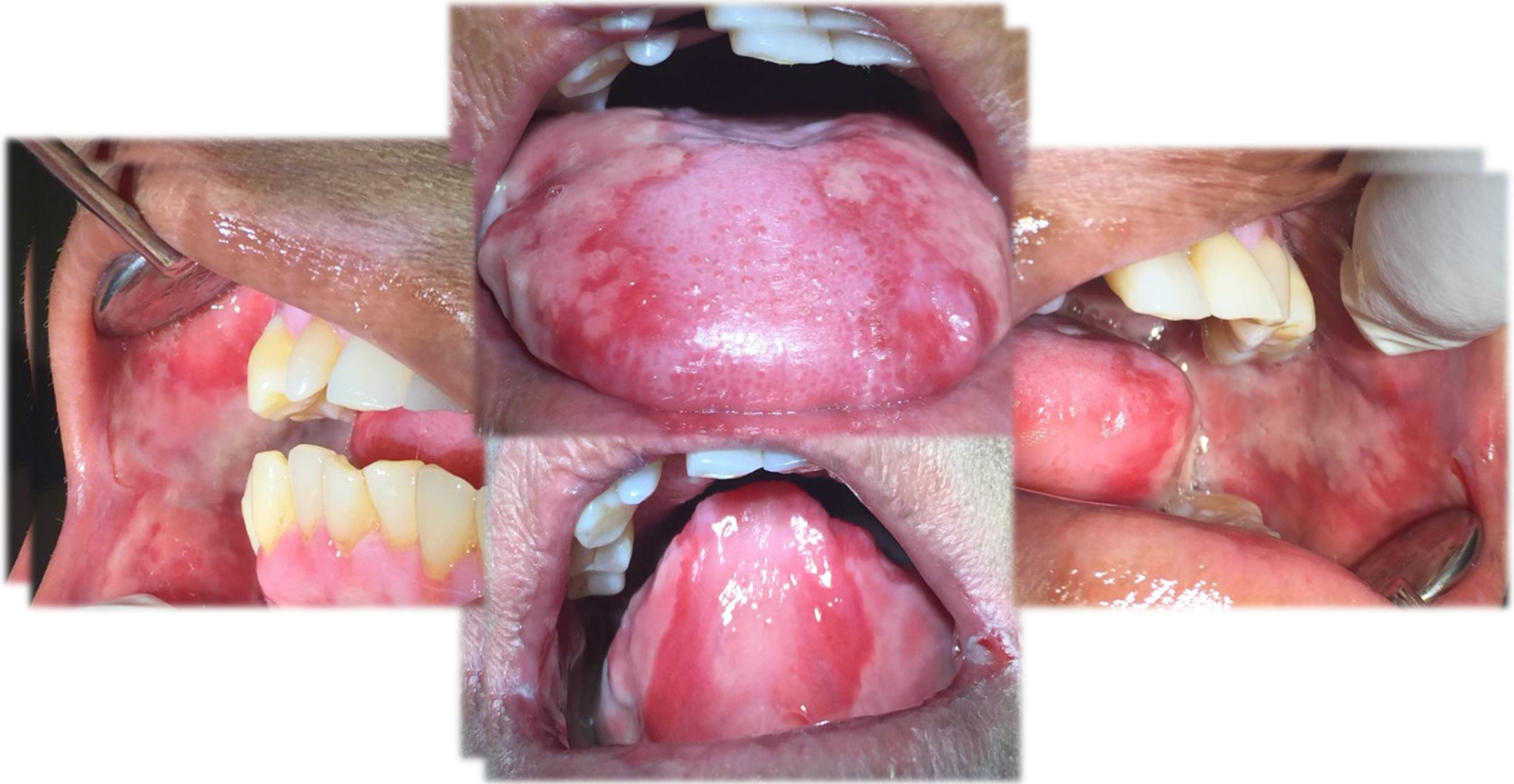


Figure 1 and 2 Tejada Domínguez, F.J*. Ruiz Domínguez, M.R, Enferm. glob. no.18 Murcia feb. 2010

Wk	day	Symptom during CT RT	Treatment	
			Laser	supportive
1	D 1-5	-		
2	D 6-10	-		
3	D11-15	-		
4	D20	Mucositis Gr 3	LLLT	Mechanical cleaning Difflam , kamistad gel
5	D23	OM Gr 3 of hard and soft palate above uvula, vestibules lower of lower arch, sore throat-ulceration	Request LLLT cont 3 d/wk	
6		Improving of OM Candidiasis	LLLT	Baking soda MW Morphine patch Nystatin solcoseryl
7		Improving of OM	LLLT	

