Role of Imaging in IMRT for Head and Neck Cancers

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Role of Imaging in HN

- Selection
- Accurate delineation to drive precision planning
- Accurate delivery – verification and adaptation
- Biomarker – prognostication and prediction
- Medical record - documentation
Modern Paradigm – Increasingly Less Forgiving..

Technological improvement in conformal dose delivery
   Ability to deliver higher biological doses
   Less penumbral safety net

   Better understanding and quantification of sources of error
      Tighter CTV – PTV margins

Reduction of competing events which sensor eventual local failure
   Better staging procedures / patient selection
   Improved systemic agents
   Others… HPV, better outcomes
Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02


See accompanying editorial on page 2941 and article on page 2989

ABSTRACT

Purpose
To report the impact of radiotherapy quality on outcome in a large international phase III trial evaluating radiotherapy with concurrent cisplatin plus tirapazamine for advanced head and neck cancer.

Patients and Methods
The protocol required interventional review of radiotherapy plans by the Quality Assurance Review Center (QARC). All plans and radiotherapy documentation underwent post-treatment review by the Trial Management Committee (TMC) for protocol compliance. Secondary review of noncompliant plans for predicted impact on tumor control was performed. Factors associated with poor protocol compliance were studied, and outcome data were analyzed in relation to protocol compliance and radiotherapy quality.

Results
At TMC review, 25.4% of the patients had noncompliant plans but none in which QARC-recommended changes had been made. At secondary review, 47% of noncompliant plans (12% overall) had deficiencies with a predicted major adverse impact on tumor control. Major deficiencies were unrelated to tumor subsite or to T or N stage (if N+), but were highly correlated with number of patients enrolled at the treatment center (< five patients, 29.8%; ≥ 20 patients, 6.4%; P < .001). In patients who received at least 60 Gy, those with major deficiencies in their treatment plans (n = 87) had a markedly inferior outcome compared with those whose treatment was initially protocol compliant (n = 502): 2 years overall survival, 50% v 70%; hazard ratio (HR), 1.99; P < .001; and 2 years freedom from locoregional failure, 54% v 78%; HR, 2.37; P < .001, respectively.

Conclusion
These results demonstrate the critical importance of radiotherapy quality on outcome of chemoradiotherapy in head and neck cancer. Centers treating only a few patients are the major source of quality problems.
Evidence for Importance of Quality Radiotherapy in Advanced HN Cases
Evidence for Importance of Quality Radiotherapy in Advanced HN Cases
TROG 02.02 JCO 2010

• Inferential data
• 24% decrement in FFLRF at 2yr
• 20% decrement in OS at 2yr
• Reached SS on MVA incorporating established prognostic factors

• Numerous implications for trial design

• “powerfully” demonstrates the importance of quality radiotherapy in order to achieve optimal outcome

“This is more important in the era of IMRT”??
IMRT is a very useful tool for “precision mis-hit”

Intended benefits of conformal delivery methods are realised only when potential sources of error are recognised, quantified and managed
Case study

**T3N0M0 SCC OROPHARYNX**

**HOW USEFUL ARE FDG PET IMAGES??**
- EUA
  - Confirmed the above
- Biopsy
  - Moderately differentiated SCC
- Assigned clinical stage
  - T3N0M0
• On Examination clinically
  – L sided tongue base firmness crossing midline
  – Extends onto L tonsillar fossa
• Staging CT
CT

- Backbone of 3D imaging
- Planning template for RT
- Geometrically accurate
- CT density electron density information
- Standard – readily available
- CT dose = problem – but not
- Artefacts, beam hardening, lack of soft tissue information
- Vast experience, speed of acquisition, motion
- Template image easily generated for verification
Target definition protocol - ROC

- CT simulation
  - Immobilization
  - Bite block
- Mutimodality image acquisition
  - CT – contrast and non contrast
  - MRI – T2 and GdT1
  - FDG PET – in cast
  - F MISO - protocol
- Image co-registration
  - PET vs. planning CT
  - Fiducial – PET
  - Vs. MI
  - Coreg planning vs PET CT and utilise transformation matrix..
PET and SCC HNN - Background

