Advances in Treatment and Supportive Care for Patients Receiving Head and Neck Radiotherapy

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June 1, 2019

Outline

- Radiation basics
- Head and neck radiation therapy developments
- HPV-associated oropharynx cancer
- Immunotherapy
- Supportive care
  - Mucositis
  - Nutrition
  - Swallowing
  - Skin
  - Dry mouth
  - Dental decay
  - Lymphedema
  - Trismus

Objectives

- Identify recent advances in the combination of radiation and systemic therapy for head and neck cancer patients
- Learn how to counsel patients about the role of the HPV virus in oropharynx cancers
- Identify best practices for management of mucositis and other toxicities of head and neck radiation

Radiation basics

Marie and Pierre Curie discovered and chemically purified radium around 1900

Pierre Curie strapped a sample of radium to his arm for 10 hours. Wound resembled a burn, then turned to scar after 52 days. He suggested its use for cancer.

Radiation basics

- Gray (Gy): Unit of absorbed dose. Joules/kilogram.
  - “The prostate tumor was treated to a dose of 81 Gy.”
- rad: Old unit of absorbed dose. 100 rad = 1 Gy.
  - “The prostate tumor was treated to a dose of 8100 rad.”
- X-ray: form of high-energy electromagnetic radiation
  - “Our linear accelerator produces X-rays with a maximum energy of 18 MeV.”
- Gamma ray: similar to X-ray, but produced by radioactive decay of atomic nucleus
  - “The radioactive cobalt-60 used for Gamma Knife treatment produces 1.25 MeV gamma rays.”

Radiation basics

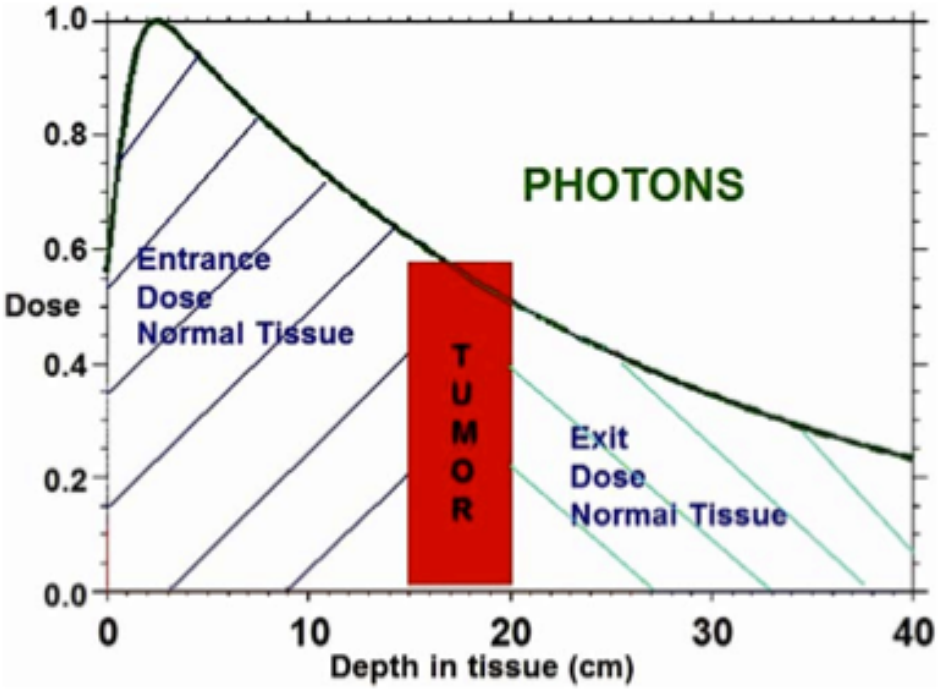
- External beam radiation therapy
  - Treats from outside the patient
  - Usually delivered with linear accelerator: electrons accelerated to high energy, hit metal target producing X-rays
  - Gantry can rotate 360 degrees around patient, delivering beams from multiple angles

http://www.varian.com/us/oncology/radiation_oncology/clinac/clinac_21ex23ex.html

Radiation basics

External beam radiation therapy

- Dose deposition is highest just below skin, then decreases as photons are attenuated

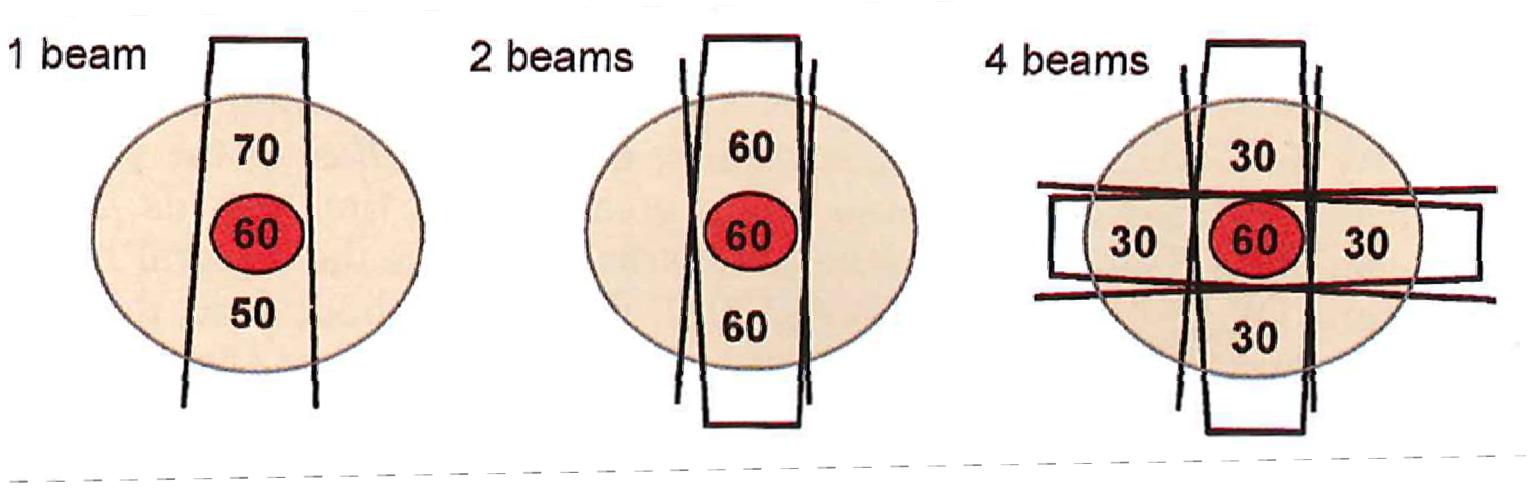


http://www.varian.com/us/oncology/radiation_oncology/clinac/clinac_21ex23ex.html

Radiation basics

External beam radiation therapy

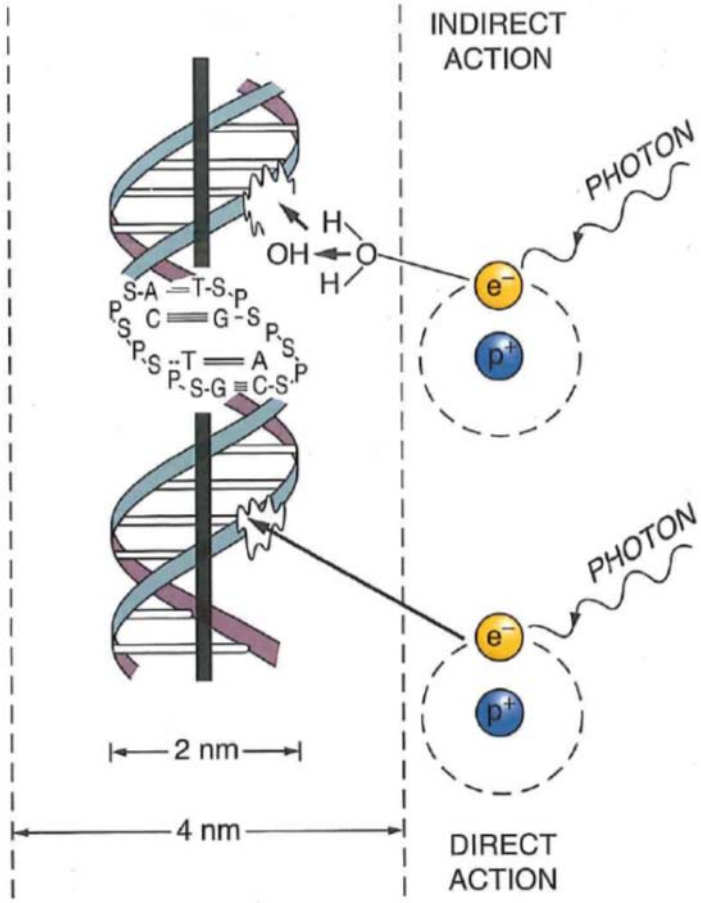
- Multiple beam angles usually used, to focus high dose region on target



Goitein, Radiation Oncology: A Physicist's-Eye View, 2008

How radiation works

- Radiation kills cells through DNA damage
- Can directly hit DNA, or ionize water molecules→damaging free radicals
- Double stand breaks recombine to create lethal chromosomal aberrations
- High dose rate radiation overwhelms DNA repair machinery



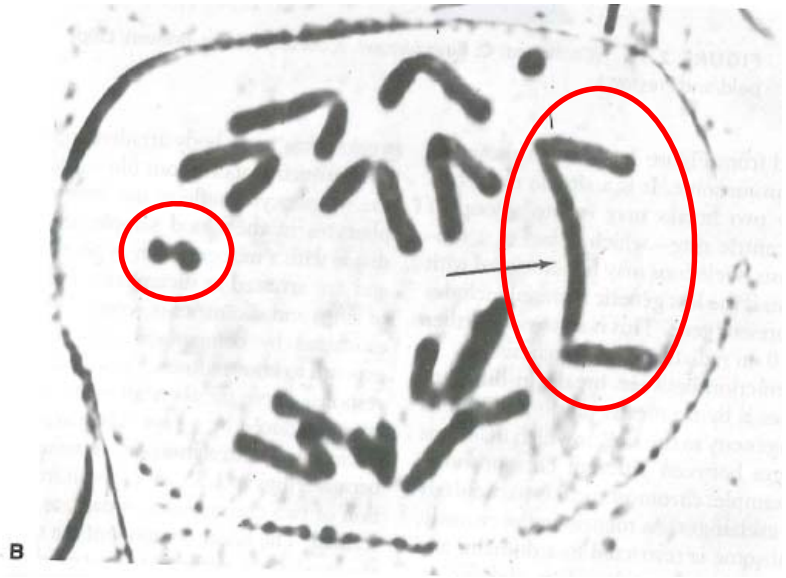
Hall and Giaccia, Radiobiology for the Radiologist, 7th ed.