AMPLIFICATION

- Reactive oxygen species
- Second messengers
- Pro-inflammatory cytokines and pathways
- Signaling molecules also participate in a positive-feedback loop that amplifies the original effects of radiation and chemotherapy
  - TNF-α activates NF-κB and sphingomyelinase activity in the mucosa, leading to more cell death
- Metabolic byproducts of colonizing microorganisms are all believed to play a role in amplifying the tissue injury

ULCERATION

- Thinning of mucosal lining, may slough off and then become red, inflamed and ulcerated
- The ulcers may become covered by a yellowish white fibrin clot called a pseudomembrane
- Ulcers may range from 0.5 cm to greater than 4 cm



PAIN CONTROL

- *Short-term relief*
  - Topical anesthetic mouthrinse
  - 2% viscous lidocaine
  - Saline mouth rinses
  - Ice chips
- Coating agents
  - Sucralfate: commonly used , no significant decrease in the pain control
  - Topical agents, most patients with severe mucositis require systemic analgesics, often including opioids, for satisfactory pain relief
- Use of narcotic drug:
  - Transdermal fentanyl
  - Morphine mouth rinse
  - Doxepin mouth rinse

ORAL DECONTAMINATION

- Microbial colonization exacerbates the severity of oral mucositis

- **Lozenges** composed of polymyxin E, tobramycin, and amphotericin B may be effective in mucositis prevention in patients with H&N RT

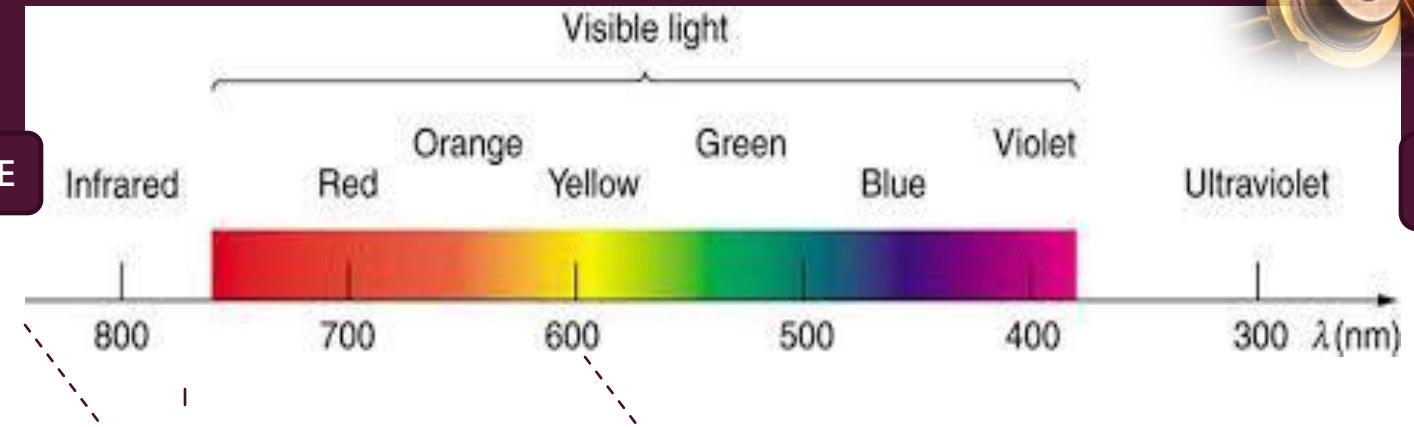
Q. IS LASER THERAPY SCIENTIFICALLY WELL DOCUMENTED?

