2019
21-23 JUNE
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SUPPORTIVE CARE
MAKES EXCELLENT
CANCER CARE POSSIBLE

New technologies, new toxicities: New radiotherapy modalities

MASCC/ISOO
Annual Meeting on Suppportive Care in Cancer
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MASCC
Multinational Association of Supportive Care in Cancer

ISOO
INTERNATIONAL SOCIETY of ORAL ONCOLOGY

#MASCC19

Conflict of Interest Disclosure

Sue Yom, MD PhD MAS

- Salary: UCSF
- Royalty: UpToDate, Springer
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- Ownership Interest (stocks, stock options or other ownership interest excluding diversified mutual funds): None
- Other: None

Major acute side effects

- Most effects located within the treatment area
- Take place within days to weeks
- Denudation of epithelial and mucosal surfaces
  - skin, oral mucosa, pharyngeal/esophageal mucosa, bowel mucosa, bladder lining, urethra/ureter
- Acute dryness
  - salivary glands, tear glands, sweat glands of axilla, tracheobronchial lining, genital mucosa
- Swelling and edema
  - brain swelling within intracranial compartment, closure of trachea or main bronchus or any lumen which may obstruct
- Fatigue: cytokine-based inflammatory reaction

Major late side effects

- Strictly within the treatment area
- Fibrosis: Loss of elasticity and healing ability due to diffuse scarring, damage of blood vessels and connective tissue
  - Pharynx, heart and lung fibrosis, proctitis and cystitis
- Epilation: Hair bearing skin within the radiation field
- Dryness: Salivary, tear, sweat glands, genitalia
- Lymphedema: #1 most commonly reported complication in breast radiation patients, but occurs in any treated lymphatic area e.g. neck, groin
- Neurologic: cognitive decline over years, optic neuropathy, brachial plexus
- Secondary malignancy: <5 excess cancers in 1000 pts at 15 yrs, vs heme malignancies at 5-10 years

Many toxicities of HN radiation and chemoradiation

Acute / Subacute

- Pain
- Xerostomia
- Mucositis
- Dermatitis
- Dysgeusia
- Dysphagia
- Nausea
- PEG dependence

Late effects

- Dental decay, ORN
- Esophageal stricture
- Hearing loss
- Neck fibrosis
- Endocrinopathy (hypothyroidism)
- Cognitive function
- Carotid stenosis
- Brachial plexopathy
- Cranial neuropathy

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Major strategies to reduce HN radiation toxicity

- Conformal radiation and “organ at risk” avoidance
  - Radiation planning
  - Radiation dose/volume reduction
  - OAR avoidance
- Preventive care while on treatment
  - Reducing severe acute effects → ↓ “acute on late” effects
  - Radioprotectants
- Supportive care interventions
  - Survivorship incl. long-term subsite-specific expertise
  - Radioreversants
- Proton therapy

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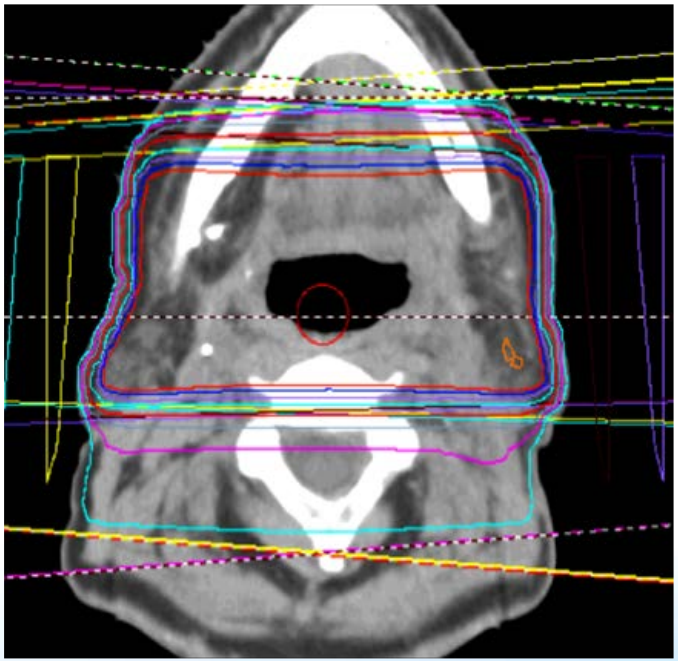
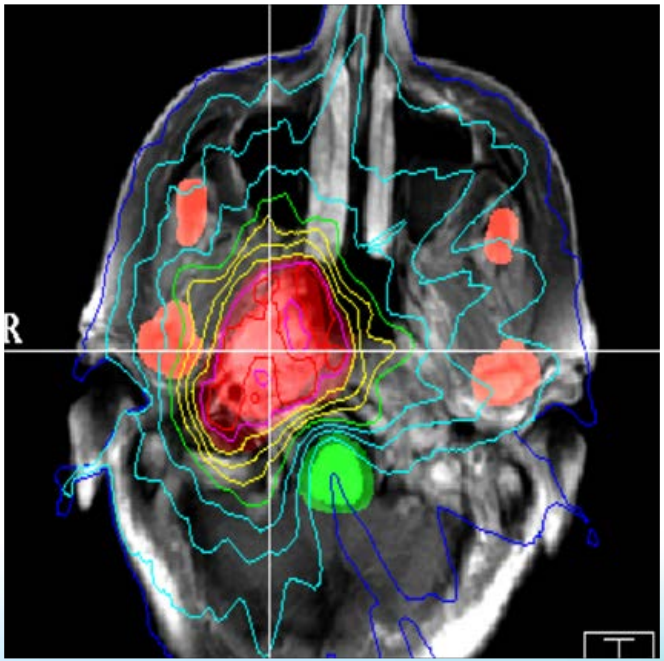
1. Conformal IMRT technology and “organ at risk” avoidance

