Intensity-modulated Radiotherapy and Image Guidance in Head and Neck Cancer

ENT Grand Rounds

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Before we start with the excitement that is Radiation Oncology in action
Let’s Review some hot topics in H&N Oncology
...from a Radiation Oncology Viewpoint
Human Papillomavirus in H&N Cancer

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer


NEJM 2010; 36:24-35
Human Papilloma Virus in H&N Cancer

- Predominantly HPV type 16
- Expression of viral oncoproteins E6 and E7 inactivates p53 and pRb tumor suppressor oncogenes leading to malignant transformation
- P16 is a cyclin-dependent-kinase inhibitor induced as a consequence of pRb inactivation by HPV E7 oncoprotein
- Oropharyngeal primaries
Human Papilloma Virus in H&N Cancer

- Analysis of RTOG 0129 Study
- 721 patients with stage III/IV H&N cancers
  - Accelerated fractionated RT + chemo vs. standard fractionated RT + chemo
  - 433 (60%) had oropharyngeal cancer
- Needed enough patients to evaluate the effect of HPV with potential confounding factors including SMOKING
Human Papilloma Virus in H&N Cancer

- Analysis limited to Oropharyngeal tumors
- HPV-positive cancers had **better** overall survival and progression-free survival than HPV-negative cancers
- Median follow-up 4.8 years; 3 year rates are:
  - Overall survival: 82.4% vs. 57.1%
  - Progression-free survival: 73.7% vs. 43.4%
Human Papilloma Virus in H&N Cancer

- Even after adjusting for performance status, tumor stage and smoking status, HPV-positive tumors had a 58% reduction in risk of death compared with HPV-negative tumors.

- The major determinants of overall survival (ranked by recursive partitioning analysis):
  
  - #1 HPV status
  - #2 Number of pack years tobacco smoking (≤10 vs. >10)
  - #3 Nodal stage No to N2a vs. N2b to N3 for HPV+
  - Tumor stage: T2 or T3 vs. T4 for HPV - tumors
Tobacco Smoking in RTOG 0129

- Tobacco smoking found to be independently associated with overall and progression-free survival.
- Risk of death and cancer relapse increases by 1% for each additional pack-year smoked.
- This magnitude of tobacco effect is seen for both HPV+ and HPV- cancers.
Human Papilloma Virus in H&N Cancer: 3 year overall survival

- **Low Risk** patients- HPV+ (except N2b/N3 smokers): 93%
- **Intermediate Risk** patients: HPV+ N2b/N3 smokers & HPV- T2/T3 nonsmokers: 70.8%
- **High Risk** patients: HPV- tumors (except T2/T3 nonsmokers): 46.2%
Human Papilloma Virus in H&N Cancer: Overall Survival
Human Papilloma Virus in H&N Cancer

FDA approved in boys in 2009...to prevent genital warts
Induction Chemotherapy: It’s Baaack!

- Induction chemotherapy followed by RT exciting approach in 1980s and 1990s for locoregionally advanced H&N cancer
- **Organ preservation**: VA Larynx Trial, EORTC hypopharynx trial
- Most long-term analyses show **no improved survival** over RT alone
- Concurrent chemotherapy and radiation has become **standard approach**
Chemoradiation for Nasopharynx Cancer: Improved Survival over RT alone

Three year survival was 76% after chemoRT vs. 46% after RT alone (p<.001).

Al-Sarraf et al JCO 1998; 16:1310-1317
Induction Chemotherapy Followed by RT + chemotherapy: Posner et al

NEJM 2007; 357:1705-1715
Induction Chemotherapy Followed by RT + chemotherapy: Posner et al

- 501 patients with stage III/IV H&N cancers
- Randomized to two different induction chemotherapy regimens:
  - TPF: Docetaxel, cisplatin, 5FU x 3 cycles
  - PF: Platinum, 5FU x 3 cycles
- Then everyone received chemoradiation
- 70-74 Gy in 2 Gy fractions plus weekly carboplatin
Induction Chemotherapy Followed by RT + chemotherapy: Posner et al

- Median follow up 42 months

- TPF resulted in 30% reduction in risk of death
- Median survival: 71 months after TPF vs 30 months after PF
- Three year overall survival: 62% vs 48% (p=0.002)

- Grade 3 and 4 neutropenia 83% vs. 56% (p<0.001)
Induction Chemotherapy Followed by RT + chemotherapy: Posner et al overall survival
Is it better than ChemoRT alone?: Paradigm Study

- A Randomized Phase III Trial Comparing Sequential Therapy With TPF/ Chemoradiation (ST) to Cisplatinum-Based Chemoradiotherapy With Accelerated Concomitant Boost Radiotherapy (CRT) For Locally Advanced Squamous Cell Cancer of the Head and Neck ("The Paradigm Study")
- No results yet
- Induction chemotherapy approach for fit patients and Big (T4 or N3) tumors needing quick response
Postoperative Chemoradiation

