Image-guided IMRT for Head and Neck Cancer

Reggio Emilia, Italy
October 21, 2011

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T2N1M0 SCC of Base of the Tongue
Conventional RT

IMRT
Therapeutic Outcome of Oropharyngeal Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Def. CRT (n=153)</th>
<th>Def. IMRT (n=12)</th>
<th>Post-op CRT (n=142)</th>
<th>Post-op IMRT (n=14)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Acute Grade 3-4</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mucositis</td>
<td>25%</td>
<td>42%</td>
<td>20%</td>
<td>21%</td>
</tr>
<tr>
<td></td>
<td>P=0.134</td>
<td></td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td><strong>Late Grade 2-3</strong></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>xerostomia (12m post-RT)</td>
<td>84%</td>
<td>30%</td>
<td>77%</td>
<td>17%</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td></td>
<td>P&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Chao et al. Radiotherapy & Oncology, 2001
# Tumor Control by IMRT vs non-IMRT in Patients with Oropharyngeal Carcinoma

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Median F/U</th>
<th>2yr LRC</th>
<th>2yr DFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Def. Non-IMRT</td>
<td>153</td>
<td>3.5 yr (1.6-17.7)</td>
<td>68.3%</td>
</tr>
<tr>
<td>Def. IMRT</td>
<td>31</td>
<td>3 yr (12-58)</td>
<td>87.5%</td>
</tr>
<tr>
<td>Post-op Non-IMRT</td>
<td>142</td>
<td>3.9 yr (1.3-19.8)</td>
<td>75.7%</td>
</tr>
<tr>
<td>Post-op IMRT</td>
<td>43</td>
<td>2.8 yr (9-60)</td>
<td>95.0%</td>
</tr>
</tbody>
</table>

*Data compiled from Chao et al. Radiotherapy & Oncology, 61:275, 2001 and Chao et al. IJROBP 59:43-50, 2004*
### Loco-regional Control of Oropharyngeal Carcinoma

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>IMRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>70-90%</td>
<td>T1-2</td>
<td>92%</td>
</tr>
<tr>
<td>30-70%</td>
<td>T3-4</td>
<td>87-94%</td>
</tr>
</tbody>
</table>
T2N1M0 SCC of Base of the Tongue

# Target Delineation and Dose Spec in 2011

**Definitive**

<table>
<thead>
<tr>
<th></th>
<th>CTV1</th>
<th>CTV2</th>
<th>CTV3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT 35 fx</td>
<td>70/2.0</td>
<td>63/1.8</td>
<td>56/1.6</td>
</tr>
<tr>
<td>IMRT 33 fx</td>
<td>70/2.1</td>
<td>60/1.8</td>
<td>54/1.6</td>
</tr>
<tr>
<td>2D 35 fx</td>
<td>70/2.0</td>
<td>60/2.0</td>
<td>50/2.0</td>
</tr>
</tbody>
</table>

**Post-op**

<table>
<thead>
<tr>
<th></th>
<th>CTV1</th>
<th>CTV2</th>
<th>CTV3</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMRT 30 fx</td>
<td>63/2.1</td>
<td>60/2.0</td>
<td>54/1.8</td>
</tr>
<tr>
<td>2D 30 fx</td>
<td>66/2.0</td>
<td>60/2.0</td>
<td>50/2.0</td>
</tr>
</tbody>
</table>

T2N1M0 SCC of Base of the Tongue
Step One: Identify GTVp/n

- **GTVp**
- **GTVn**
Step 2: Add CTV1

Defined as GTVp/n plus 10 mm of margin

Truncating around normal structures <10mm margin
Paraspinal
Platysma
Step 3: Add CTV2

- CTV margin ~ 5mm
- CTV2-Coverage remaining tongue base
- Level IB
- Level IIA/B
- Level V

Legend:
- GTVp
- GTVn
- CTV 1
- CTV 2
Step 4: Add CTV3

- Submandibular gland
- Level II (a/b) contralateral neck CTV³
A Involved side coverage to jugular foramen

B Contralateral coverage (NED) neck begins at top C1

Jugular foramen
Variations in CTV Target Delineation for Head and Neck IMRT

**An International Survey**

Theodore S. Hong, Wolfgang A. Tomé, Richard J. Chappell, Paul M. Harari

University of Wisconsin
Department of Human Oncology

20 institutions

H&N IMRT Practice Heterogeneity

Courtesy of Dr. Harari
Local failure in RTOG-0022 protocol variations

- 4 of 53 patients with evaluable plans had major protocol variations due to underdose of PTV66.