Conventional plan vs IMRT for oropharynx cancer





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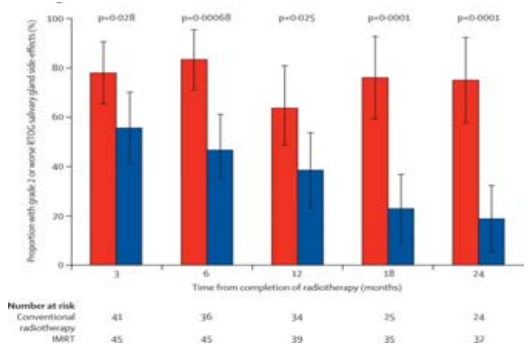
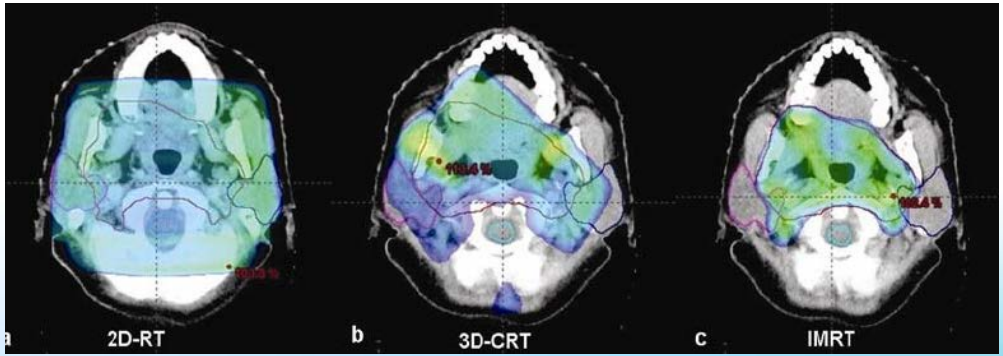
Importance of radiation technique in HN cancer

PARSPORT
- N = 94 from 6 UK centres
- 3D conventional RT vs IMRT
- Difference in proportion of patients suffering ≤gr2 xerostomia at 1 year



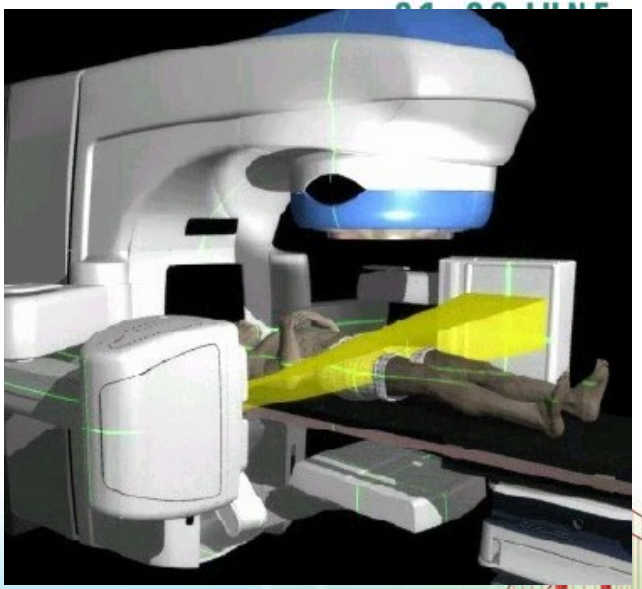
Nutting, Lancet Oncology 2011



Conebeam CT reduces toxicity effects

- VMAT head and neck radiotherapy **with conebeam CT guidance**
- PTV margin of 5 mm (N=206) → 3 mm margin (N=208)
- Xerostomia not better but mucositis and dysphagia were

	3mm margin	5mm margin	p value
– Acute grade 3 toxicity	53.8%	65%	0.032
– **Acute grade 3 mucositis**	**30.8%**	**42.2%**	**0.008**
– **Acute grade 3 dysphagia (PEG)**	**22.1%**	**33.5%**	**0.026**
– **Three-month PEG rate**	**11.1%**	**20.4%**	**0.012**
– 2-year grade ≥2 xerostomia	15.8%	19.4%	0.8
– 2-year loco-regional control	79.9%	79.2%	1.0
– 2-year disease-free survival	71.5%	72.7	0.6
– 2-year overall survival	75.2%	75.1%	0.9