How radiation works

Anaphase of *Tradescantia paludosa* plant. Note bridge, fragment after irradiation.

Unirradiated

Irradiated



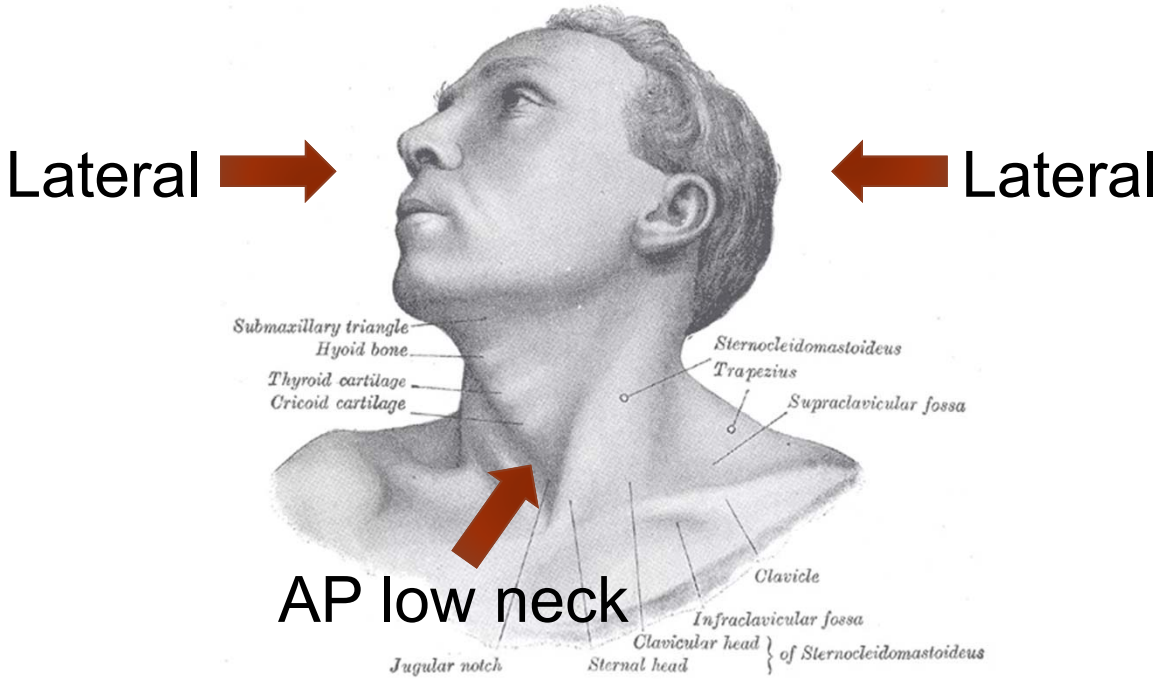
Hall and Giaccia, Radiobiology for the Radiologist, 7th ed.

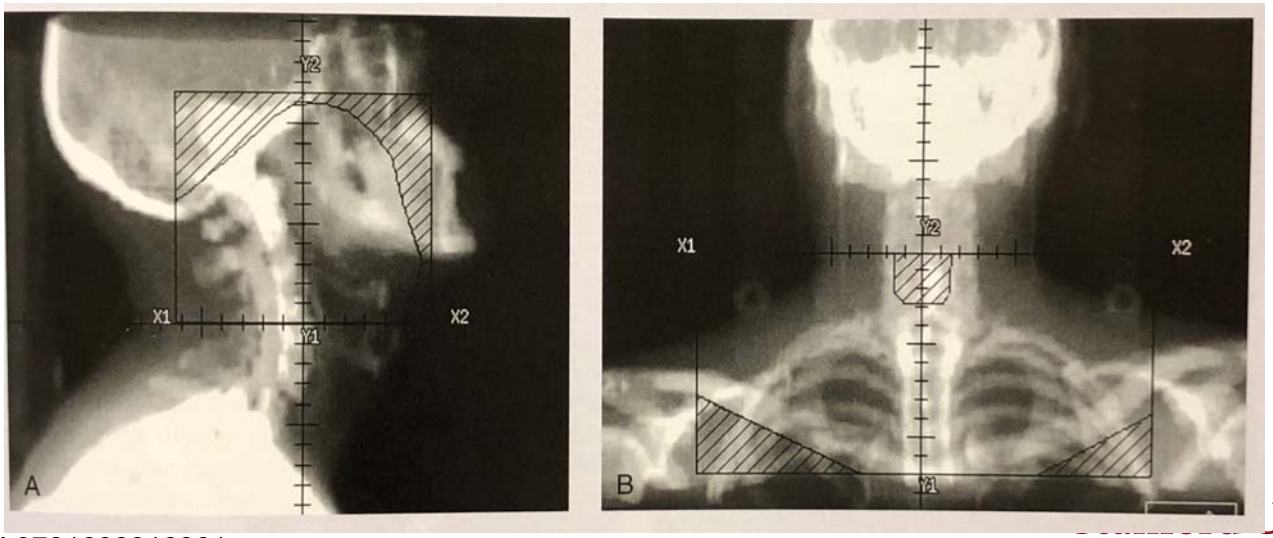
How radiation works

- After irradiation, most cells die by mitotic catastrophe
- Tissues with rapid turnover exhibit early effects: tumor, skin, mucosa
- Tissues with slow turnover exhibit late effects: nervous system, kidney

Hall and Giaccia, Radiobiology for the Radiologist, 7th ed.

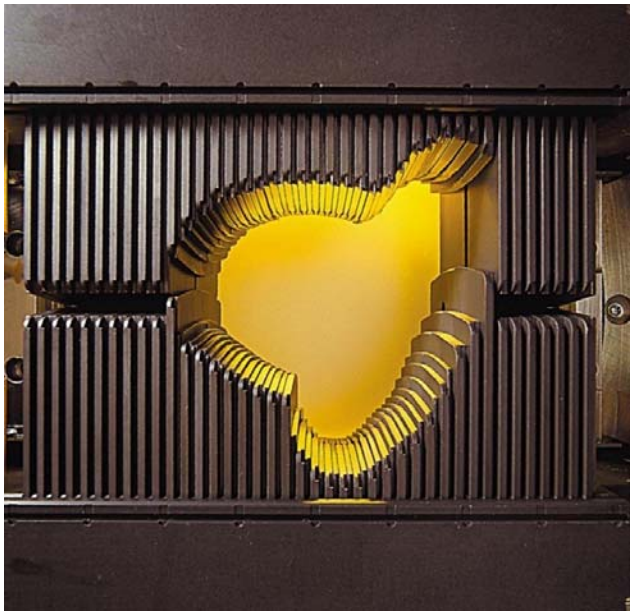
Old head&neck radiation approach





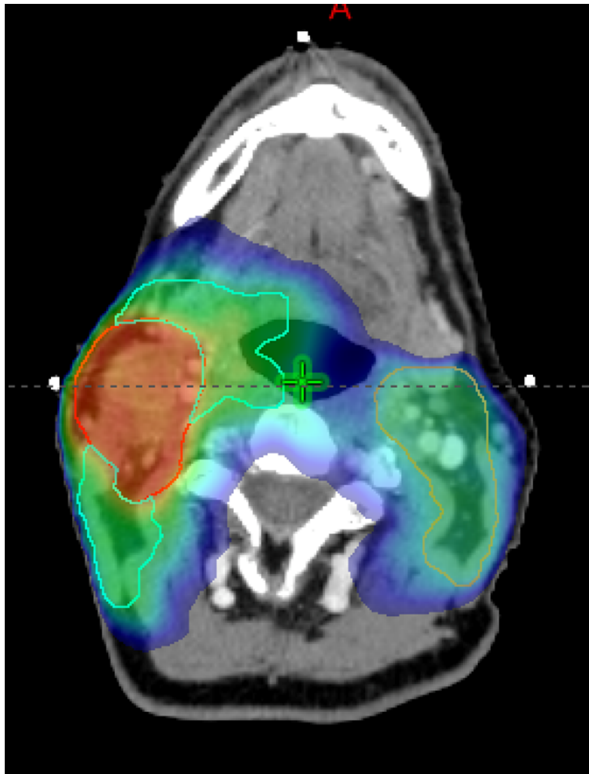
Garden, Beadle, Ang, ISBN 9781608316861

Modern radiation: intensity-modulated radiation therapy (IMRT)

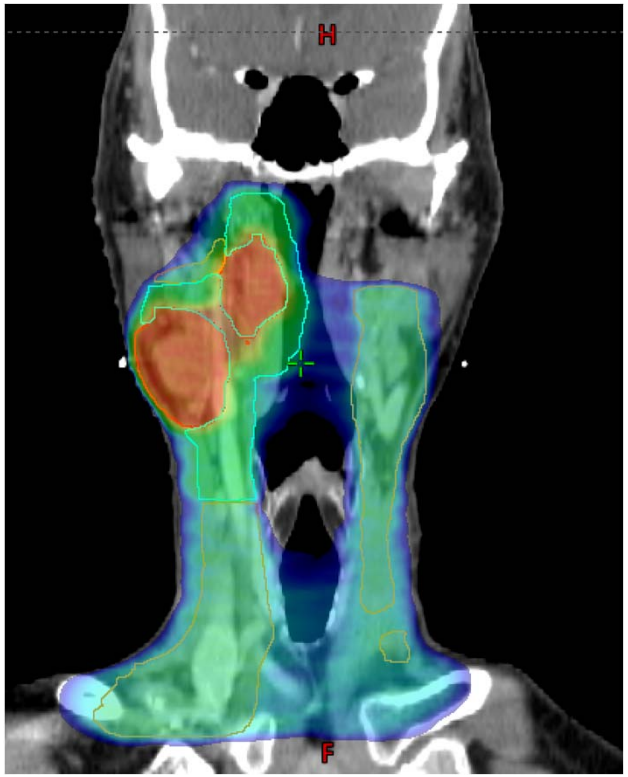


Modern radiation: intensity-modulated radiation therapy (IMRT)