- $^{18}$F-FDG PET - visualisation of metabolic activity
- Based on the observation of enhanced glycolysis in cells
- Highly sensitive technique but with variable specificity
- Possible utility in staging, detection of occult primary and response assessment, and prognostication
- Target definitions studies with suggestion of its utility in radiotherapy....
• PET/CT on site / collaboration
• Routine use in mucosal SCC H&N staging / re-staging
  – Specificity for nodal disease cf CT/MR
  – 10-15% metastatic upstaging
  – Second primary
  – Occult primary
  – Response assessment

• Cautious optimism re: its role in RTP
PET delineation—Literature

• Suggestion in the head and neck literature
  – All hypothesis generating, small studies only
• Reduction in apparent inter and intra expert / observer error
• CT / MR / FDG-PET GTV – different
  • Various methodologies of PET contouring
    – Quantitative vs qualitative, automated delineation
• But what is the gold standard?
  • Phantom studies using various thresholding strategies
  • Primary SCC not spherical, varied uptake within lesion, gradual density of clonogens from centre of tumor
  • Approximates histological GTV than MRI and CT – Gregoire
• BTV dose escalation – IMRT planning studies and clinical
Hypoxia-targeted radiotherapy dose painting for head and neck cancer using \(^{18}\)F-FMISO PET: A biological modeling study

**J. H. Chang et al.**

**Abstract**

This study investigated the use of \(^{18}\)F-fluoro-2-deoxy-D-glucose (FMISO) PET-guided radiotherapy dose painting for potentially overcoming the radioclinical effects of hypoxia in head and neck squamous cell carcinomas (HNSCCs). The study cohort consisted of eight patients with HNSCC who were planned for definitive radiotherapy. Hypoxic subvolumes were automatically generated on pre-radiotherapy FMISO PET scans. Three radiation plans were generated for each patient: a standard (STD) radiotherapy plan to a dose of 70 Gy, a uniform dose escalation (UDE) plan to the standard target volume to a dose of 84 Gy, and a hypoxia dose-painted (HDP) plan with escalation only to the hypoxic subvolumes to 84 Gy. Plans were compared based on tumor control probability (TCP) and normal tissue complication probability (NTCP) for both uncomplicated tumor control probability (UTCP). Results: The mean TCP increased from 78% with STD plans to 95% with the use of UDE plans (p < 0.001) and to 93% with HDP plans (p < 0.001). The mean parotid NTCP increased from 26% to 14% with the use of UDE plans (p = 0.003), and the mean mandible NTCP increased from 25% to 23% with the use of UDE plans (p = 0.001). There were no statistically significant differences between any of the NTCPs between the STD plans and HDP plans. The mean UTCP increased from 86% with STD plans to 66% with HDP plans (p = 0.011) and dropped to 27% with UDE plans (p = 0.190). Conclusions: Hypoxia-targeted radiotherapy dose painting for head and neck cancer using FMISO PET is technically feasible, increases the TCP without increasing the NTCP, and increases the UTCP. This approach is superior to uniform dose escalation.

**Table II. Target objectives and OAR constraints.**

<table>
<thead>
<tr>
<th>Target objectives</th>
<th>Prescription dose at each dose level</th>
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</thead>
<tbody>
<tr>
<td>PTV prescription dose</td>
<td>( D_{\text{isp}} &gt; \text{prescription dose} )</td>
</tr>
<tr>
<td>( D_{\text{isp}} &gt; 93% \text{ of prescription dose} )</td>
<td></td>
</tr>
<tr>
<td>( D_{\text{isp}} &lt; 110% \text{ of prescription dose} )</td>
<td></td>
</tr>
<tr>
<td>( D_{\text{isp}} &lt; 115% \text{ of prescription dose} )</td>
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</tbody>
</table>