Navran A et al , Radiother Oncol. 2018

1B. Reducing radiation dose for select patients

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NRG-HN002: A Randomized Phase II Trial for Patients with P16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

RESULTS NEAR MATURITY

Other surgery-based or heavy chemotherapy-based approaches developing

Eligibility

- OP SCCA
- ≤10 pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

Central review
p16+ IHC

Declare Intent
Unilat vs Bilat Neck XRT

N = 296

Arm 1: 60 Gy XRT (2Gy/fx) in 6 weeks + cisplatin 40 mg/m2 weekly x 6 cycles

Arm 2: 60 Gy XRT (2 Gy/fx) at 6 fractions/week for 5 weeks

NRG-HN005: A Randomized Phase II/III Trial of De-intensified Radiation Therapy for Patients with Early Stage, p16-Positive, Non-Smoking-Associated Oropharyngeal Cancer

Eligibility

- Oropharynx SCCA
- p16+
- ≤10 pack-yr
- T1-2N1 or T3 N0-1

Randomized Phase II

N = 363
1y PFS, 1y MDADI

RANDOMIZE

- 70 Gy in 6 weeks + cisplatin 100 mg/m2 x 2 cycles — Control arm from 1016
- 60 Gy in 6 weeks + cisplatin 100 mg/m2 x 2 cycles — Exp. arm 1
- 60 Gy in 5 weeks + nivolumab 240 mg x 6 cycles — Exp. arm 2

Phase III continuation

N = 116 pts PER ARM
2y PFS, 1y MDADI

RANDOMIZE

- 70 Gy in 6 weeks + cisplatin 100 mg/m2 x 2 cycles
- *1 or 2 experimental arms*

N = 595 if 2 arms go forward
N = 711 if 3 arms go forward
(QOL N = 378 per 2-arm comparison)

NRG ONCOLOGY™

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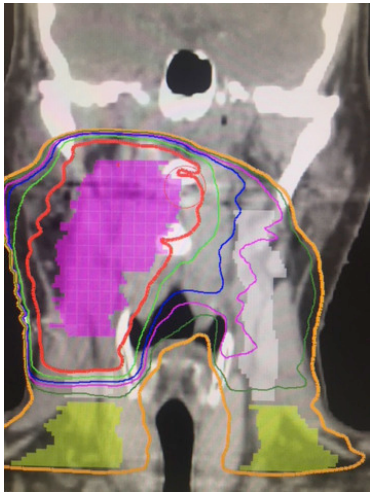
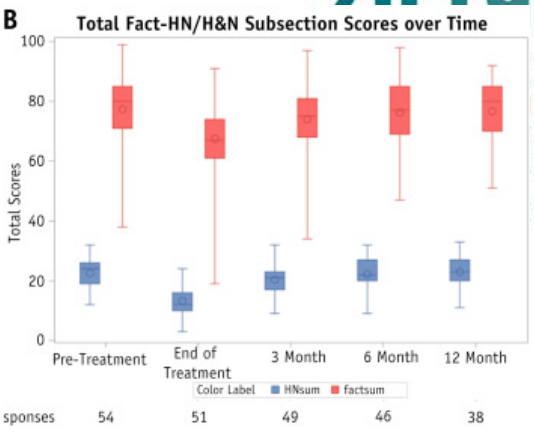
Prophylactic neck – “elective” dose reduction



- Locally advanced SCCHN of the oral cavity, oropharynx, larynx, or hypopharynx
- Sequential-boost IMRT: 36 Gy with boost to 70 Gy
- Upper neck received 40-45 Gy
- Weekly cisplatin at 35 mg/m^2
- Primary phase II endpoint = elective nodal failure
- N = 54 (57% HPV+, 65% 7th ed stage IVA)
- At 3 years, there was no elective nodal failure
- 3-year survival was 91%
  - 85% in HPV-negative
  - 96% for HPV+
- FACT-HN back to pre-RT baseline by 6 months

