New technologies, new toxicities: New radiotherapy modalities

MASCC/ISOO
Annual Meeting on Supportive Care in Cancer
www.mascc.org/meeting

Follow us on Twitter: @CancerCareMASCC

#MASCC19
Conflict of Interest Disclosure

Sue Yom, MD PhD MAS

- Salary: UCSF
- Royalty: UpToDate, Springer
- Receipt of Intellectual Property Rights/Patent Holder: None
- Consulting Fees (e.g., advisory boards): Galera
- Fees for Non-CME Services Received Directly from a Commercial Interest or their Agents (e.g., speakers’ bureau): None
- Contracted Research: Merck, Genentech, Bristol-Myers Squibb, BioMimetix
- 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

<table>
<thead>
<tr>
<th>Acute / Subacute</th>
<th>Late effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain</td>
<td>Dental decay, ORN</td>
</tr>
<tr>
<td>Xerostomia</td>
<td>Esophageal stricture</td>
</tr>
<tr>
<td>Mucositis</td>
<td>Hearing loss</td>
</tr>
<tr>
<td>Dermatitis</td>
<td>Neck fibrosis</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>Endocrinopathy (hypothyroidism)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>Cognitive function</td>
</tr>
<tr>
<td>Nausea</td>
<td>Carotid stenosis</td>
</tr>
<tr>
<td>PEG dependence</td>
<td>Brachial plexopathy</td>
</tr>
<tr>
<td></td>
<td>Cranial neuropathy</td>
</tr>
</tbody>
</table>
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
1. Conformal IMRT technology and “organ at risk” avoidance
Conventional plan vs IMRT for oropharynx cancer
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

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

Navran A et al, Radiother Oncol. 2018
1B. Reducing radiation dose for select patients
NRG-HN002: A Randomized Phase II Trial for Patients with P16 Positive, Non-Smoking Associated, Locoregionally Advanced Oropharyngeal Cancer

Eligibility
- OP SCCA
- $\leq 10$ pack-year
- T1-T2 N1-N2b
- T3 N0-N2b

N = 296

RESULTS
NEAR MATURITY
Other surgery-based or heavy chemotherapy-based approaches developing

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

<table>
<thead>
<tr>
<th>Eligibility</th>
<th>Control arm from 1016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oropharynx SCCA</td>
<td>Exp. arm 1</td>
</tr>
<tr>
<td>p16+</td>
<td>Exp. arm 2</td>
</tr>
<tr>
<td>( \leq 10 ) pack-yr</td>
<td></td>
</tr>
<tr>
<td>T1-2N1 or T3 N0-1</td>
<td></td>
</tr>
</tbody>
</table>

**Randomized Phase II**

- **N = 363**
  - 1y PFS, 1y MDADI

**Randomize**

- **70 Gy in 6 weeks + cisplatin 100 mg/m² x 2 cycles**
- **60 Gy in 6 weeks + cisplatin 100 mg/m² x 2 cycles**
- **60 Gy in 5 weeks + nivolumab 240 mg x 6 cycles**

**Randomize**

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

**Phase III continuation**

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

- **N = 595 if 2 arms go forward**
- **N = 711 if 3 arms go forward**
- (QOL N = 378 per 2-arm comparison)
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/m²
- 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
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 $\geq 60$ 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 $\geq 2$ 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
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
- Other objective measurements
  - Tongue strength, jaw opening, cervical range of motion, suprahypoid 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.
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

- 220 HNC patients randomized to Helium-Neon low level laser therapy (λ = 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 cm², 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.
3. Supportive care interventions after treatment
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

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

• 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
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
WHY protons for HNC?

- Protons are attractive for radiotherapy because of their physical dose distribution.
Proton therapy reduces radiation dose to oral cavity
WHAT WILL THE SLOPE OF ENLIGHTENMENT BRING FOR PROTON THERAPY?