- Standard established by RTOG 9501 and EORTC 22931
- Bernier combined these two trials
- Benefit of adding cisplatin to RT seen in patients with positive surgical margins or malignant lymph nodes with extracapsular extension.
Postoperative Chemoradiation: Early postop Paclitaxel followed by RT + Paclitaxel/cisplatin RTOG 0024

- Does earlier therapy after surgery improve outcome?
- 70 patients (phase II data)
- Positive margins, extracapsular extension or multiple positive nodes
- Paclitaxel 80 mg/m² postop weeks 2, 3 and 4
- Then RT (60 Gy/6 weeks) started week 4 to 5
- Paclitaxel 30 mg/m² plus cisplatin 20 mg/m² added during final 3 weeks of RT
- Journal Clin Oncol 2009; 27:4727-4732
Postoperative Chemoradiation: Early postop Paclitaxel followed by RT + Paclitaxel/cisplatin RTOG 0024

- Median follow up 3.3 years
- 12% grade 4/5 toxicity - including one death from MI
- Two year overall survival 64.7%

- Rates of locoregional control, disease-free survival and overall survival exceeded RTOG 9501 even after adjusting for performance status, primary site, positive margins and extracapsular extension
Postoperative Chemoradiation: Early postop Paclitaxel followed by RT + Paclitaxel/cisplatin RTOG 0024
Accelerated Radiation: What’s the status?

- Chemoradiation established therapy for locally advanced unresectable H&N cancers
- Radiobiologists support the idea of accelerated radiotherapy—giving the same dose of radiation over shorter course (6 weeks instead of 7)
- Theoretically should decrease tumor repopulation

- RTOG 0129: Phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas
Not RTOG 0129 Again!

- 721 analyzable patients
- **Accelerated chemoRT**: 72 Gy/42 fractions/6 weeks plus two cycles of cisplatin 100 mg/m2
- **Standard chemoRT**: 70 Gy/35 fractions/7 weeks plus three cycles of cisplatin 100 mg/m2

- **Overall**: NO DIFFERENCES
- 5 year overall survival: **59% vs. 56%**
- Disease-free survival: **45% vs. 44%**
- Grade 3-4 acute mucositis: **33% vs 40%**
- Grade 3-4 late toxicity: **26% vs 21%**
- Treatment effect similar for HPV+ and HPV- patients
Cetuximab + Radiation for High Risk H&N Cancer

- Cetuximab is a monoclonal antibody blocking the epidermal growth factor receptor (EGFR)
Radiation + cetuximab for H&N Cancer: Bonner et al

Radiotherapy plus Cetuximab for Squamous-Cell Carcinoma of the Head and Neck

James A. Bonner, M.D., Paul M. Harari, M.D., Jordi Giralt, M.D., Nozar Azarnia, Ph.D., Dong M. Shin, M.D., Roger B. Cohen, M.D., Christopher U. Jones, M.D., Ranjan Sur, M.D., Ph.D., David Raben, M.D., Jacek Jassem, M.D., Ph.D., Roger Ove, M.D., Ph.D., Merrill S. Kies, M.D., Jose Baselga, M.D., Hagop Youssoufian, M.D., Nadia Amellal, M.D., Eric K. Rowinsky, M.D., and K. Kian Ang, M.D., Ph.D.*

NEJM 2006; 354:567-578
Radiation + cetuximab for H&N Cancer: Bonner et al

- Phase III trial
- 424 patients
- Stage III/IV oropharynx, hypopharynx or larynx cancers

- RT alone (70-76.8 Gy)
- RT + cetuximab
- Cetuximab loading dose 400 mg/m2 one week before RT then 250 mg/m2 weekly with radiation
Radiation + cetuximab for H&N Cancer: Bonner et al

- Median follow up is 54 months
- Overall results favor the addition of cetuximab to radiation at three years
  - Overall survival: 55% vs. 45% (p=0.05)
  - Locoregional control: 47% vs. 34% (p<0.01)

- Cetuximab was associated with increased grade 3-5 acneiform rash: 17% vs. 1% (p<0.001)
Radiation + cetuximab for H&N Cancer: Bonner et al

Improved Survival

**Figure 2.** Kaplan–Meier Estimates of Overall Survival among All Patients Randomly Assigned to Radiotherapy plus Cetuximab or Radiotherapy Alone.

The hazard ratio for death in the radiotherapy-plus-cetuximab group as compared with the radiotherapy-only group was 0.74 (95 percent confidence interval, 0.57 to 0.97; P = 0.03 by the log-rank test). The dotted lines indicate the median survival times.
Chemoradiation + cetuximab for H&N Cancer

- Cetuximab associated with skin necrosis
- Results from RTOG 0522 pending
- Accelerated RT + cisplatin for Stage III/IV H&N cancer with or without cetuximab
- Closed March 2009
When do we add postoperative radiation?
IMRT and Image Guided Radiotherapy for H&N Cancer: What are they Doing in the Basement??!!