Axial



Coronal



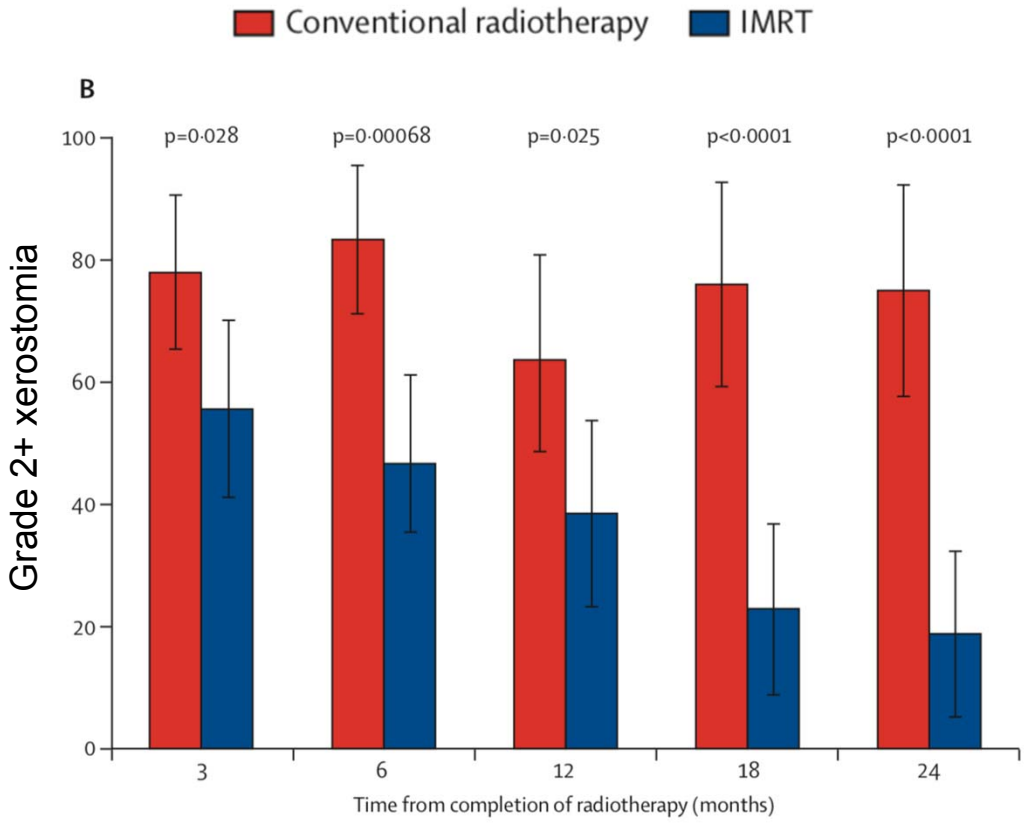
Some things we try to spare from getting high dose

- Parotid glands (dry mouth)
- Submandibular glands (dry mouth)
- Oral cavity (mucositis, dry mouth)
- Pharyngeal constrictor muscles (late swallowing)
- Larynx (voice function, swallowing)
- Esophagus (esophagitis, swallowing)
- Brainstem/cerebellum (nausea, fatigue)

IMRT data

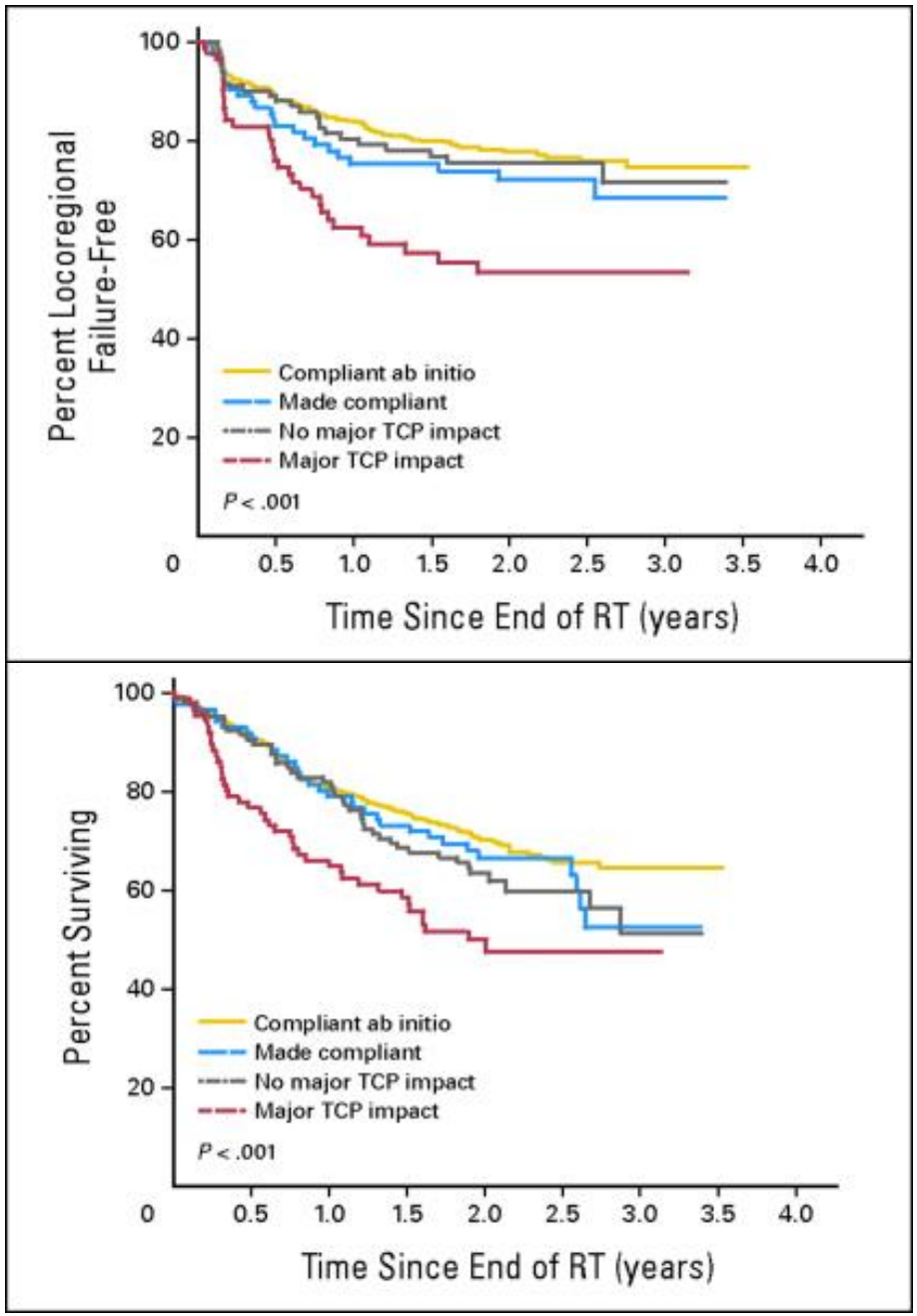
PARSPORT trial (Nutting, Lancet Oncol 12:127, 2011)

- 94 patients with pharyngeal SCC
- Randomly assigned to conventional RT or parotid-sparing IMRT
- Less late xerostomia in IMRT arm, similar disease control



Radiation quality is critical!

- Re-analysis of TROG 02.02 trial (Peters JCO 28:18, 2010)
- 687 patients treated with definitive RT for HNSCC
- Central review of CT and radiation plan
- 25% had noncompliant plans, 12% had major deficiencies
- 2-year overall survival 50% if major deficiency (red line), 70% if not
- Lower enrollment centers had much higher deficiency rate. Regional variation (one Eastern European country had 93% major deficiency!!)

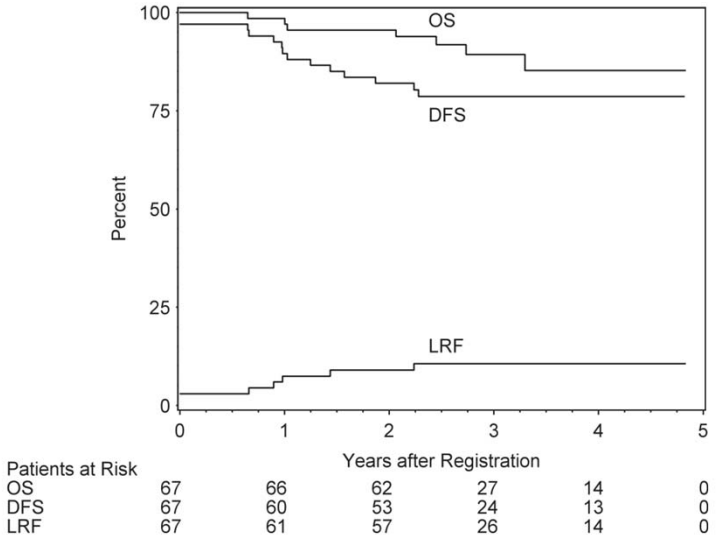


Head and neck SCC is sensitive to radiation

Early stage tumors

RTOG 00-22

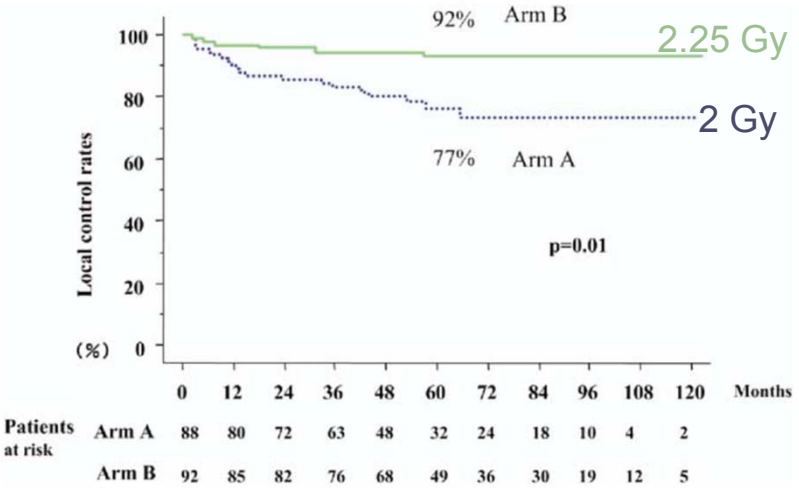
67 patients. T1-2, N0-1 squamous cell carcinoma of oropharynx. Single arm. IMRT radiation alone, 66 Gy in 30 fractions in 6 weeks.



Osaka trial

180 patients. T1N0 glottic SCC

Randomized to 2 Gy per fraction vs. 2.25 Gy per fraction (hypofractionated). Total dose 56.25-66 Gy.



Eisbruch IJROBP 76:5, 2010; Yamazaki IJROBP 64:1, 2006.