"HYPE CYCLES"

- Sliding Into the Trough
  - Beyond adopters
  - Negative press begins
  - Supplier consolidation and failures
    - Second/third rounds of venture capital funding
- Climbing the Slope
  - Less than 5 percent of the potential audience has adopted fully
  - Methodologies and best practices developing
- Entering the Plateau
  - High-growth adoption phase starts: 20% to 30% of the potential audience has adopted the innovation
  - Third-generation products, out of the box, product suites
  - Second-generation products, some services
ARE CHANGES IN INSURANCE COMING?

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.
DEVELOPMENT OF MODEL-BASED APPROACHES

Original Investigation

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

Joachim Widder, MD, PhD, Arjen van der Schaaf, PhD, Philippe Lambin, MD, PhD, Corrie A.M. Marjine, MD, PhD, Jean-Philippe Pignon, MD, PhD, Coen R. Rasch, MD, PhD, Ben J. Slotman, MD, PhD, Marcel Verheij, MD, PhD, and Johannes A. Langendijk, MD, PhD

Department of Radiation Oncology, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands; Department of Radiation Oncology, School for Oncology and Developmental Biology (SODIB), Maastricht University Medical Center, Maastricht, The Netherlands; Department of Radiation Oncology, Leiden University Medical Center, Leiden, The Netherlands; Department of Radiation Oncology, Erasmus Medical Center Cancer Institute, Rotterdam, The Netherlands; Department of Radiation Oncology, Academic Medical Center, Amsterdam, The Netherlands; Department of Radiation Oncology, VU Medical Center, Amsterdam, The Netherlands.

Individual patients (arbitrary ΔNTCP values)

Eligible for photons (73 %)

Eligible for RCTs (16 %)

Eligible for protons (11 %)

ΔNTCP (%)
<table>
<thead>
<tr>
<th>Department</th>
<th>Medical Personnel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otolaryngology-Head and Neck Surgery</td>
<td>Patrick Ha, MD, Ivan El-Sayed, MD, Daniel Knott, MD, William Ryan, MD, Rahul Seth, MD, Chase Heaton, MD, Jonathan George, MD, Andrea Park, MD, Trina Sheedy, PA</td>
</tr>
<tr>
<td>Medical Imaging</td>
<td>Christine Glastonbury, MD, Javier Villanueva-Meyer, MD, Rob Flavell, MD, Tom Hope, MD</td>
</tr>
<tr>
<td>Dermatology</td>
<td>Sarah Arron, MD, PhD, Siegrid Yu, MD, Roy Grekin, MD, Isaac Neuhaus, MD</td>
</tr>
<tr>
<td>Radiation Oncology</td>
<td>Joyce Tang, RN, Ludene Wong, RN, Jennifer Bohm, RN, Alicia Rigby, NP, Kim Guan, Jason Chan, MD, Priyanka Ghosh, MD</td>
</tr>
<tr>
<td>Medical Oncology</td>
<td>Alain Algazi, MD, Ann Tittiger, RN, Christine Kim, NP</td>
</tr>
<tr>
<td>Clinical Research</td>
<td>Carter Hultman, Julia Klein, Manpreet Narwal, Carolina Tiznado</td>
</tr>
<tr>
<td>ZSFGH Oncology</td>
<td>Terry Friedlander, MD, Jackie Wang, MD, Judy Cheng, MD</td>
</tr>
<tr>
<td>Dental Oncology/OMFS</td>
<td>Maria Thompson, DDS, Jennifer Perkins, DDS, MD</td>
</tr>
<tr>
<td>Radiobiology</td>
<td>Mary Barcellos-Hoff, PhD</td>
</tr>
<tr>
<td>Pathology</td>
<td>Annemieke Van Zante, MD, Richard Jordan, MD</td>
</tr>
<tr>
<td>Cancer Immunotherapy Program</td>
<td>Lawrence Fong, MD, Matt Spitzer, PhD</td>
</tr>
</tbody>
</table>

*ORAL, HEAD AND NECK CANCER CLINICAL AND RESEARCH GROUP*