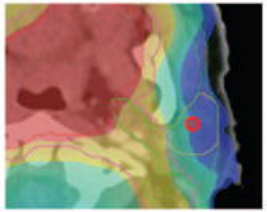


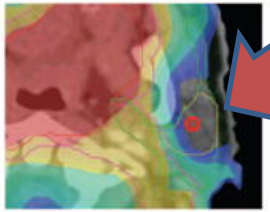
Maguire et al, IJROBP 2018

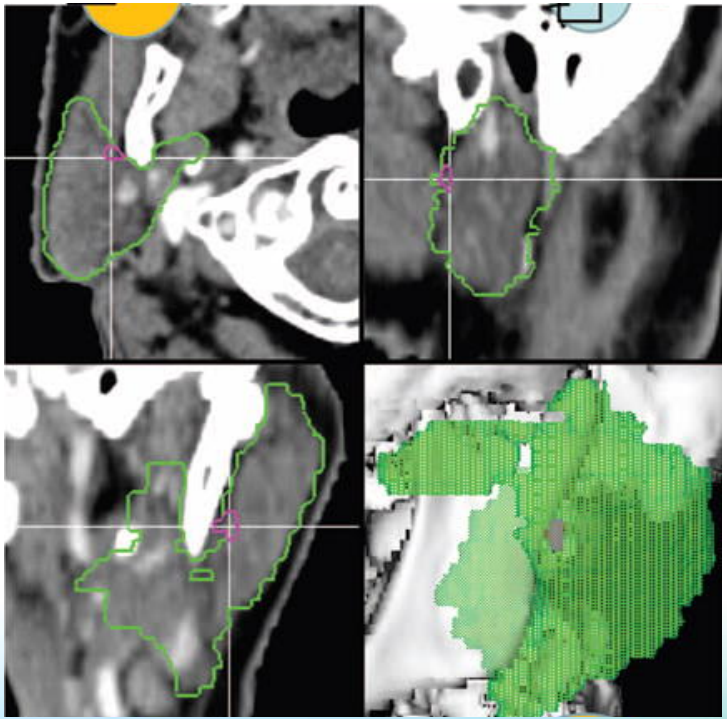
1c. Reducing dose to select critical organs

OAR planning interventions: salivary stem cells

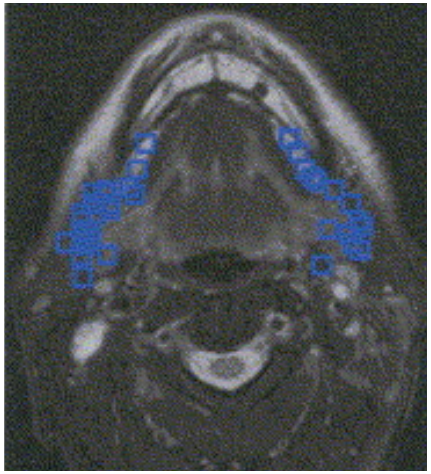
- van Luijk et al. rat parotid model
- Salivary function dependent on site irradiated – not on mean dose
- Stem-cell containing region at first branching of Stensen's duct
- Dose to stem cell region was highly predictive of gland function
- Area that we frequently spare already?





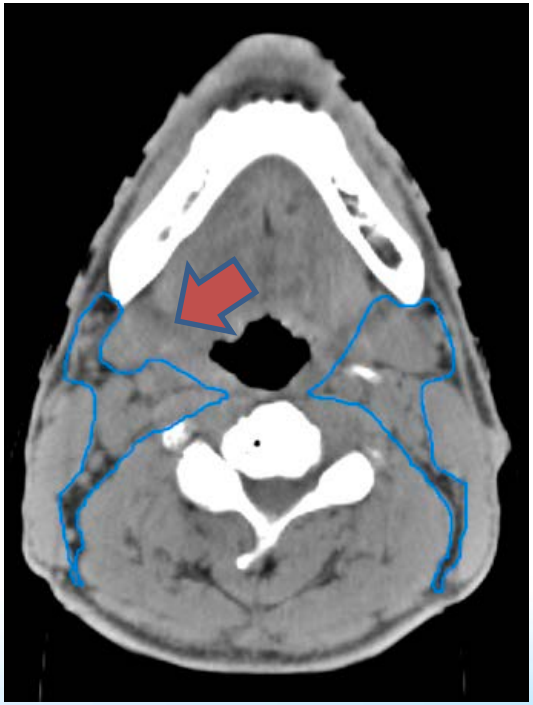


Submandibular avoidance

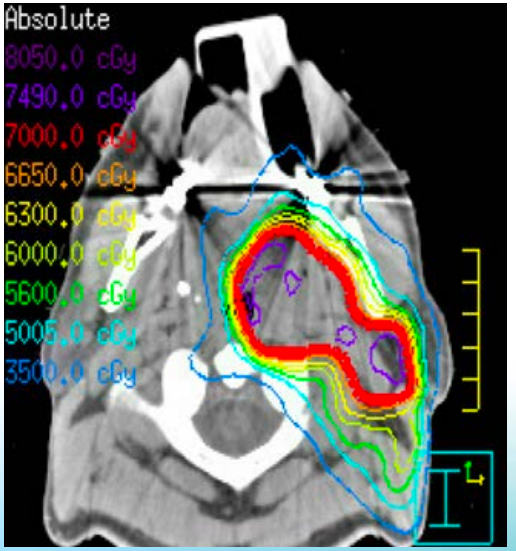


Lymph nodes are lateral and anterior to SMG

Poon et al, IJROBP 2004



"From all the published studies (n = 11, with 1116 patients treated in total), the incidence of contralateral regional failure in patients with oropharyngeal cancer treated to one side of the neck is 2.4%. The incidence was higher in patients with tumours involving the midline (12.1%)." - Al-Mamgani, Eur J Cancer. 2017