Head and neck SCC is sensitive to radiation

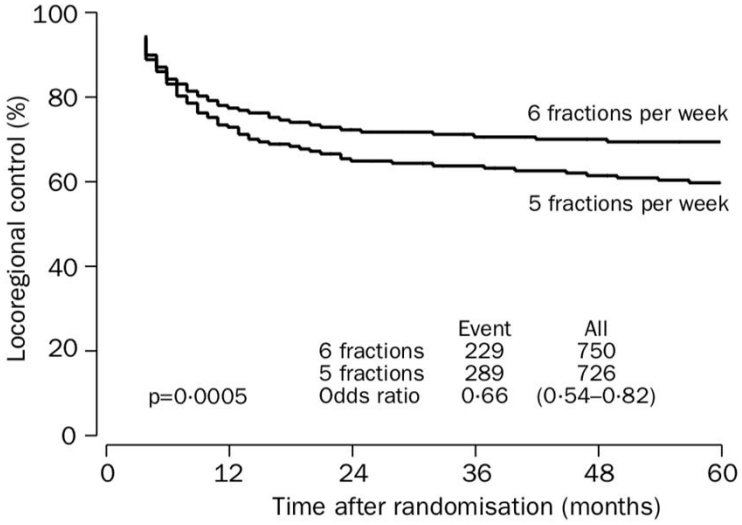
Locally advanced tumors

DAHANCA 6/7

1485 patients, SCC of larynx, pharynx, oral cavity, stage I-IV (~46% stage III-IV)

Randomized to 5 vs. 6 fractions/week.

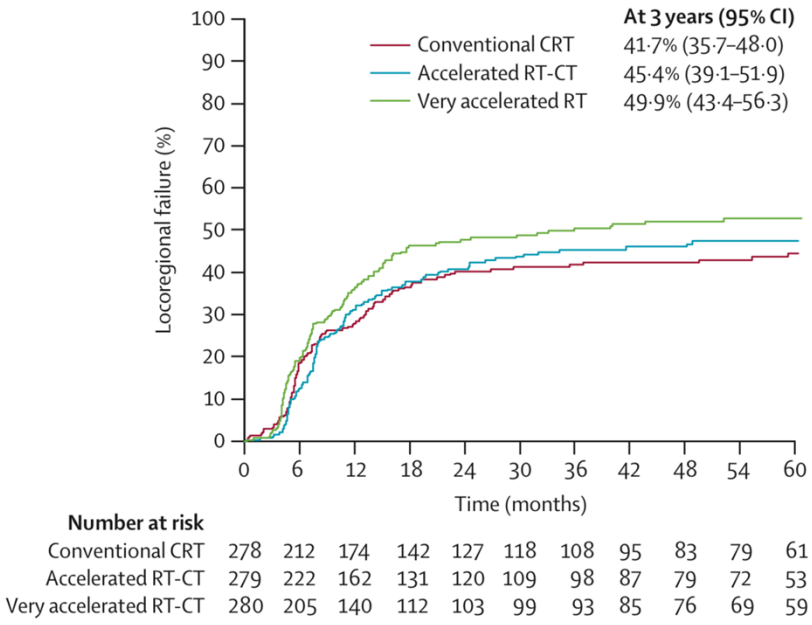
Dose: 62-68 Gy



GORTEC 99-02

840 patients, SCC of larynx, pharynx, oral cavity, stage III-IV.

Randomized to chemo+RT (carbo/5-FU), chemo+accelerated RT, or hyperfractionated RT alone (64.8 Gy in 3.5 weeks).



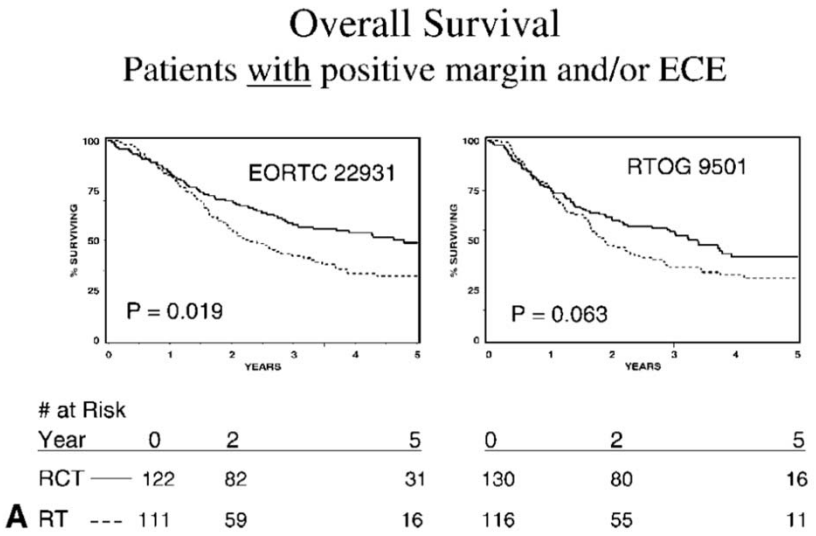
Overgaard Lancet 362, 2003; Bourhis Lancet Oncol 13:145, 2012.

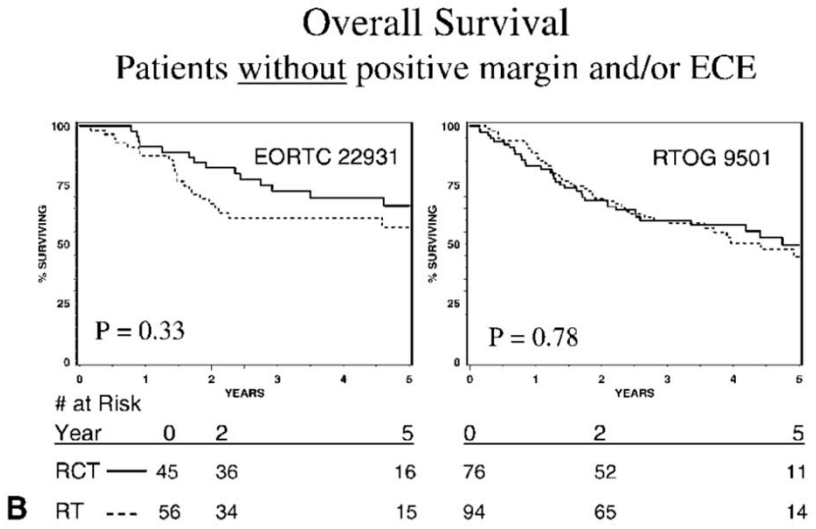
Head and neck SCC radiation indications

- Definitive treatment of early stage cancers of pharynx and larynx (AJCC 7th ed.)
  - T1-2, N0-1 oropharynx
  - T1N0 nasopharynx
  - T1-2 N0 larynx/hypopharynx
- With chemotherapy, definitive treatment of locally advanced disease
  - T3-4 or N2-3 oropharynx
  - T2-4 or N+ nasopharynx
  - T3-4 or N+ larynx/hypopharynx
- Not the best definitive treatment for oral cavity, generally

Head and neck SCC radiation indications

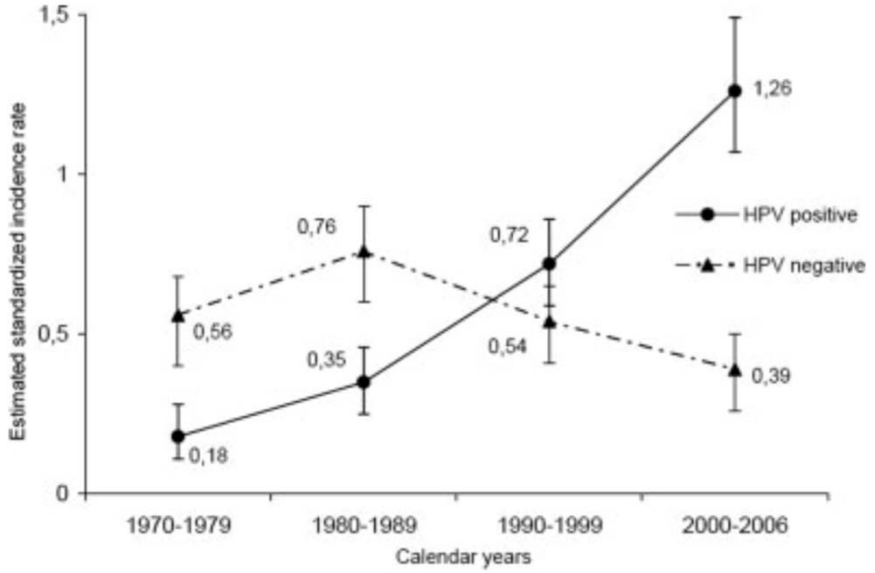
- Post-operative without chemotherapy
  - › General indications: T3-4, N2-3, close/positive margin, LVSI, PNI, ECE
- Post-operative with chemotherapy
  - › Definitely add chemo: ECE or positive margin (Bernier, Head&Neck 2005)
  - › Maybe add: if meets several inclusion criteria for EORTC 22931 study
    - T3-4, N2-3, PNI, LVSI, low/posterior nodes (level IV/V)





HPV associated oropharynx cancer

- Human papillomavirus (HPV) increases risk of cervical, anal cancers
- Rapid rise of HPV-associated oropharynx cancer
- In Stockholm County, Sweden, incidence per 100,000 people increased 7-fold from 1970s to 2000s
- Less likely to have history of smoking/drinking



Nasman, Int J Cancer 125,362 (2009)

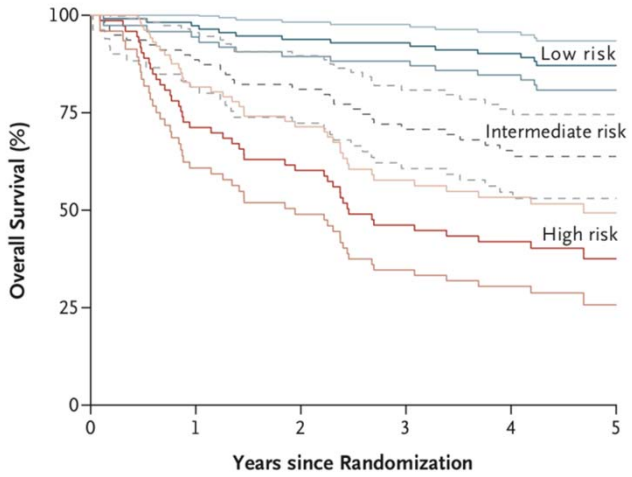
HPV associated oropharynx cancer

- Usually HPV-16 genotype
- How test?
  - p16 immunohistochemistry (p16 positive usually means HPV positive)
  - In situ hybridization to detect HPV DNA
- Patient counseling
  - Most likely acquired HPV infection soon after becoming sexually active
  - No need for precautions with partners – they probably clear any active HPV infection. Oral HPV DNA detected in 65% of oropharynx cancer patients, only 4% of partners
  - HPV vaccine given at young age appears to reduce oral HPV infection rate
  - But, no evidence for vaccination once have this kind of cancer

D'Souza et al. J Clin Oncol. 2014;32(23):2408.
Chaturvedi et al. J Clin Oncol. 36:262, 2018.