- **Answer: YES**
- > **130** double-blind positive studies confirming the clinical effect of LLLT
- More than **3000** research reports are published
- LLLT in **dental literature alone (370 studies already in 1999), more than 90% of these studies do verify the clinical value of laser therapy**
- About 250 papers are **annually** published in peer reviewed scientific papers

BANGKOK HOSPITAL

RADIO WAVE

10^4 m



GAMMA-RAYS

10^{-14} m

LLL WAVELENGTH REGION

BANGKOK HOSPITAL

- Photobiomodulation Therapy (PBMT), Cold Laser Therapy, Low Level Laser Therapy (LLLT), soft laser
- Improve tissue repair, reduce pain and inflammation
- Treatments take about 10-20 minutes and should be applied two or more times a week
- The ability to modulate a variety of metabolic events through photophysical and biochemical processes explains the effects of this therapy

MECHANISMS OF LLL

EFFECT ON MITOCHONDRIA

- Acceleration of electron transfer
- Generate of ROS

EFFECTS ON CELLULAR METABOLISM

-Redox state change
-Ion component change

→ Increase the effectiveness of cell metabolism

LLL increase cell metabolism by stimulating mitochondrial activity, acting as analgesic, anti-inflammatory, and reparative agents in mucosal lesions

Prophylaxis

Prevention?

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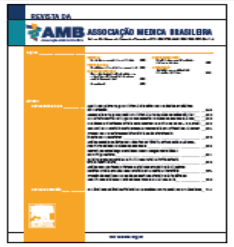


Original article

Laser therapy in oral mucositis control: a meta-analysis☆

André Luiz Peixoto Figueiredo[a], *Liliane Lins*[a,b,*], *Ana Carolina Cattony*[a], *Antônio Fernando Pereira Falcão*[c]

[a] *Escola Bahiana de Medicina e Saúde Pública, Salvador, BA, Brazil*
[b] *Medicine School of Bahia, UFBA, Salvador, BA, Brazil*
[c] *Faculty of Dentistry, Universidade Federal da Bahia (UFBA), Salvador, BA, Brazil*

- LT is 10 times more effective in controlling OM to < grade 3

Supportive Care in Cancer
August 2011, Volume 19, Issue 8, pp 1069–1077

A systematic review with meta-analysis of the effect of low-level laser therapy (LLLT) in cancer therapy-induced oral mucositis

Jan Magnus Bjordal, Rene-Jean Bensadoun, Jan Tunèr, Lucio Frigo, Kjersti Gjerde, Rodrigo AB Lopes-Martins

Bjordal JM[1], Bensadoun RJ, Tunèr J, Frigo L, Gjerde K, Lopes-Martins RA.

Author information

Abstract

PURPOSE: The purpose of this study is to review the effects of low-level laser therapy (LLLT) in the prevention and treatment of cancer therapy-induced oral mucositis (OM).

METHODS: A systematic review and meta-analysis of randomised placebo-controlled trials of LLLT performed during chemotherapy or radiation therapy in head and neck cancer patients.

RESULTS: We found 11 randomised placebo-controlled trials with a total of 415 patients; methodological quality was acceptable at 4.10 (SD ± 0.74) on the 5-point Jadad scale. The relative risk (RR) for developing OM was significantly (p = 0.02) reduced after LLLT compared with placebo LLLT (RR = 2.03 (95% CI, 1.11 to 3.69)). This preventive effect of LLLT improved to RR = 2.72 (95% CI, 1.98 to 3.74) when only trials with adequate doses above 1 J were included. For treatment of OM ulcers, the number of days with OM grade 2 or worse was significantly reduced after LLLT to 4.38 (95% CI, 3.35 to 5.40) days less than placebo LLLT. Oral mucositis severity was also reduced after LLLT with a standardised mean difference

CONCLUSIONS: There is consistent evidence from small high-quality studies that red and infrared LLLT can partly prevent development of cancer therapy-induced OM. LLLT also significantly reduced pain, severity and duration of symptoms in patients with cancer therapy-induced OM.

LASER THERAPY IN ORAL MUCOSITIS

- ***Recommendation*** in favor of low-level laser therapy (LLLT) for the prevention of oral mucositis in patients receiving high-dose chemotherapy for HSCT with or without total body irradiation
- ***Suggestion*** for LLLT in the prevention of oral mucositis in patients receiving H&N RT without concomitant chemotherapy

(based on 24 studies)

The Mucositis Study Group of the Multinational Association of Supportive Care in Cancer and International Society of Oral Oncology (MASCC/ISOO) 2014

NEW INTERVENTION ?