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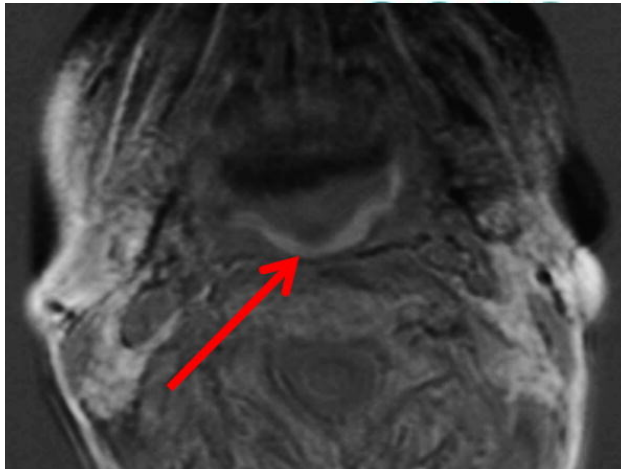
Swallowing muscle avoidance

- "Swallowing sparing IMRT"
- Doses to SWOARs prioritized – example Dmeans
  - mean dose to superior pharyngeal constrictor muscle (41.5 Gy)
  - mean dose to supraglottic larynx (54.3)
  - mean dose to middle PCM (46.8 Gy)
  - minimize proportion of esophageal inlet receiving ≥ 60 Gy (35.4 Gy)
- Accepted a shift of dose to oral cavity and neck; reduced coverage down to 95% of PTV; accepted reasonable parotid/cord doses
- Greatest improvement in NTCP of RTOG grade ≥2 swallowing dysfunction (8.6%) for:
  - neck irradiation
  - <75% overlap between SWOARs and PTV
  - tumor in larynx, oropharynx, oral cavity or nasopharynx
  - for other patients improvement was 3.1%

van der Laan, R&O 2013
Christianen, R&O 2016



T2-weighted subtraction: fibrosis

Messer, R&O 2016

2. Maximal preventive care while on treatment

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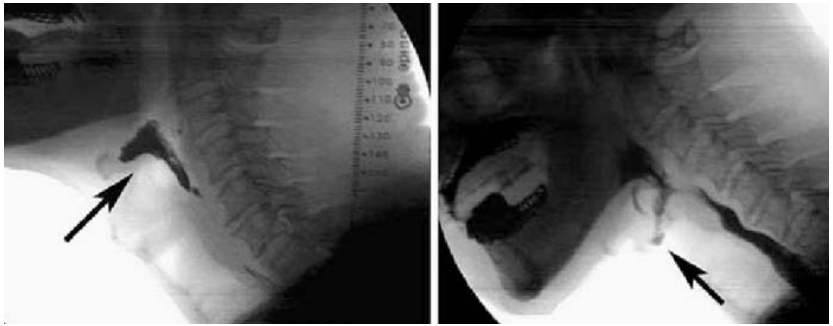
Preventive/Supportive Intervention: calcium phosphate rinses, oral moisturization

Reduce acute on chronic damage

Preventing Dysphagia: UCSF Swallowing Therapy Protocol

- Pre-, Mid-, and Post-RT evaluations and training
- Flexible endoscopic evaluation of swallowing (FEES)
  - Visualization of anatomy, mucosal surfaces, and secretions
  - High sensitivity to detect trace penetration and aspiration
- Videofluoroscopic study (VFSS)
  - Radiographic views of oral, pharyngeal, and esophageal phases
  - Objective spatial and temporal kinematic measures



residual bolus in vallecula

supraglottic penetration

- Other objective measurements
  - Tongue strength, jaw opening, cervical range of motion, suprahyoid muscle strength, salivary flow
- Compensatory postural or positional strategies
- Strength-based and range of motion swallowing exercises

It is considered unethical in the Netherlands not to offer swallowing therapy to a patient

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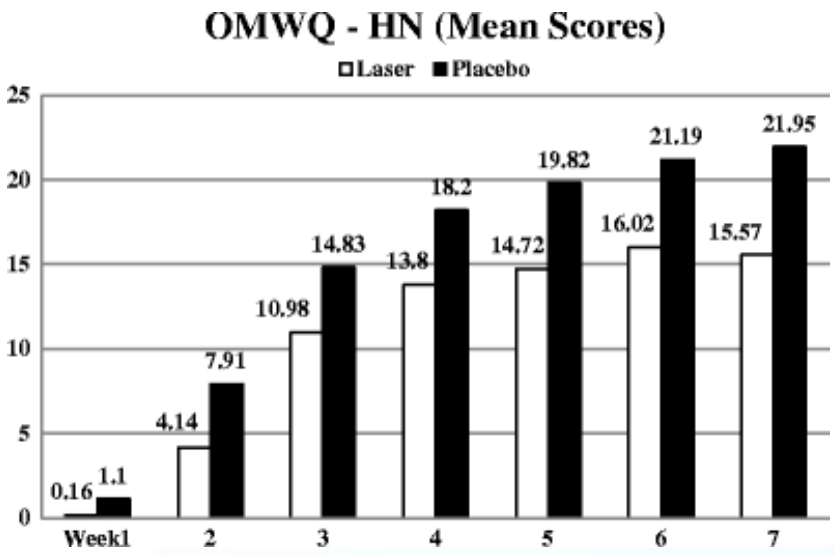
Radioprotectants under development