De-intensification for HPV associated oropharynx cancer

- Better prognosis than HPV-negative tumors
- Ang NEJM 2018: re-analysis of RTOG 0129 data (stage III-IV HNSCC treated with chemoRT, either accelerated or standard RT)
- If HPV positive and 10 py or less smoking history, → low risk group, 3-year survival 93%
- If HPV positive and >10py and N2b-N3 (AJCC 7th ed.), → intermediate risk group, 3-year survival 71%
- Standard tx with 70 Gy RT + cisplatin has high late morbidity—can we de-intensify?

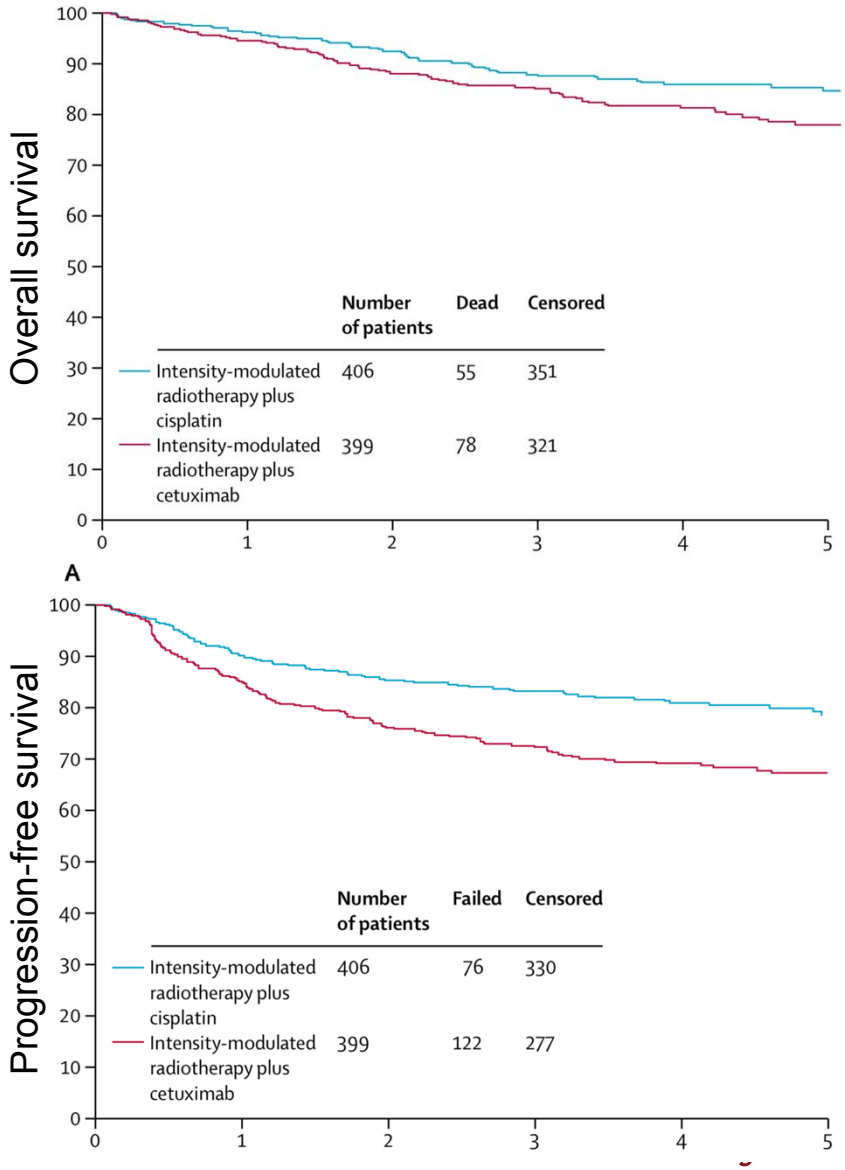


No. at Risk						
Low risk	114	111	106	102	95	46
Intermediate risk	79	70	64	54	44	24
High risk	73	52	43	33	28	8

De-intensification for HPV associated oropharynx cancer

<u>Strategy #1: Reduce systemic therapy intensity</u>

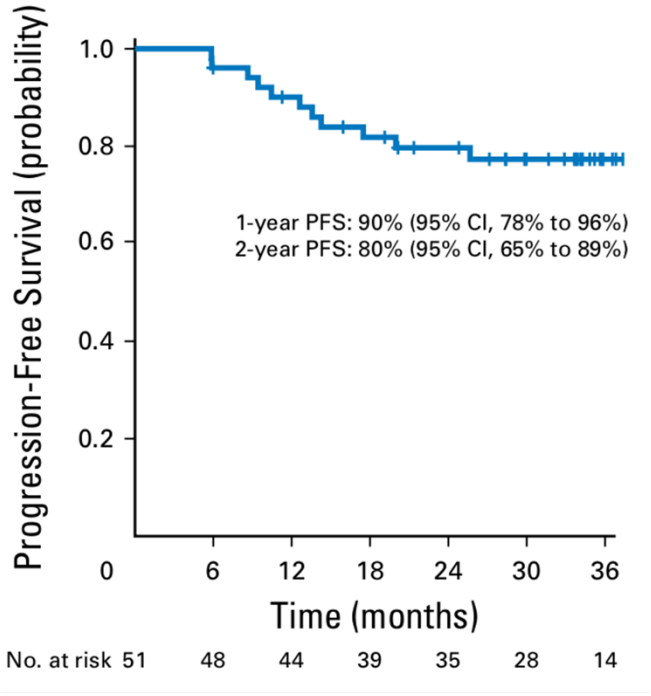
- RTOG 1016 (Gillison, Lancet 2018)
  - Phase III. 987 patients with p16 (+) oropharyngeal cancer
  - ~93% stage IV (AJCC 7th ed.)
  - Accelerated RT (70 Gy in 6 weeks) + either cisplatin (100 mg/m^2 q3 weeks) or weekly cetuximab
  - Cetuximab had inferior disease control and survival
  - Decreased grade 3+ acute AEs with cetuximab, but no difference in late AEs or feeding tube dependence



De-intensification for HPV associated oropharynx cancer

Strategy #2: Induction chemo to select well-behaving tumors

- ECOG E1308 (Marur JCO 2016)
  - Single arm phase II
  - 90 patients with HPV (+) and/or p16 (+) stage III-IV oropharynx ca. 28% >20py smoking
  - 3 cycles cix/taxol/cetuximab, followed by RT+cetuximab
  - Primary site, nodes: complete clinical response→54 Gy. Otherwise 69 Gy.
  - 70% had primary site CR, 58% had nodal CR
  - If primary site CR, 2-year PFS 80%
  - Promising result considering included plenty of smokers



De-intensification for HPV associated oropharynx cancer

Strategy #2: Induction chemo to select well-behaving tumors

- Univ. of California study (Chen Lancet Oncol 2017)
  - Single arm phase II
  - 45 patients with p16 (+), stage III-IV oropharynx cancer. 20% >20py
  - 2 cycles carbo/taxol, followed by RT+taxol
  - Complete or partial response by CT → 54 Gy, otherwise 60 Gy (both de-escalated)
  - 2-year PFS 92%
  - 5% late grade 3+ toxicity rate

De-intensification for HPV associated oropharynx cancer

Strategy #3: De-intensify all patients

- NRG HN002
  - Randomized phase II
  - Locally advanced oropharynx, stage III-IV
  - 60 Gy RT vs 60 Gy RT+ weekly cisplatin (both de-escalated)
  - Finished accrual of 295 patients, no results reported yet

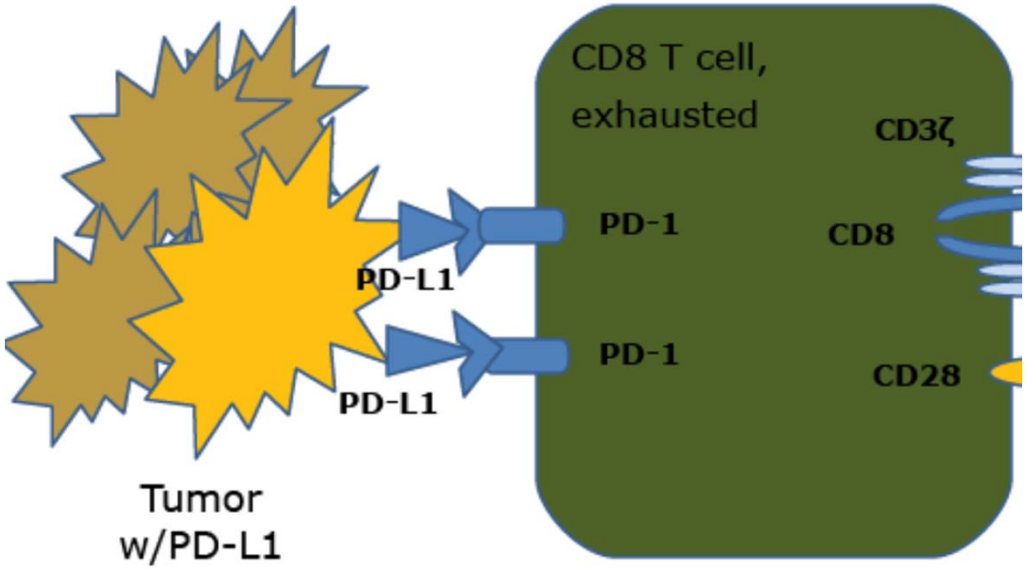
De-intensification for HPV associated oropharynx cancer

Summary

- De-intensification still investigational, do not do off protocol
- Many questions
  - How select best patients? Is induction chemo helpful?
  - Include higher risk patients? (T4, bilateral nodes, >10 pack year)
  - De-intensify radiation, chemo, or both?