THERAPEUTIC INTERVENTIONS

1. Growth factors (KGF-1) and cytokines
2. Anti-inflammatory agents
3. Antimicrobials, coating agents, anesthetics, and analgesics
4. Laser and other light therapy
5. Cryotherapy
6. Natural and miscellaneous agents

ANTI-INFLAMMATORY AGENTS

- **Benzydamine hydrochloride** is a NSAIDs

- Inhibit the production of pro-inflammatory cytokines such as tumor necrosis factor-α and interleukin-1β

- Recommendation
  - ***PREVENT oral mucositis*** in patients with H&N cancer who were receiving moderate-dose RT up to 50 grays in patients *not receiving concomitant chemotherapy*

BARRIER PROTECTION

- Coating agents : Gelclair, Mugard, Episil

- Mouthrinse: Caphasol, Neutrasal is a mouth rinse to prevent and treat oral mucositis

NATURAL AND MISCELLANEOUS AGENTS

- Zinc is an essential trace element
  - required for some tissue repair processes
  - antioxidant effect
- Zinc supplementation in patients receiving H&NRT, was found a positive effect (50 mg tid during radiation period)
- A new suggestion was developed in favor of zinc in patients with oral cancer undergoing RT or chemo-radiation

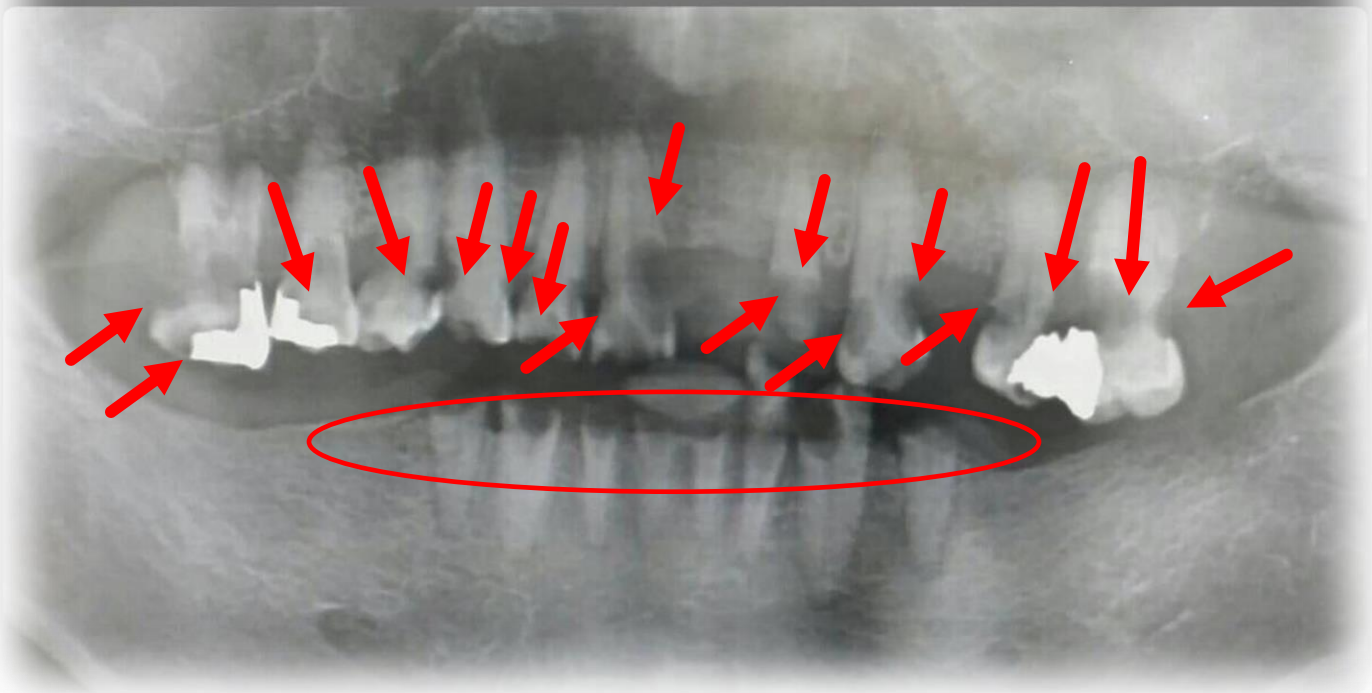
ORAL CAVITY CARE CASE II

Month	Symptom	Treatment
6 month F/U	DRY MOUTH, Gingivitis- plaque induced Dental caries of all teeth at cervical Proximal caries 14,15,16,45	Re-fabricate Fluoride tray
10 month F/U	Hyposalivation Remineralized of carious teeth (Except two)	Continue palliative on dry mouth management Fillings and scaling
12 month F/U	Hyposalivation No caries	OHI Scaling
18 month F/U	Good OH	