- Palifermin – binds keratinocyte growth factor receptor
  - Reduced grade 3-4 oral mucositis in placebo-controlled phase III study of HN patients receiving chemoradiation
  - Not approved due to lack of improvement in narcotic use, pain, or compliance
- GC4419 – mimetic of antioxidant superoxide dismutase
  - Granted Fast Track and Breakthrough Therapy designations by FDA for severe oral mucositis induced by RT with or without systemic therapy – in phase III
  - IV formulation
- RRx-001 – binds and oxidizes hemoglobin
  - Phase II
- SGX94 (dusquetide) – Innate Defense Regulator
  - Phase III
- BMX-001 - mimetic of manganese superoxide dismutase
  - Subcutaneous injection – in phase II

Preventing mucositis: Low level laser therapy



Gautam Support Care Cancer 2013

- 220 HNC patients randomized to Helium-Neon low level laser therapy (= 632.8 nm) or not
- Five sessions per week
- Dosage = 3.0 J/point at 12 anatomical sites for total of 36 J
- Irradiated area = 1 cm^2, irradiation time/point = 125 s
- Oral Mucositis Weekly Questionnaire-Head and Neck and FACT-HN scores were lower in LLL
- Onerous workflow. Difficult to set up.

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3. Supportive care interventions after treatment

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RTOG 0537 ALTENS vs PILOCARPINE - Results

- Endpoint: change in Xerostomia-Related Quality of Life Scale score over 9 months from enrolling
- N = 148, 96 completed XeQOLS
- Changes in XeQOLS at 9 and 15 months were −0.53/−0.27 (P=0.45) and −0.6/−0.47 (P=0.21)
- Grade 1-3 adverse events in 20.8% of ALTENS and 61.6% of PILOCARPINE
- Significantly less toxicity with ALTENS
- Machine is expensive, many patients prefer traditional acupuncture

Wong et al, Int J Radiat Oncol Biol Phys. 2015;92(2):220-7.

Preventing ORN – UCSF dental oncology approach

- Pre-RT clearance by Dental Oncology
  - Comprehensive oral examination with full-mouth and panoramic radiographs, to exclude retained root tips or bone lesions
  - Custom plastic guards to prevent scatter off metal crowns/posts
  - 1.1% neutral sodium fluoride, 5 minutes daily
  - Cleanings every 3-6 months
  - Evaluate risk from planned radiation doses to teeth/mandible
- Prompt referral to experienced OMFS/FPRS
  - Extractions of grossly carious/hopeless teeth, in the OR if feasible
  - Implants/recon in the OR if feasible
  - Extract loose, impacted, or infected teeth within planned 50 Gy region
  - Risk of ORN is mild <40 Gy, moderate at 40-60 Gy, high at 60 Gy

AI-assisted ADVANCE prediction of INDIVIDUAL dental dose

PlanMD view:

- Use diagnostic imaging to generate tumor contour
- AI-driven search through library of prior radiation plans to estimate anticipated dose distribution
- Predict doses to individual segments of the dental structure
- Enables individualized anticipatory management

- Accepted for presentation at ASTRO 2019

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Treating ORN

- No implants/extractions ever allowed without RadOnc clearance
  - Dental implants only in select cases with antibiotic prophylaxis
  - Extractions with atraumatic technique, antibiotics and chlorhexadine
- Treatment of ORN
  - PENTACLO: vitamin E 1000 IU and pentoxifylline 400 mg TID ± clodronate (oral bisphosphonate) x 6-12 months
  - UCSF approaches: pentoxifylline, vit E and vit C, amoxicillin/Augmentin
  - Hyperbaric oxygen – controversial but occasionally effective
    - Marx Protocol: 20 dives prior to extraction, 10 dives post-extraction
    - We use 40-50 dives for serious cases