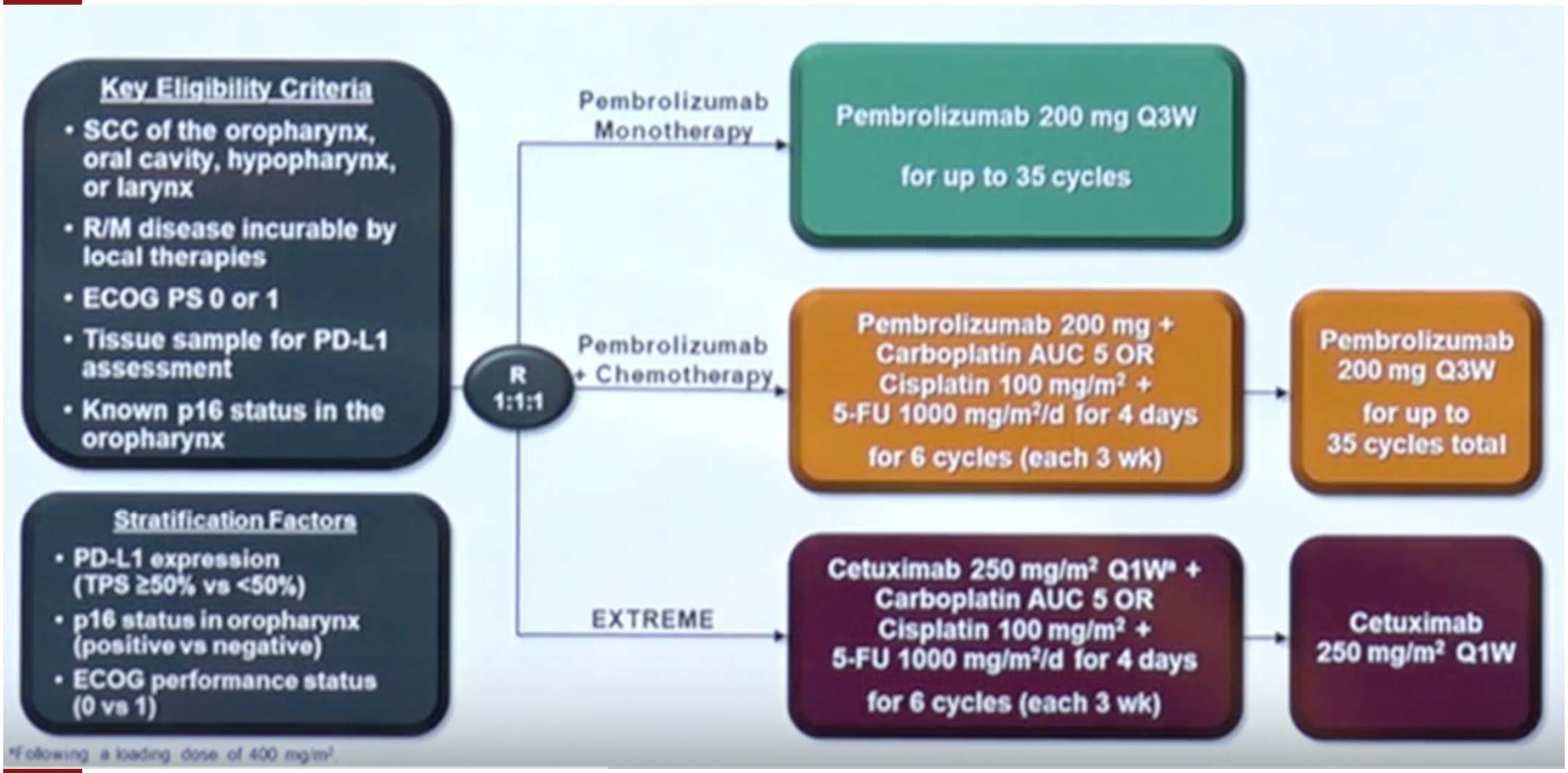
Immunotherapy

- Immune system critical to fighting cancer cells
- Anti-PD-1 / anti-PD-L1 antibody drugs
  - Nivolumab
  - Pembrolizumab
  - Durvalumab
  - Etc.



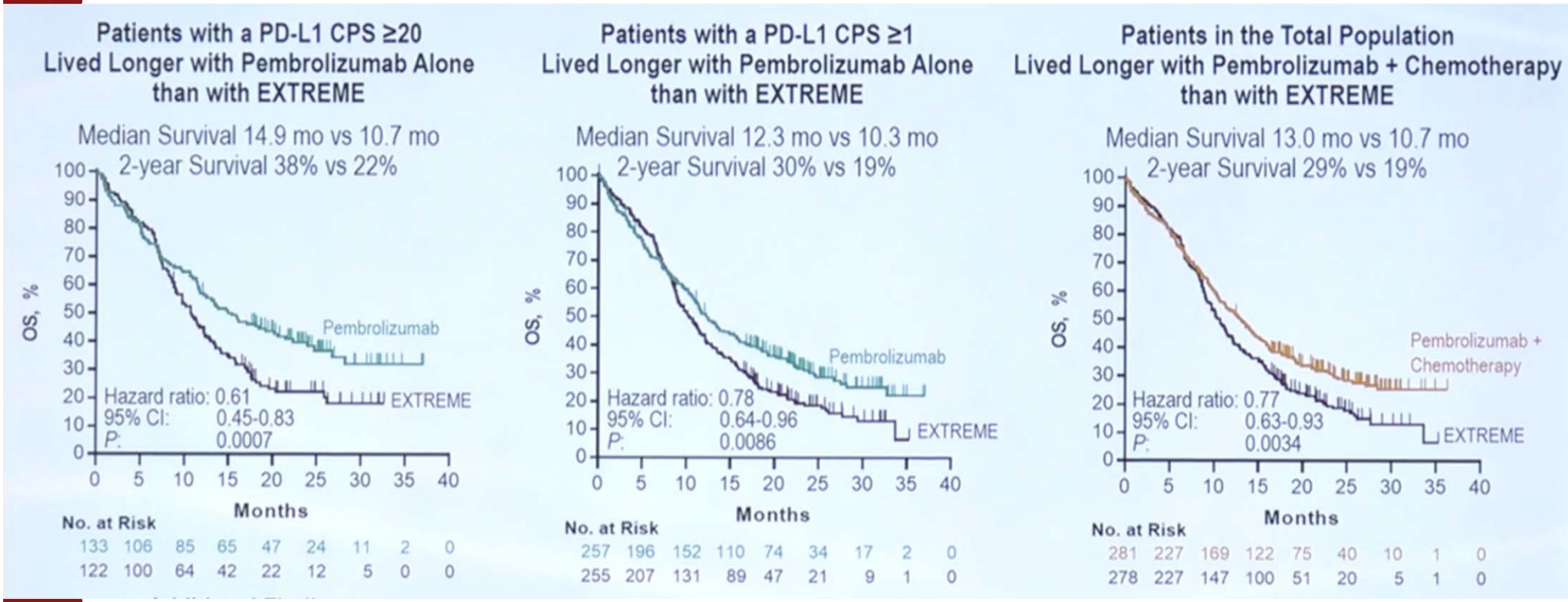
UpToDate

Immunotherapy: metastatic head and neck SCC



Burtness et al., ESMO 2018 Congress

Immunotherapy: metastatic head and neck SCC

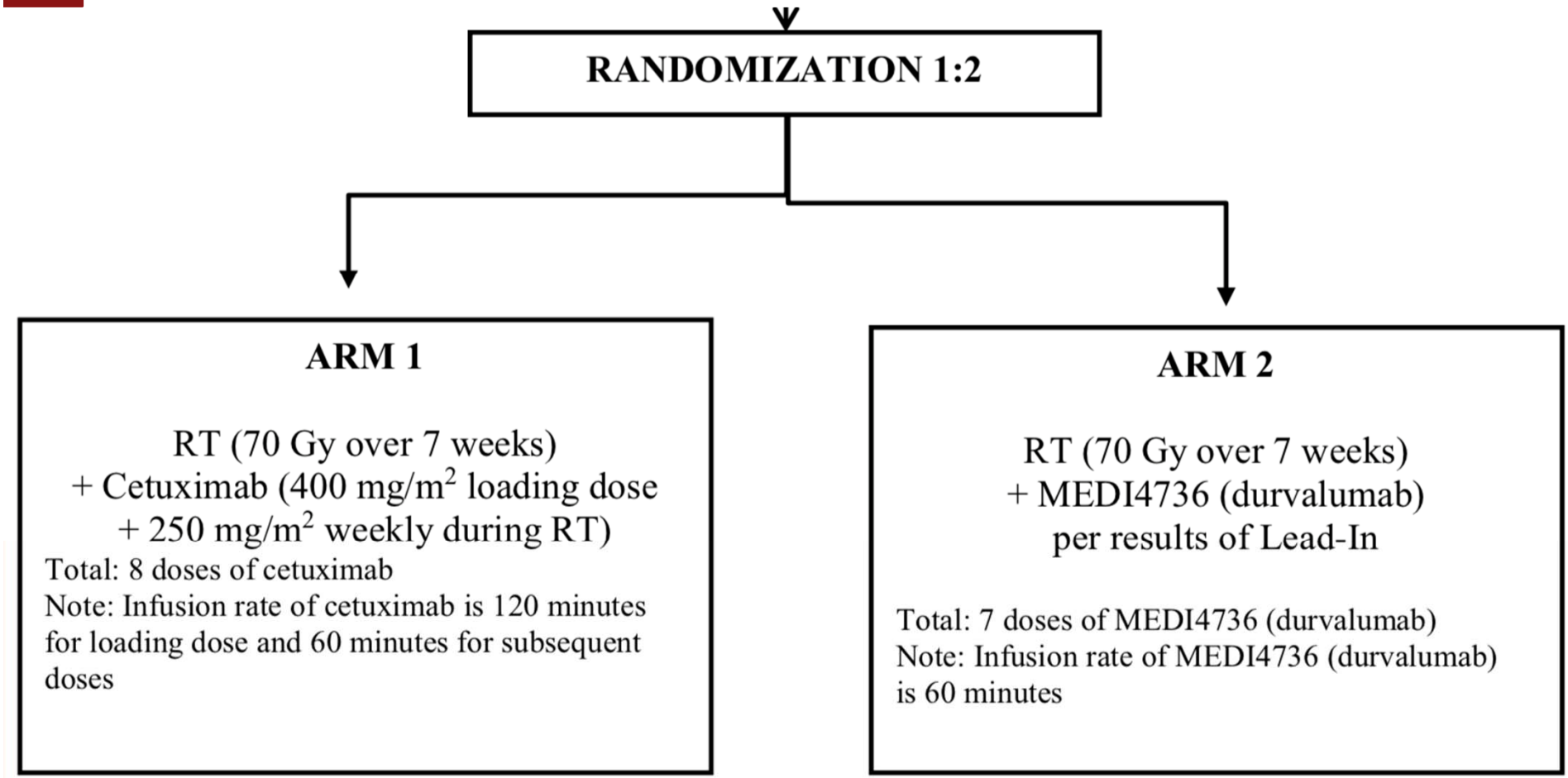


Burtness et al., ESMO 2018 Congress

Immunotherapy: non-metastatic head and neck SCC

NRG HN004 trial for radiation patients who can't get cisplatin

- https://clinicaltrials.gov/ct2/show/NCT03258554



Symptoms/quality of life

- Head and neck cancers and treatments cause many issues
- Vanderbilt head and neck symptom survey areas:
  - Mouth pain
  - General pain
  - Swallowing problems (solids, liquids)
  - Nutrition
  - Mucous
  - Dry mouth
  - Taste/small
  - Voice
  - Teeth
  - Hearing
  - Trismus
  - Neck/shoulder range of motion