**OAR constraint**

<table>
<thead>
<tr>
<th>Brainstem</th>
<th>BTM</th>
<th>PRV</th>
</tr>
</thead>
<tbody>
<tr>
<td>( D_{\text{isp}} &lt; 54 \text{ Gy} )</td>
<td>( D_{\text{isp}} &lt; 54 \text{ Gy} )</td>
<td>( D_{\text{isp}} &lt; 60 \text{ Gy} )</td>
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<tr>
<td>( D_{\text{isp}} &lt; 45 \text{ Gy} )</td>
<td>( D_{\text{isp}} &lt; 50 \text{ Gy} )</td>
<td>( D_{\text{isp}} &lt; 60 \text{ Gy} )</td>
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<td>( D_{\text{isp}} &lt; 26 \text{ Gy} )</td>
<td>( D_{\text{isp}} &lt; 20 \text{ Gy} )</td>
<td>( D_{\text{isp}} &lt; 20 \text{ Gy} )</td>
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<td>( D_{\text{isp}} &lt; 75 \text{ Gy} )</td>
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<td>( D_{\text{isp}} &lt; 75 \text{ Gy} )</td>
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**Figure 1.** The FMISO PET/CT scan of a patient with a T3N2b oro-pharyngeal squamous cell carcinoma is shown (A). The GTVH, PTVH, PTV3 and PTV1 are outlined in yellow, green, blue and red, respectively. The dose distributions for the STD plan (B), the HDP plan (C) and the UDE plan (D) are demonstrated using ‘colorwash’ with red indicating higher doses and blue indicating lower doses.

**Figure 2.** The DVHs are shown for the same patient shown in Figure 1. Solid lines represent the STD plan, dashed lines represent the HDP plan, and dotted lines represent the UDE plan.
Problems with PET

• T3 Supraglottic SCC
• No uptake seen
• Superficial tumors
Problems with PET

• Lack of anatomical definition
• Oversimplifies the geometry of lesion which are often complex
Problems with PET

- Tracers uptake signal specific processes e.g. FDG
- Tumor – heterogeneous even within one lesion
- Reason for under representation
• False positives for pet
  – Muscular activity
  – Lymphoid tissue
  – Salivary tissue
  – Brown fat

  – Inflammation
  – Over correction – high density material
Case Study

T4N2 NPC

CT+PET +/- MRI
• 21F nasopharyngeal Ca

• presented with Left neck masses
• blocked left ear, recently TMJ pain
• Globus sensation
• Weight stable
• no symptoms of metastatic dis

• Pmhx: tonsillectomy 2013
• hayfever
• asthma- exercise induced

• Social : at home with parents
• works as receptionist at real estate company
• graduated from uni in Auckland (Visual Arts)
• non-smoker
• ETOH- weekend- (socially)
• o/ex; looks well, comfortable
• left oropharynx looks more full than right but mucosa intact
• left neck: 2 nodes both very mobile; 1. level 2/5, about 1.5cm, the other level 3/4 about 1.5cm
• FNE: nasopharynx mucosa also intact but entire pharyngeal axis compressed.

• discussed rationale for chemoRT- 70Gy IMRT
• likely for concurrent and adjuvant chemo- sent referral to med onc
• discussed side-effects: acute and late incl fibrosis, risk to teeth with xerostomia, hypothyroidism and thyroid ca. second malig, carotid artery, ORN, requirement to see dentist long term

• will see dentist asap
• bloods today
• PET friday
• MRI ASAP
MRI

- Exquisite soft tissue definition
- Skull base, nasopharynx, oropharynx
- Brainstem, optic structures, cranial nerves spinal cord etc

- Hot topic – MRI simulator / linac...
- Standard sequences T1T2 other functional studies emerging as clinical standard

- Disadvantages – availability, access, distortion hence geometrically inaccurate, lower sensitivity and specificity in neck cf PET. Studies..
Figure 1. Coregistration between the macroscopic specimen (MC), CT, and FDG PET images. Volumes are displayed on transverse, coronal, and sagittal planes. The outline shows the GTV delineated with each modality, and the small cross represents the same point in space for each of the modalities. Infiltration of the parathyroid muscles on the left side is clearly visible on the macroscopic images.
POSITIONAL VERIFICATION WITH 3D IMAGE GUIDANCE
Rationale for CBCT in H&N

• Tight-ish margins and conformal dosimetry
• Improved anatomical definition / visualization
• Problems with 2D Imaging
  – Observer variability
  – Subtle yet significant rotation – difficult to quantify
  – Deformation
  – Parallax error
  – Time taken to deliberate – observer variability in interpretation
  – Action error
• Easy get??
  – Immobilization
  – Lack of significant physiological movement
• To deliver the promise of geometric conformation
Plan subtraction (3, -3, -3) -1
Dose Range (10 to 5) Gy
CBCT Protocol – outcome so far...