Delanian IJROBP 2011

4. Reducing radiation dose to the oral cavity with proton therapy

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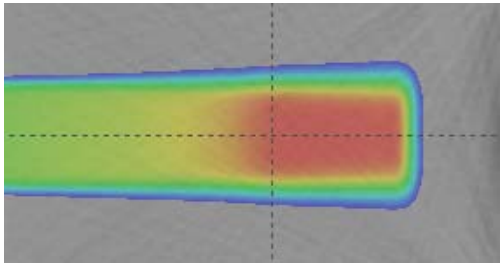
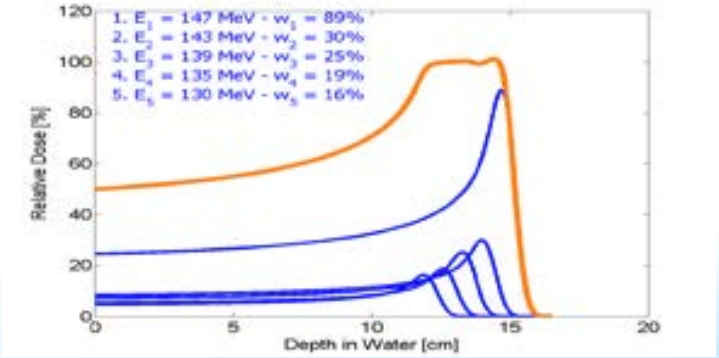
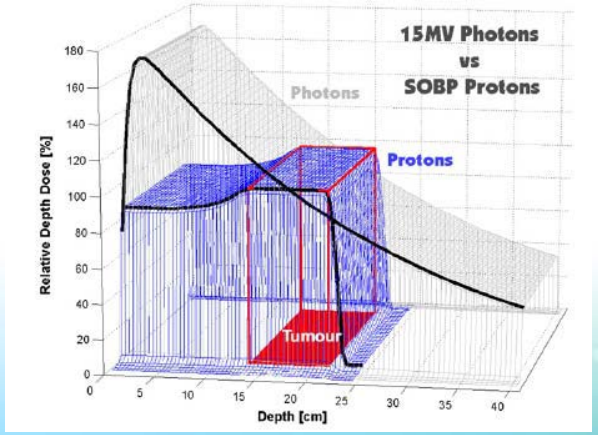
WHY protons for HNC?

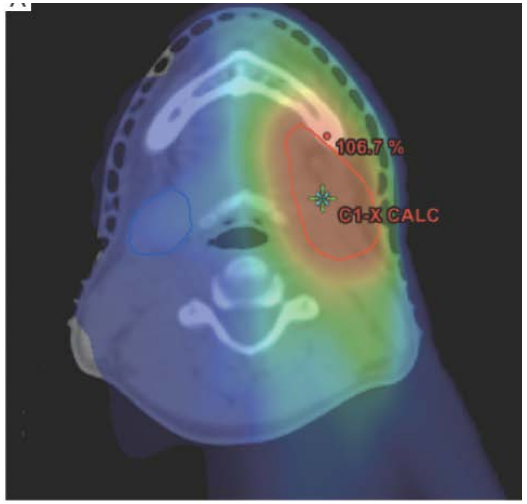
- Protons are attractive for radiotherapy because of their physical dose distribution

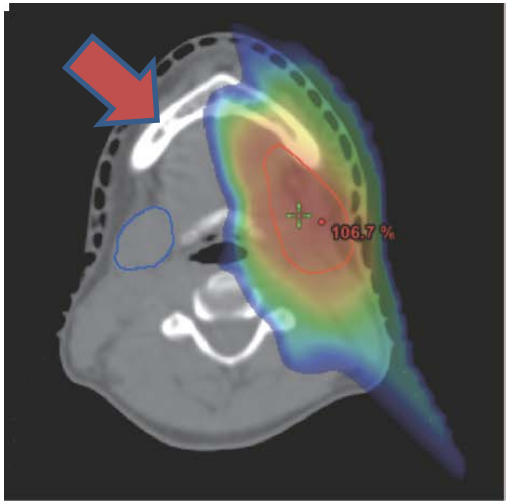






Proton therapy reduces radiation dose to oral cavity





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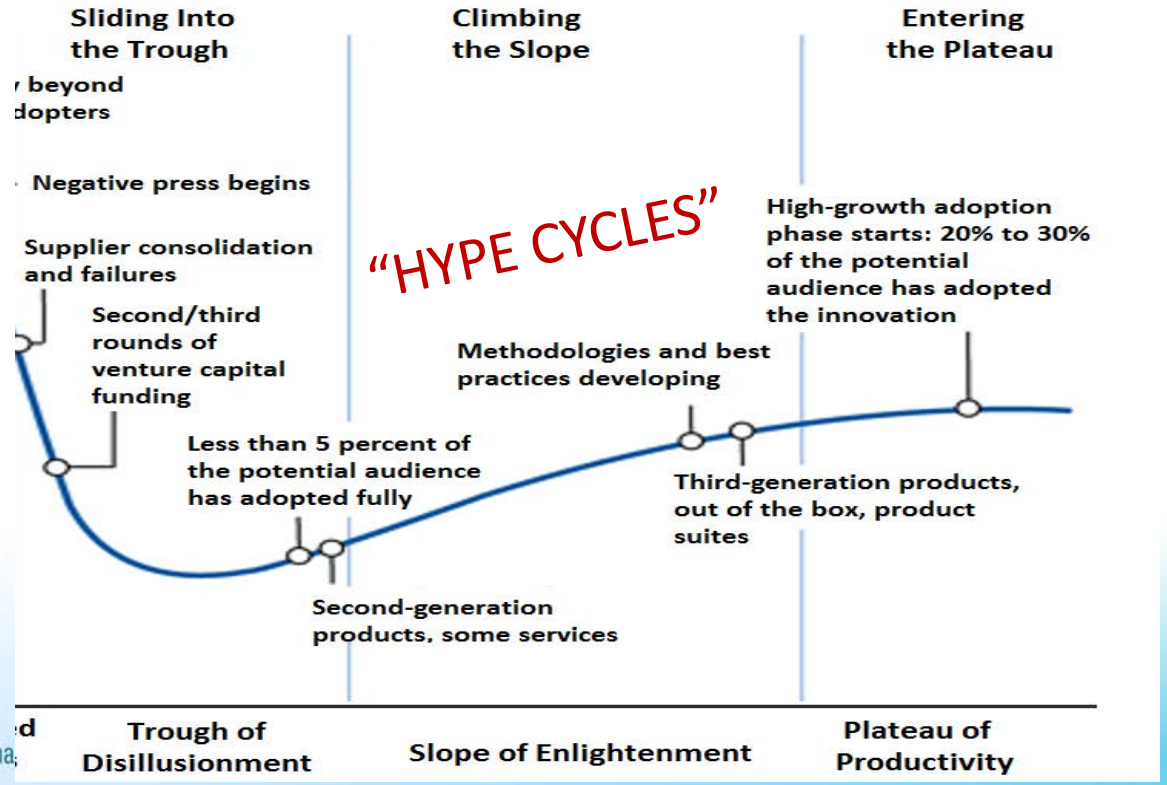
WHAT WILL THE SLOPE OF ENLIGHTENMENT BRING FOR PROTON THERAPY?