And don't forget…

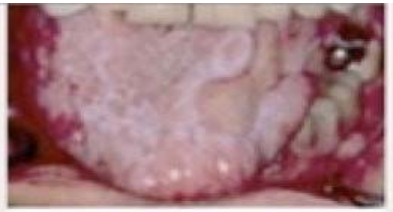
- Fatigue
- Insomnia
- Nausea
- Constipation/diarrhea
- Anxiety
- Depression
- Financial problems

Ridner et al. Oral Oncology 2018 83:25-31

Mucositis

- Extremely common and bothersome during head&neck radiotherapy
- Scales: WHO, RTOG, CTCAE

WHO grading

Grade 1	Grade 2	Grade 3	Grade 4
			
Grade 1 Erythema Unpleasant sensation (pain)	Grade 2 Erythema Ulcers Pain Can eat solids	Grade 3 Ulcers Significant pain Only a liquid diet is possible	Grade 4 Ulcers Intolerable pain Feeding by mouth impossible, enteral or parenteral feeding obligatory Cannot talk

https://slideplayer.com/slide/9153727/

Mucositis: Magic Mouthwash

- Multi-drug liquid mixture to help with mucositis
- Many names/formulations
  - Magic Mouthwash
  - Triple mix
  - BMX
  - Noll's solution
  - Pink lady
  - Seattle mouth wash
  - Stanford mouth wash (I've never heard of it)
  - Magic swizzle

Mucositis: Magic Mouthwash

- Often includes ingredients such as:
  - antihistamine (such as diphenhydramine/Benadryl)
  - numbing (such as lidocaine)
  - antacid (such as Maalox)
  - antifungal (such as nystatin)
  - antibiotic (such as tetracycline)
  - steroid (such as dexamethasone)
  - coating agent (such as sucralfate)
  - Water

- Compounded ($$$), or patient mixes
- Shelf life, refrigeration

Mucositis: Magic Mouthwash

- Randomized trial in patients with chemotherapy-induced mucositis

Vol. 90 No. 1 July 2000

ORAL SURGERY
ORAL MEDICINE
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ORAL MEDICINE

Editor: Martin S. Greenberg

Randomized clinical trial of the effectiveness of 3 commonly used mouthwashes to treat chemotherapy-induced mucositis

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UNIVERSITY OF CALIFORNIA, SAN FRANCISCO

Mucositis: Magic Mouthwash

Patients

- 200 patients receiving chemotherapy known to cause mucositis
- Had mucositis at study entry
- Excluded if getting radiation

Intervention

- Randomized to 12 days of one of three mouth washes:
  - Salt and baking soda
  - Chlorhexidine gluconate 0.12%
  - Magic mouthwash
    - 25% lidocaine 0.5%
    - 1.25% Benadryl
    - 73.75% Maalox

Mucositis: Magic Mouthwash

Results

- Similar time to resolution of signs/symptoms: mean in the 3 groups ranged from 6.6-6.2 days, p=0.59)
- No large difference in mean pain scores between groups, p=0.75

My conclusions

- Potential criticisms:
  - This Magic Mouthwash had very little lidocaine
  - Other rinses were both active against mucositis (no placebo arm)

News > Medscape Medical News > Oncology News

Experts: Magic Mouthwash Should 'Vanish Into Thin Air'

But Phase 3 Trial Is Contrary, May Materialize Soon

Nick Mulcahy
November 28, 2018

Choosing Wisely®
An initiative of the ABIM Foundation

American Academy of Nursing

View all recommendations from this society

Released April 23, 2015

Don't use mixed medication mouthwash, commonly termed "magic mouthwash," to prevent or manage cancer treatment-induced oral mucositis.

Mucositis: Magic Mouthwash, Doxepin

- Alliance A21304 trial (Sio et al., JAMA 2019;321(15))

Patients

- 275 patients receiving head and neck radiation, with mucositis pain

Intervention

- Randomized to one of 3 mouth washes (swish and spit):
  - Doxepin (25 mg in 5 mL)
  - Magic Mouthwash (1:1:1 2% viscous lidocaine, Benadryl, Maalox)
  - Placebo (water with sugar-free sweetener)

Outcomes

- Primary: give 1 dose, find mean pain score over next 4 hours
- Secondary: pain scores during optional continuation phase, etc.

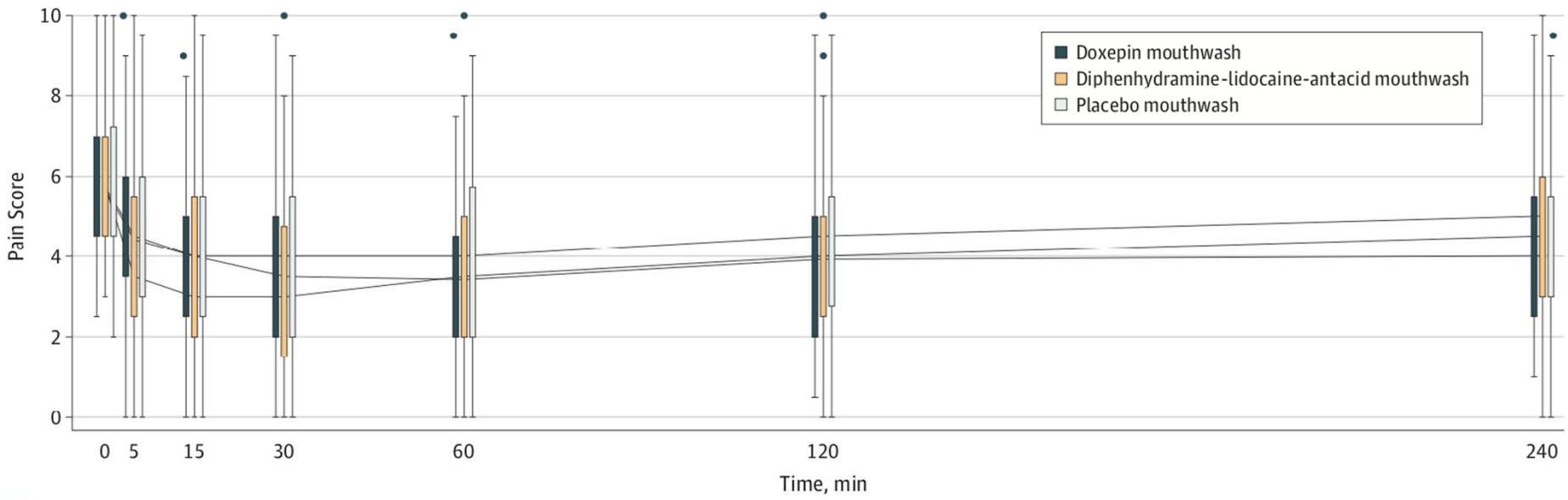
Mucositis: Magic Mouthwash, Doxepin

- Alliance A21304 trial (Sio et al., JAMA 2019;321(15))

Results: primary endpoint

- Small improvement in pain over next 4 hours for doxepin and Magic Mouthwash (2.9-3.0 points better than placebo)

Figure 2. Pain Scores Over Time During Cycle 1 for Doxepin, Diphenhydramine-Lidocaine-Antacid, and Placebo Groups



Mucositis: Magic Mouthwash, Doxepin

- Alliance A21304 trial (Sio et al., JAMA 2019;321(15))

Results: secondary endpoints

- 46% of patients participated in continuation phase. No significant differences in mean mouth pain score.
- Side effects: doxepin had more stinging/burning, drowsiness, unpleasant taste

My conclusions

- Small pain benefit to Magic Mouthwash or doxepin, more side effects with doxepin
- I use these differently from trial: instruct patients to take soon before eating.

Oncology/Hematology > Other Cancers

'Magic Mouthwash' Little Help for Radiation-Induced Mucositis

— Only statistical improvements in pain scores for head and neck cancer patients

by Ian Ingram, Deputy Managing Editor, MedPage Today
April 16, 2019

Science News *from research organizations*

Magic mouthwash effective treatment for mouth sore pain caused by radiation therapy

Date: April 16, 2019

Source: Mayo Clinic

Summary: 'Magic mouthwash,' an oral rinse containing diphenhydramine, lidocaine and antacids, significantly reduced pain from oral mucositis, mouth sores, in patients receiving radiation therapy for cancers of the head and neck when compared to plaecbo.

Magic Mouthwash: Take home points

- Instead of compounding, have patient mix the Magic Mouthwash (much cheaper)
- Caution patients not to swallow large amounts of lidocaine
  - Numbs pharynx and larynx, could cause aspiration
  - If swallow large amounts, could cause systemic toxicity
    - CNS: seizures, sleepiness
    - Cardiovascular: hypotension, arrhythmias