We are located on the 4th floor Kohler Pavilion
IMRT in the News

- NYT: Radiation (IMRT) horror stories; Woman has massive hole burned in chest because several doctors and physicists didn’t know “in” from “out”

- By Dan Nguyen | Published: January 24, 2010
- New York Times
IMRT

- IMRT is Intensity Modulated Radiotherapy

- It involves Inverse Treatment planning

- In conventional (3D) RT, the radiation oncologist/dosimetrist chooses a treatment pattern and either accepts the dose to target and normal tissues or chooses another pattern.

- This can involve number of fields, orientation of fields and weighting of fields
IMRT

- With **Inverse Treatment Planning**: Volumes are *contoured*

  1) Targets – tumor, high-risk nodal volumes
  2) Normal structures to avoid – spinal cord, parotids, mandible, larynx
**IMRT: Inverse Planning**

- In Inverse Planning, start with desired doses
- Target doses to tumors and at-risk volumes (nodes)
- Constraint doses to normal tissues

- Treatment objectives can be **prioritized**
- **Example:** Keep both parotids mean dose <26 Gy (low)
  - Cover tumor + margin: 95% to receive 70 Gy (moderate)
  - No point of spinal cord to receive more than 50 Gy (high)

- Planning **software** then designs the best plan to reach these treatment objectives
IMRT: Intensity Modulation

- Requires the ability to break treatment port up into multiple smaller subsets (field segments or pencil beams).

- We use **multileaf collimation** to do this
IMRT: Basics

Target

Organ-at-risk
3D-CRT
IMRT: Simplified
These pencil beams “see” only the target

No organ-at-risk radiation exposure

High reward
No/low risk
These pencil beams “see” more target than organ-at-risk

Reward and penalty
This pencil beams “sees” less target than organ-at-risk

Low reward/high penalty
IMRT Simplified
IMRT Simplified
3D-CRT  IMRT

Improved tumor conformal dose planning and superior normal tissue sparing
Multileaf Collimation In Action
IMRT for Parotid Sparing
IMRT for Larynx Sparing
Postoperative IMRT for Oral Tongue Cancer with Parotid Sparing
Image-Guided Radiotherapy (IGRT)

- What is IGRT?

- The utilization of direct imaging and/or tracking techniques to guide the daily delivery of radiation to a specified target volume.

IGRT allows precision and accuracy in fractionated radiotherapy.
Precision vs. Accuracy

Precision vs. accuracy: IMRT vs. IGRT

Precise, not accurate (IMRT without IGRT)

Accurate, but not precise (wide margin radiotherapy)

Precise and accurate (IMRT with IGRT)

Courtesy of Todd Scarbrough, M.D.
Types of IGRT

- MV Port Films
- KV Imaging (reduced dose, diagnostic quality)
- CT Imaging (both MV & KV)
MV Port Films

- Considered minimum standard-of-care
- Obtained on first day of treatment and compared to DRR
- Often obtained weekly for verification
- Remaining days set up to skin marks taking into account most recent shifts
- Setup based on bony anatomy
- Poor quality/minimal detail
- Advantage is they show you beams-eye view (BEV) of target area
MV Port Films
KV Imaging

- Reduced radiation dose compared to MV Port Films
- Diagnostic quality images
- Excellent for bony anatomy matching
- Can be applied immediately prior to treatment in treatment position
- Minimal soft tissue information. Fiducials may be required for target tracking.
Varian Trilogy Linac

• KV imager mounted at right angle
• Not a Port! **You will not see your field!!**
• Retracts to body of gantry when not in use
Bony Anatomy Match
Bony Anatomy Match
Bony Anatomy Match
Bony Anatomy Match
Bony Anatomy Match
Bony Anatomy Match
Bony Anatomy Match
Bony Anatomy Match
Volumetric IGRT

- CT-based imaging techniques
- Both MV and kV possible
- Cone Beam CT (CBCT)
  - Gantry-mounted kV CBCT
- Tomotherapy utilizes MV CBCT
Gantry-Mounted kV CBCT

- Very convenient
- CT acquisition over 1 minute of gantry rotation
- Fast image reconstruction
- Integrated planning system allows direct overlay of planning CT scan with structure/target contours visible
- Anatomy match performed
- Automatic couch adjustment based on match
- Couch can move in essentially any direction to facilitate anatomy matches
Varian Trilogy with OBI

←kV Imager arms retracted

kV Imager arms extended→
CBCT Anatomy Match
ExacTrac® consists of two kV x-ray units recessed into the Linac room floor and two ceiling-mounted amorphous silicon flat panel detectors.
ExacTrac from Brainlab

- Stereoscopic x-rays are acquired from the console. An immediate and automatic on-screen comparison of Digitally Reconstructed Radiographs (DRRs) and x-ray images is completed to verify patient setup.
- ExacTrac® calculates any required patient shift and the remote Robotic couch aligns the patient to the correct isocenter point including automatically correcting rotational setup errors (6 degrees).
- Millimeter accuracy with “2-minute” setup
Varian Robotic Treatment Couch

Movement in \textbf{6 degrees} including pitch, roll and yaw
IMRT and Image-guidance in H&N Cancer

Thanks for coming!