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The Multinationa

ARE CHANGES IN INSURANCE COMING?

NEWS | PROTON THERAPY | MAY 25, 2018

More Than 60 Percent of Patients Seeking Proton Therapy Initially Denied Coverage

Alliance for Proton Therapy Access launches grassroots campaign calling for state insurance commissioners to fix insurance process

May 25, 2018 — The Alliance for Proton Therapy Access has released a national report revealing the heavy emotional and financial burden that many cancer patients endure when trying to get their insurer's approval for physician-recommended proton radiation therapy. The report – Cancer Care Denied: The Broken State of Patient Access to Proton Therapy – calls on insurance commissioners in all 50 states to adopt and enforce the principles of a Cancer Patients' Timely Treatment Bill of Rights and hold insurers accountable for providing fair, timely and transparent access to cancer treatment.

US news

Aetna fined $25 million by jury after letting Oklahoma woman die of cancer

An Oklahoma jury ordered Aetna to pay the fine after the health insurer denied a 54-year-old cancer patient proton therapy, a form of radiation treatment. While Aetna described the therapy as "experimental," treatment is covered for Medicare patients above 65, a fact that came up during the trial.

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DEVELOPMENT OF MODEL BASED APPROACHES

International Journal of Radiation Oncology biology • physics
www.redjournal.org

Original Investigation

The Quest for Evidence for Proton Therapy: Model-Based Approach and Precision Medicine

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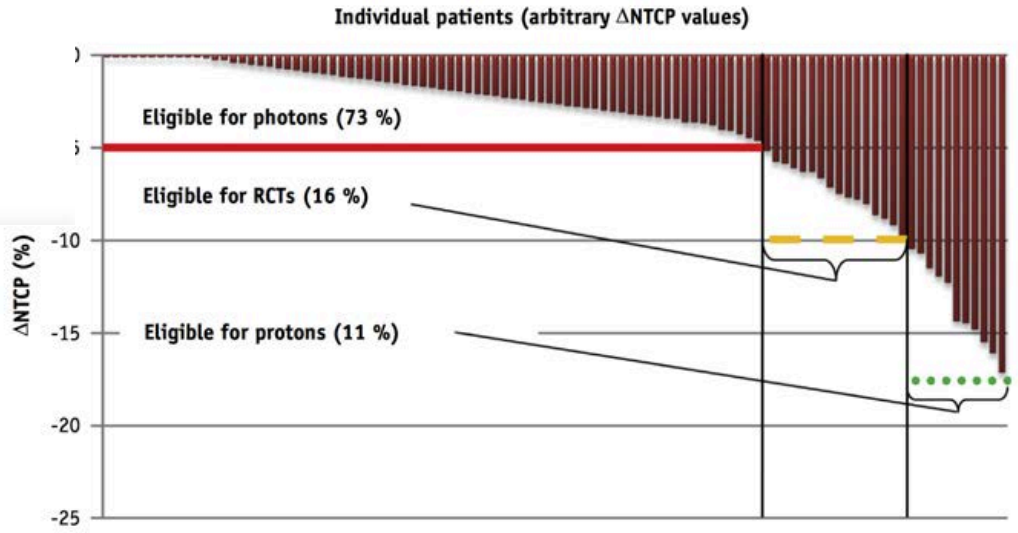

UCSF

HELEN DILLER FAMILY COMPREHENSIVE CANCER CENTER

ORAL, HEAD AND NECK CANCER CLINICAL AND RESEARCH GROUP

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Javier Villanueva-Meyer, MD
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Tom Hope, MD

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Siegrid Yu, MD
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