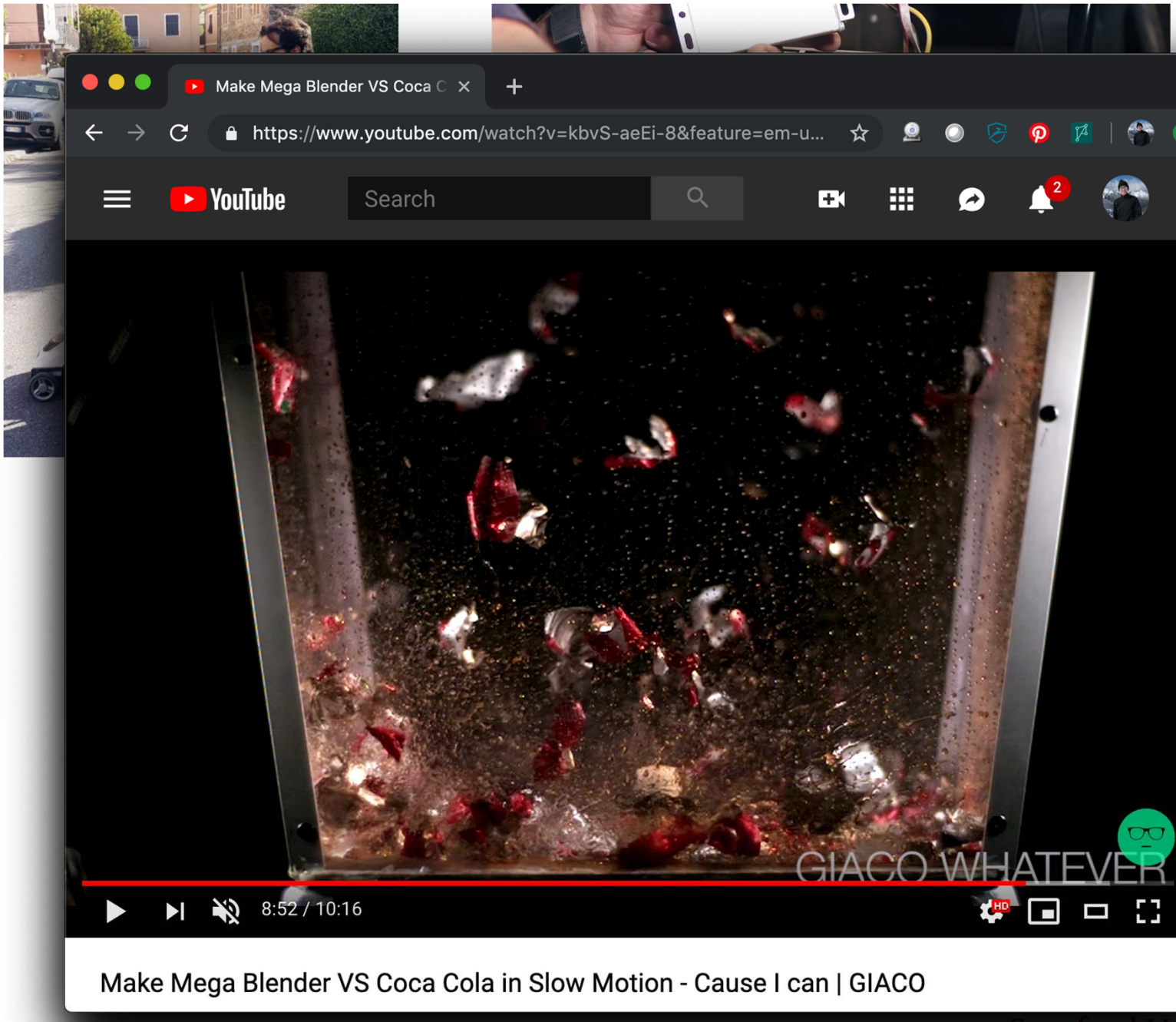
Torp K, Simon L. Lidocaine toxicity. StatPearls, 2019. https://www.ncbi.nlm.nih.gov/books/NBK482479/

Mucositis: summary

- Few evidence-based treatments to prevent or manage
- Stanford rad/onc standard practice:
  - Salt and baking soda rinses many times a day
    - 1 tsp salt
    - 1 tsp baking soda
    - 4 cups water
  - Magic Mouthwash or doxepin
  - Gabapentin 300 mg TID for mucositis pain, can titrate up gradually to 900 mg TID every 2-3 days if well tolerated
  - Tylenol or Advil
  - Opioids

Nutrition

- Try to maintain stable weight during radiation
  - › Dose calculations; mask fit
  - › Healing from treatment
- High calorie foods
- Supplements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Make Mega Blender VS Coca Cola in Slow Motion - Cause I can | GIACO

Nutrition

- Enteral feeding supplementation often needed for patients receiving chemoradiation (PEG, NG tube)
  - Prophylactic strategy: place PEG before start treatment
  - Reactive strategy: place PEG tube if 10-15% body weight loss
- Prophylactic advantages: Less weight loss; easier hydration; no need for urgent placement
- Reactive advantages: Usually can avoid PEG (infection risk etc.); forces patient to use their swallowing muscles

Nutrition

- Randomized Swedish trial of prophylactic vs reactive PEG placement (Silander et al. Head&Neck 34:1, 2012)
- 134 patients with locally advanced head and neck cancer were randomized before treatment (2002-2006)
- 1 patient in prophylactic PEG arm died from complications of PEG placement
- 73% of reactive PEG arm patients eventually had tube placed
- Prophylactic PEG arm had:
  - Slightly less weight loss
    - Mean of 8.8 vs 9.6 kg at 6 months, p=0.08
- Less dysphagia (93% vs. 80% able to eat normal diet)
- Improved quality of life at 6 months, same at 12 and 24 mo.

Swallowing

- Dysphagia common after radiation
  - Dysfunction of pharyngeal constrictor muscles
  - Dry mouth
  - Anatomic changes after tumor regression
- Speech language pathologist
- Swallowing exercises during/after radiation may help prevent dysphagia (but, time-consuming!)
  - Meta-analysis: Greco et al. Int J Radiat Oncol Biol Phys 101:421, 2018

Swallowing exercises

Target	Exercises
Set 1: mandibular & neck range of motion exercises	Therabite: 7-7-7 protocol
	*both groups were instructed on the therabite
	Mouth open wide stretch. Repeat × 10
	Neck Stretch: sit on the palm of your right hand, bring left hand over your head and place just above your ear
	Stretch your head gently toward the left shoulder—hold 5 s—then drop chin down 5 times or until your chin gets down to your chest
	Move slowly. Then begin in middle position and do (1) 5 s hold with head extending back. Repeat to right by sitting on left hand
Set 2: labial range of motion exercises	Lip protrusion/retraction. Pucker and smile x 10
Set 3: lingual range of motion and strengthening exercises	Elevation, depression, lateralization, protrusion, anterior-posterior motion x 10 in each direction
	Retract tongue, hold 3 s, repeat × 10
Set 4: pharyngeal strengthening exercises	Masako Maneuver, repeat × 5
	Mendelsohn Maneuver, repeat × 5
	Effortful Swallow with mist bottle or liquids, repeat × 10
Swallowing	Swallow frequently throughout the day
	Continue eating and drinking by mouth, even when tube use starts
	Use spray mist bottle and other dry mouth products
	Stay hydrated

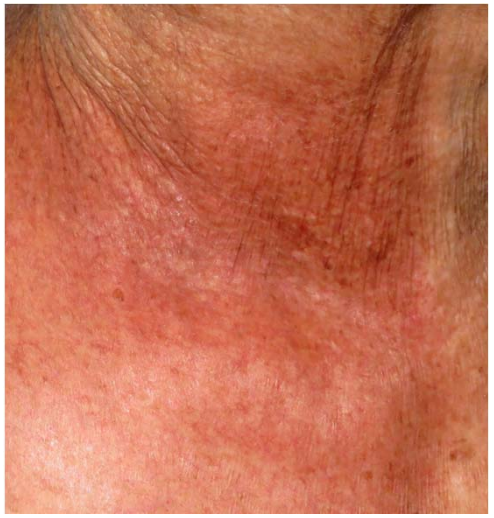
Messing et al. Dysphagia 32:487, 2017

Skin

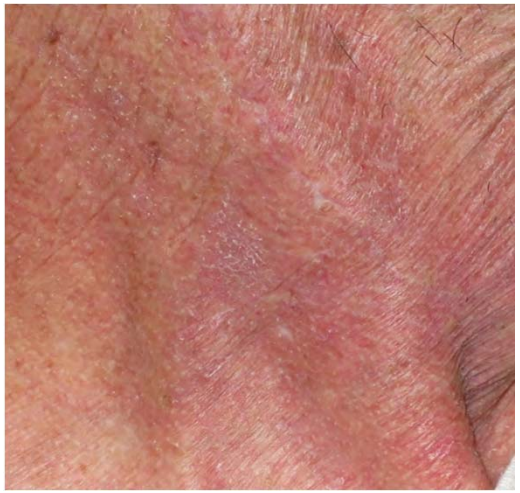
Radiation skin reaction stages

1. Mild erythema

2. Bright erythema



3. Dry desquamation



4. Moist desquamation

Skin

- Moisturizers BID-TID for all patients
- Itchy skin: topical steroid, I use OTC hydrocortisone 1%
- Moist desquamation treatment:
  - Domeboro or Dakin's soaks TID
  - Non-adherent dressings

very few high quality trials to guide this

Dry mouth / xerostomia

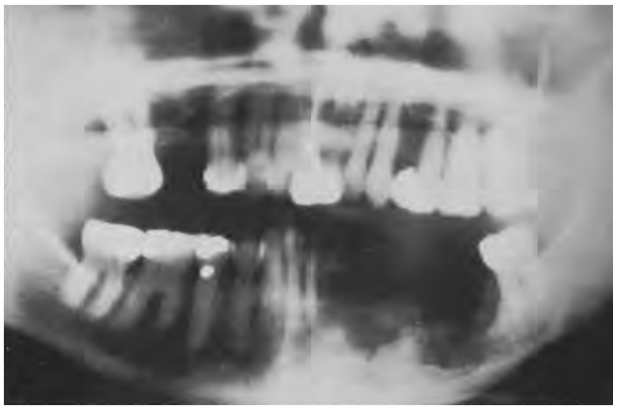
- Common during and after radiotherapy
- Intensity-modulated radiation therapy reduces this
- Water bottle, humidifier at night
- Products: often contain xylitol (stimulates saliva), lubricants, humectants

Dental decay

- Radiation causes in several ways
  - Decreased blood supply to mandible
  - Changes to saliva (less volume; more acidic)
- Recommendations:
  - Meticulous dental hygiene (brush, floss)
  - Rx strength fluoride toothpaste, or fluoride trays
  - Dental visits 2-3x / year

Dental decay: tooth extractions

- Risk of osteoradionecrosis (ORN) of mandible after dental extractions in irradiated field
- Classic randomized trial (Marx et al., JADA 111:49, 1985)
  - 74 patients who required tooth extraction in area of mandible that got >=60 Gy radiation
  - Antibiotics arm: penicillin before and for 10 days after surgery
  - Hyperbaric oxygen arm: HBO, 20 sessions before and 10 sessions after extraction
  - ORN rate: 23% in antibiotics arm, 2.6% in HBO arm
- But, recent studies have suggested lower risk of ORN



Dental decay: tooth extractions

- HOPON trial (Shaw et al., Int J Radiat Oncol Biol Phys 2019 PMID 30851351)
- Randomized phase 3 multicenter trial
- 144 patients planned for dental extractions or implants in mandible that got >50 Gy radiation
  - Antibiotics arm: chlorhexidine rinse + amoxicillin
  - HBO arm: same as antibiotics arm, + 30 HBO dives
- Trial stopped early after 100 patients evaluable due to futility (low rate of ORN in both arms)
- Rate of ORN at 6 months: 6% in both arms
- *Why different results from Marx 1985 study?*

Misc.

- Lymphedema
  - Self massage instructions
    https://www.uhn.ca/PatientsFamilies/Health_Information/Health_Topics/Documents/Do_Lymphatic_Self-massage_Face_Head_Neck.pdf
- Trismus (reduced jaw opening)
  - Therabite, popsicle sticks

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