- More accurate, reproducible and reliable data on set up deviation
- Time saved
- Auto couch shift
- Now zero tolerance online protocol
- Wealth of data
• Images provide far more information required for 3D EPID paradigm
  – Deformation

• DOF of correctional action
  – Translation / Rotation
  – Doesn’t correct for deformation
Definition of Adaptive Radiation Therapy

• Reacting to significant geometric changes
  – Data acquired from 4D or repeat 3D images
  – Not correctable by couch shift, rotation
  – Triggered by assessment of deforming geometry or resultant dosimetry
Rationale for Adaptation

CLINICAL INVESTIGATION

SPATIAL AND DOSIMETRIC VARIABILITY OF ORGANS AT RISK IN HEAD-AND-NECK INTENSITY-MODULATED RADIOTHERAPY

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Purpose: The accuracy of intensity-modulated radiotherapy (IMRT) delivery may be compromised by random spatial error and systematic anatomic changes during the treatment course. We present quantitative measurements of the spatial variability of head-and-neck organ-at-risk and demonstrate the resultant dosimetric effects.

Methods and Materials: Fifteen consecutive patients were imaged weekly using computed tomography during the treatment course. Three-dimensional displacements were calculated for the superior and inferior brainstem, C1, C6, and T2 spinal cord, as well as the lateral and medial aspects of the parotid glands. The data were analyzed to show distributions of spatial error and track temporal changes. The treatment plan was recalculated on all computed tomography sets, and the dosimetric error was quantified in terms of the maximal dose difference (brainstem and spinal cord) or the mean dose difference and the volume receiving 26 Gy (parotid glands).

Results: The mean three-dimensional displacement was 2.9 mm for the superior brainstem, 5.4 mm for the inferior brainstem, 3.5 mm for the C1 spine, 5.6 mm for the C6 spine, and 6.6 mm for the T2 spine. The lateral aspects of both parotid glands showed a mean translation of 0.85 mm/week, and glands shrank by 4.9% per week. The variability of the maximal dose difference was described by standard deviations ranging from 3.6% (upper cord) to 4.0% (lower cord). The translation of the left parotid resulted in an increase of the mean dose and the volume receiving 26 Gy.

Conclusion: Random spatial and dosimetric variability is predominant for the brainstem and spinal cord and increases at more inferior locations. In contrast, the parotid glands demonstrated a systematic medial translation during the treatment course and thus sparing may be compromised.

Intensity-modulated radiotherapy, IMRT, Head and Neck, Spinal cord, Brainstem, Parotid.

Fig. 1. Example of rapidly changing anatomy during conformal radiotherapy for head-and-neck cancer. (a) Computed tomography slice taken at treatment simulation; (b) corresponding computed tomography slice taken 2 weeks into radiotherapy.
CLINICAL INVESTIGATION

ADAPTIVE PLANNING IN INTENSITY-MODULATED RADIATION THERAPY FOR HEAD AND NECK CANCERS: SINGLE-INSTITUTION EXPERIENCE AND CLINICAL IMPLICATIONS

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Purpose: Anatomic changes and positional variability during intensity-modulated radiation therapy (IMRT) for head and neck cancer can lead to clinically significant dosimetric changes. We report our single-institution experience using an adaptive protocol and correlate these changes with anatomic and positional changes during treatment.

Methods and Materials: Twenty-three sequential head and neck IMRT patients underwent serial computed tomography (CT) scans during their radiation course. After undergoing the planning CT scan, patients underwent planned rescans at 11, 22, and 33 fractions; a total of 89 scans with 129 unique CT plan combinations were thus analyzed. Positional variability and anatomic changes during treatment were correlated with changes in dosimetric parameters to target and avoidance structures between planning CT and subsequent scans.