LONG TERM ORAL CARE

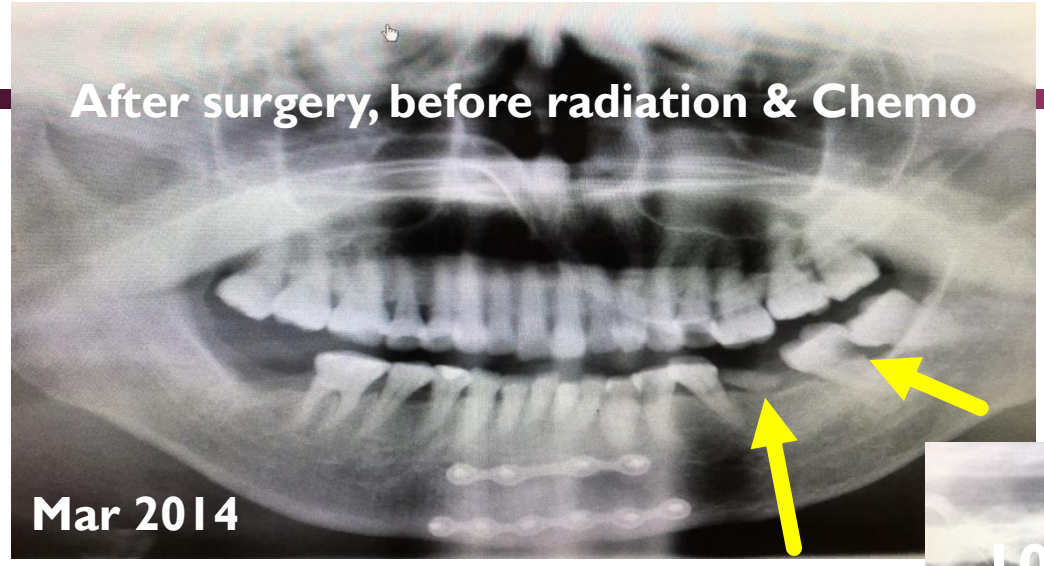
Dental caries in dry mouth

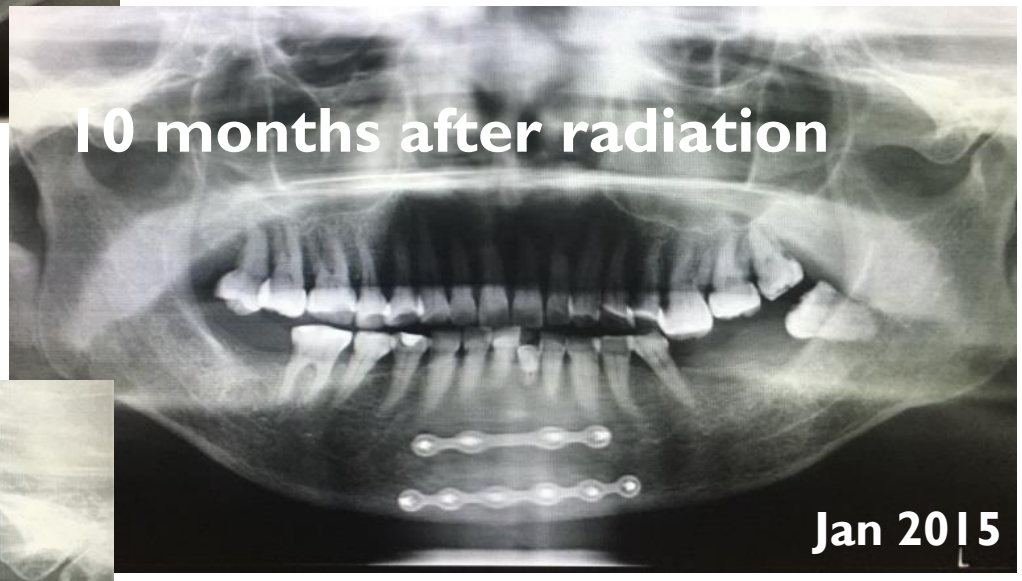
Before radiation

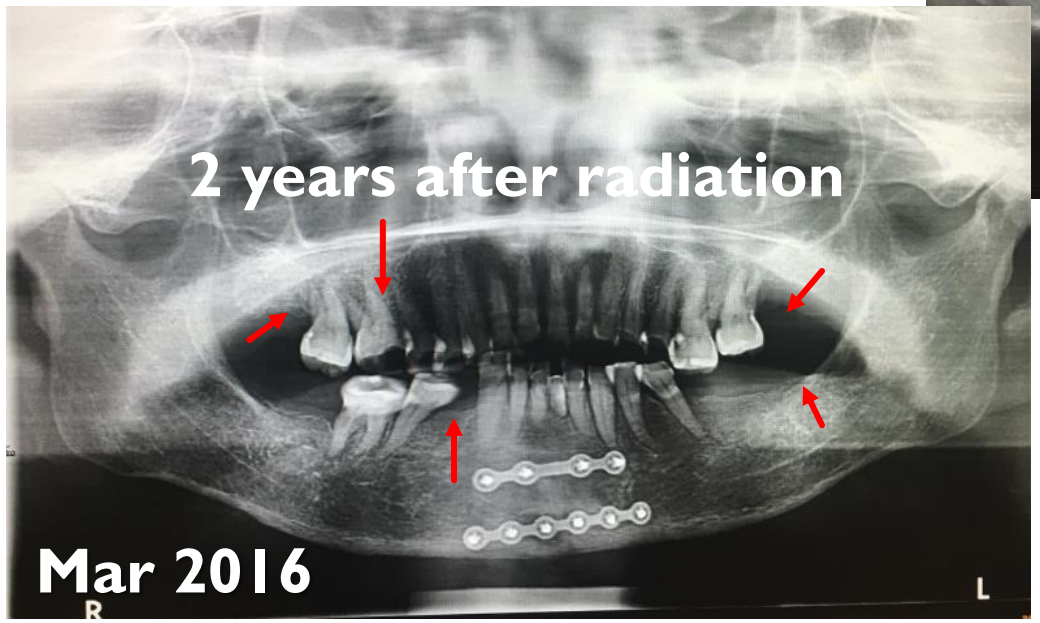


1 year after radiation

ด้วยความเอื้อเฟื้อจาก
ทพญ. นันทิยา บุญยืน


After surgery, before radiation & Chemo
Mar 2014

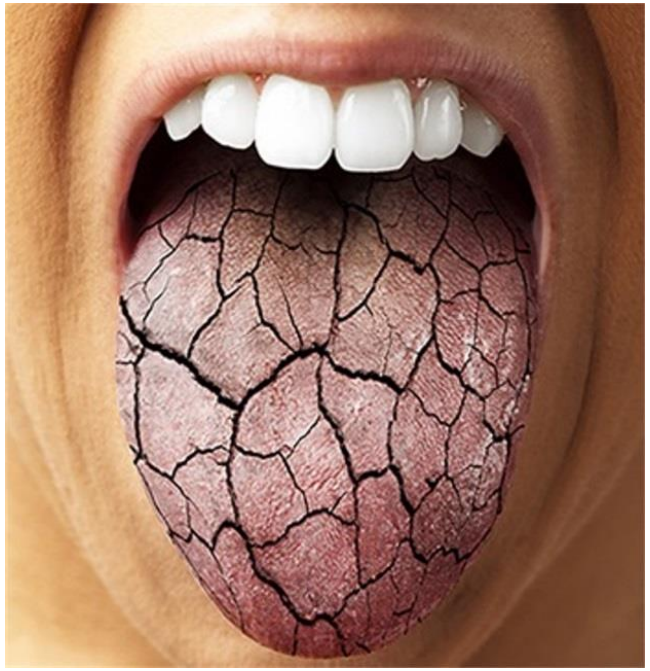

10 months after radiation
Jan 2015


2 years after radiation
Mar 2016

DRY MOUTH

Transient

Permanent



- Plenty of Water consumption
- Artificial saliva
- Rinse with a solution of half a teaspoon of baking soda half in one cup warm water several times a day to clean and lubricate the oral tissues and to buffer the oral environment
- Chew sugarless gum or sugar free lemon drops
- <u>Oral lubrication</u> :Water-soluble jellies can be used to lubricate the mouth
- Use cholinergic agents as necessary


TEAM

Thank you
for your Kind Attention

Asst. Prof. Pratanporn Arirachakaran , DDS, PhD

Paranee Phongnopakoon, RN, MSN, APN