- Local recurrence:
  - 2/4 (50%) patients with major PTV66 variation (underdose)
  - 3/49 (6%) patients without major PTV66 variations
  - \( P=0.04 \)
Outcome: Local recurrence

Treatment plan of a patient with a major PTV66 underdose
Phase III Registration Trial
TROG 02.02 (HeadSTART)

Patients with Stage III or IV SCCHN
(stratified by stage, site, hemoglobin)

Randomization

• Cisplatin, RT
• Tirapazamine, cisplatin, RT

Courtesy of Dr. Lester Peters
Accrual - 861 patients from 89 sites in 16 countries (Sep 02 – Apr 05)
Patients who had received at least 60Gy of RT to PTV2

![Graph showing tumor control rates over years following end of radiotherapy with three lines representing compliant plan by TMC, no adverse impact, and adverse impact, with statistical significance indicated as 2P < 0.0001]
Nodal CTV Delineation – Margin?
Microscopic Tumor Extension outside Nodal Capsule

- 97 ECE+ LNs from 49 patients
- Tumor extension through the LN capsule by:
  - Actual presence of tumor cells
  - Desmoplasia (associated stromal reaction)
  - Giant cell reaction to keratin
- Greatest linear distance perpendicular from external capsule border to furthest extent of tumor
  - Nearest tenth of millimeter with micrometer
  - Extrapolation when appropriate
- Largest axial diameter of LN

Results

• **96% ECE within 5 mm of capsule**

• None beyond 10 mm

• Inverse correlation between ECE incidence and distance from capsule

\[ r = 0.87 \]

4 outliers

- 5.7 mm ECE – 1.9 cm LN
- 6.0 mm ECE – 1.1 cm LN
- 8.0 mm ECE – 0.7 cm LN
- 9.0 mm ECE – 0.8 cm LN

Results

- No correlation between LN and extent of ECE
- Mean ECE
  - LN < 1 cm: 2.1 mm
  - LN > 1 cm: 2.2 mm
Nodal CTV Delineation

Advanced Knowledge-based Intelligent Tool
PHYSICS CONTRIBUTION

REDUCE IN VARIATION AND IMPROVE EFFICIENCY OF TARGET VOLUME DELINEATION BY A COMPUTER-ASSISTED SYSTEM USING A DEFORMABLE IMAGE REGISTRATION APPROACH

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Steven Bush, M.D.,§ Gregg Franklin, M.D., Ph.D.,§ Vivek Kavadi, M.D.,∥
Vichaiwood Liengswangwong, M.D.,§ William Gordon, M.D.,# Adam Raben, M.D.,‡
Jon Strasser, M.D.,‡ Christopher Koprowski, M.D.,‡ Steven Frank, M.D.,∗
Gregory Chironowski, M.D.,∗ Anesa Ahamad, M.D.,∗ Robert Malyapa, M.D., Ph.D.,**
Lifei Zhang, Ph.D.,†† and Lei Dong, Ph.D.††

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Knowledge-based Computer-assisted Target Delineation

Contouring from scratch  Computer-assisted Contouring
Advanced Knowledge-based Intelligent Tool
Accurate Delineation of GTV

Image Fusion
Diagnostic MRI ↔ Planning CT
Current Recommendation on NPC Work-Up

Imaging for distant metastases (chest, liver, bone) particularly for stage III-IV disease

FDG-PET/CT for systemic work-up + supplement locoregional assessment
**Improved Staging Accuracy by PET**

**Stage Distribution (%) in 95 patients**

Work-up by MRI (head & neck), CXR, bone scan, abdominal U/S, FDG-PET

<table>
<thead>
<tr>
<th></th>
<th>With PET</th>
<th></th>
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<tbody>
<tr>
<td>Without PET</td>
<td>I</td>
<td>II</td>
<td>III</td>
<td>IVA</td>
<td>IVB</td>
<td>IVC</td>
</tr>
<tr>
<td>I</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
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<tr>
<td>III</td>
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<td></td>
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<tr>
<td>IVA</td>
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<tr>
<td>IVB</td>
<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>IVC</td>
<td></td>
<td></td>
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</tbody>
</table>

Chang, IJROBP 2005
How FDG PET Changes RT Plan and Target Volume Delineation

- Influence RT plan for lung cancer ~30%
- Influence RT plan for H&N cancer ~40%
- Modify target volume for lung cancer 4 – 65%
- Modify target volume for H&N cancer 5 – 55%
But we need something more than FDG...
Imaging Targets of Biological Interest

Metabolic Proliferative Hypoxic Angiogenesis

Anatomical Tumor Volume (GTV) Biological Tumor Volume (BTV)

Apisarnthanarax and Chao, Radiation Research, 2005, 163:1-25
### PET Tracers DEPICT Biology

<table>
<thead>
<tr>
<th>Tracer</th>
<th>Application</th>
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<tbody>
<tr>
<td>$[^{18}\text{F}]$-FDG</td>
<td>glucose metabolism</td>
</tr>
<tr>
<td>$[^{18}\text{F}]$-FLT</td>
<td>tumor proliferation</td>
</tr>
<tr>
<td>$[^{18}\text{F}]$-FMISO</td>
<td>hypoxia</td>
</tr>
<tr>
<td>$[^{64}\text{Cu}]$-ATSM</td>
<td>hypoxia</td>
</tr>
<tr>
<td>$[^{18}\text{F}]$-F-RGD peptides</td>
<td>angiogenesis</td>
</tr>
<tr>
<td>$[^{15}\text{O}]$-Water</td>
<td>blood flow</td>
</tr>
<tr>
<td>$[^{18}\text{F}]$-F-annexin</td>
<td>apoptosis</td>
</tr>
</tbody>
</table>