Results: A total of 15/23 patients (65%) benefited from adaptive planning, either due to inadequate dose to gross disease or to increased dose to organs at risk. Significant differences in primary and nodal targets (planning target volume, gross tumor volume, and clinical tumor volume), parotid, and spinal cord dosimetric parameters were noted throughout the treatment. Correlations were established between these dosimetric changes and weight loss, fraction number, multiple skin separations, and change in position of the skull, mandible, and cervical spine.

Conclusions: Variations in patient positioning and anatomy changes during IMRT for head and neck cancer can affect dosimetric parameters and have wide-ranging clinical implications. The interplay between random positional variability and gradual anatomic changes requires careful clinical monitoring and frequent use of CT-based image-guided radiation therapy, which should determine variations necessitating new plans. © 2010 Elsevier Inc.
Fig. 1. In this patient with an unknown primary squamous cell carcinoma, the 45-Gy isodose line approaches a 5-mm avoidance structure around the spinal cord on the original plan (a). At the 24th fraction, there have been significant changes in skin separation due to weight loss and tumor shrinkage, leading to the 45-Gy isodose line encroaching on the spinal cord (b). The patient was replanned in order to avoid excess dose to the spinal cord (c).
However...

• Estimation of delivered dose is a more complex process
  – This modelling assigned the entire prescription to the altered study-set.
  – In fact regression is gradual and smooth, and truth is approximated if more frequent scans are performed
  – Propagation of cumulative dosimetry in deforming study sets...
Position reference point = center of clipbox

Reference Preset
- Scan
- Alignment Clipbox
- Structures

Alignment
- Automatic
- Bone
- Reset
- Convert To Correction

Table Correction
- Lateral: -0.07
- Longitudinal: -0.15
- Vertical: 0.05

Scan Time: ????? 12:00:00.000 AM
ART – Complete Replanning Approach
- reconstruction of delivered dose

1. Acquire regular images with good immobilization
2. Align/re-register & warp to minimize set-up error (confounders)
3. Rapid auto-contour (template & grey scale)
ART – Complete Replanning Approach

Overlay beams & re-construct "delivered dose"

Force deformation/warp for images & dose clouds

To reconstruct cumulative dosimetry
Once again.....

• Single “snapshot” assessment is likely to over estimate the dosimetric impact of geometric changes

• Also likely to be confounded by random set up variation of the day
  – Potentially large impact on dose estimation

• Dose accumulation for Adaptive assessment is a labour intense process
  – But is the right way to go
  – Deformable registration tools will speed up the process and make this a clinical reality
PHYSICS CONTRIBUTION

ASSESSMENT OF PAROTID GLAND DOSE CHANGES DURING HEAD AND NECK CANCER RADIOTHERAPY USING DAILY MEGAVOLTAGE COMPUTED TOMOGRAPHY AND DEFORMABLE IMAGE REGISTRATION

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CURRENT HN-ART WORKFLOW
• Off line
  – Combined assessment including RO - weekly
  – As opposed to online positional verification
• Look for
  – Progression in the first scan cf simulation
  – Systematic Soft tissue change / shift in high risk CTV
  – Systematic set up error
  – External contour changes
Summary

• IGRT – minimal margin for error with H&N IMRT
  – Highlights importance of precision set up
  – Emphasis on strict immobilization to minimise set up distortion
• ART →
  – Only for selected cases
  – Currently labour intense and time consuming
  – Precise assessment of delivered dose is still difficult
    • Simpler trigger to prompt the formal assessment path
  – Efficiency is the key to implementation
    • Accurate deformable registration tools for contouring, dose summation....
Summary

• Tips
  – Avoid the need to adapt
    • Ensuring inter fractional geometric stability
      – Nutritional management / hydration - PEG
      – Symptom support
      – Immobilization / fantastic cast
      – Neo-adjuvant chemo for huge nodes?? (eg.TPF??)
  • Excellent plan to start with
    – Minimise dose to OAR beyond conventional planning goals
    – room to move
  • Ongoing education
Role of Imaging in HN

– Selection
– Accurate delineation to drive precision planning
– Accurate delivery – verification and adaptation
– Biomarker – prognostication and prediction
– Medical record - documentation