*Clinical | investigational*
NIH Oncology Biomarker Qualification Initiative (OBQI)

<table>
<thead>
<tr>
<th>Benefits</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assess after one or two treatments if a tumor is responding to treatment</td>
</tr>
<tr>
<td>• Determine more definitively if a tumor is dying, even if it is not shrinking</td>
</tr>
<tr>
<td>• Identify which cancer patients are at high risk of tumor return after therapy</td>
</tr>
<tr>
<td>• Determine if a patient's tumor is likely to respond to a specific treatment</td>
</tr>
<tr>
<td>• Efficiently evaluate whether an investigational therapy is effective</td>
</tr>
<tr>
<td>• Evaluate new, promising technologies that will shorten clinical trials</td>
</tr>
<tr>
<td>• Reduce the time and resources spent during the treatment development process</td>
</tr>
<tr>
<td>• Improve the linkage between drug approval and drug coverage</td>
</tr>
<tr>
<td>• Increase the safety and appropriateness of treatment choices for cancer patients</td>
</tr>
</tbody>
</table>

3S  Swift, Safe, Save
PET-CT Image-guided Approaches in Radiation Oncology

- To guide precision therapy to tumor
- To select patients for the suitable therapy and depict treatment response at an early phase
Target Hypoxic Tumor Guided by $^{60}$Cu-ATSM PET

Chao et al. IJROBP 49: 1171-1182, 2001
Reduction & Shifting of Cu-ATSM-vivid Regions after 20 Gy

Cu-ATSM PET at 0Gy

Red - GTV
Yellow - hGTV 0Gy
Green - hGTV 20Gy

Cu-ATSM PET at 20Gy
Persistence of Cu-ATSM-vivid Regions after 20 Gy

Red - GTV
Yellow – hGTV 0Gy
Green – hGTV 20Gy
Drug Response: Imaging Options

- Anatomic
  - CT – multi-detector spiral
  - MRI
- Functional and Molecular
  - PET – FDG
  - Dynamic Contrast Enhanced MRI
- Experimental
  - Other NM
  - MRS
  - Exotic MR sequences
  - Optical
Chemotherapy Response by MRI & MRS

1 wk pre-Tx
76 cc

Day 1
AC x1
79 cc

Day 42
AC x3
26 cc

Day 70
AC x4
25 cc

Day 112
taxol x2
11 cc

Day 178
taxol x4
6 cc

Univ. of Minnesota
FDG-PET Monitoring Response to STI571 in GIST

<table>
<thead>
<tr>
<th>PROJECTION</th>
<th>PROJECTION</th>
<th>PROJECTION</th>
<th>PROJECTION</th>
<th>PROJECTION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>24 hrs</td>
<td>7 days</td>
<td>2 mos</td>
<td>5.5 mos</td>
</tr>
</tbody>
</table>

Dana-Farber Cancer Institute
Prediction of Overall Survival After Chemo in Patients with NSCLC by FDG-PET

Predict Treatment Response – a timing issue

- Whole tumor imaging characteristics vs tissue biopsy
- Depict tumor heterogeneity
- Serial non-invasive images vs serial biopsies

3 months too late?

3m post-CRT
Proliferation (Ki-67) and Apoptosis in Seg-1 Tumor Treated with Chemoradiotherapy (Taxotere + xRT)

Time (hrs):
0 4 8 12 16 24 48 72 96

Index (%):
0 10 20 30 40 50 60 70 80 90 100

Tumor Size (mm):
0 1 2 3 4 5 6 7 8 9 10

Ki-67
TUNEL
Tumor Size
FLT and FDG Time-course Biodistribution

![Graph showing FLT and FDG uptake over time after irradiation with decreasing Tumor Size, FDG Uptake, Ki-67 Expression, and FLT Uptake compared to untreated levels.]

Optimal Timing and Image-pathological Validation

Molecular Signature

Tailor CRT

Functional imaging

CRT

When? How? How much?

Functional imaging

Responder

Non-responder (alternative treatment)

Surgery
IMRT Beyond CT & FDG.....

Accumulation via Phosphorylation $[^{18}\text{F}]$FDG

Accumulation via aa Transport or Protein Synthesis

Hormones

mAb, Fragments

Drugs and ligands

Peptides

Internalization

Enzyme Activity: Inhibition, Synthesis

Reporter Probe

Hexokinase

Glut 2

Hypoxia

[18F]FLT

Reporter Gene

DNA-Synthesis

mRNA Binding

Oligonucleotides

Transport or Protein Synthesis