Advances in models of quantitative imaging: validation, predictive power and clinical trials

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Can we image for biological properties? Validation?
- Hypoxia in tumours
- Cell Density

Do biological properties affect outcomes?
- Local control as a function of volume deemed hypoxic

Do not forget normal tissue

What can we do?
- Dose boost
- Change the property

Clinical evidence?
- One arm clinical trial vs. historical data
- Randomized trial
CT: e^ density + 3D data for planning, delineation of target volumes and organs at risk, DRRs for verification

MRI: soft tissue contrast, leakage of blood

PET: metabolic activity
Validation

• Mechanistic explanation
  – FLT
• Independent measurement
  – Eppendorf probe
• Inferred, e.g., absence of X means presence of Y
  – Lack of perfusion equal hypoxia
Imaging for hypoxia

Lee et al. 2008
Imaging for hypoxia

- HNSCC
- Benign tumors
- Soft tissue tumors

Mortensen et al. 2010
$^{18}$F-DOPA for glioma imaging

- M+/− T1 contrast enhancement/no enhancement
- P+/− PET uptake/no visible uptake

Pafundi et al. 2013
18F-DOPA for glioma imaging

Pafundi et al. 2013
PET as predictor

Primary Tumor Measured Tomography in Non-Small Cell Lung Cancer: A Systematic Review

Thierry Berçot, Claude Hossard, Arnaud Scherschel, Martine Roelants, Edward F. Patz, Jr.

FIGURE 1. Graphical representation of the prognostic role of primary tumor SUV on survival in lung cancer. HR and 95% confidence interval (CI) for survival comparison in studies evaluating primary tumor SUV in lung cancer. HR > 1 implies a survival benefit for reduced primary tumor SUVmax. The square size is proportional to the number of patients included in the study. The center of the diamond-shaped lozenge at the bottom of the figure gives the combined HR of the meta-analysis and its extremities the 95% CI HR = 2.27; 95% CI 1.70–3.02 (random-effect model). Total number of patients: 1474. SUV = standardized uptake value.

JTO, 2008
Figure 3. Kaplan-Meier curves depicting the actual survival for patients with a low maximum SUV compared with those with a high maximum SUV stratified by stage. Group 1, Patients with a maximum SUV lower than the median maximum SUV in that stage (low maximum SUV group). Group 2, Patients with a maximum SUV greater than or equal to the median maximum SUV in that stage (high maximum SUV group). A, Stage Iib NSCLC (P = .048); B, stage II NSCLC (P = .028); C, stage IIIA (P = .0120).
Imaging for hypoxia

Cervical cancer pts dynamic contrast-enhanced MRI, a-d: pt with voxels showing good perfusion after 2 weeks of RT; e-h poor perfusion. Grey lines (c, g) pre-RT, blue lines – 2 weeks into RT

Mayr et al. 2012
Does it matter?

DCE-MRI prior to RT

Mayr et al. 2012
Does it matter?

DCE-MRI after 2 weeks of RT  
Mayr et al. 2012
Do not forget normal tissue

- Active bone marrow (PET, >mean SUV)
- Low fat fraction (MR, <mean FF)
- Pelvis

Slide: Jakub Pritz
What can we do?

- Change the property
- Change RT, e.g., boost, sequential or SIB
  - Delineating "high risk" volumes
  - Painting by numbers
- Adaptive therapy based on imaging to assess response to ~10 (ish) fractions

Accelerated Radiotherapy With Carbogen and Nicotinamide for Laryngeal Cancer: Results of a Phase III Randomized Trial

Carbogen gas and radiotherapy outcomes in prostate cancer
Kent Yip and Roberto Alonzi
Prostate cancer RT: SIB for IPL

• Literature review: “prostate cancer SIB (IPL, DIL) radiotherapy”
• 19 papers identified
  9 RT planning
    ✓ 4 nodes/seminal vesicles/prostate
    ✓ 5 IPL
  8 radiotherapy experience/outcomes
    ✓ 7 nodes/seminal vesicles/prostate
    ✓ 1 IPL (Fonteyne et al. 2008, University of Ghent), modest escalation from 78 (median dose to PTV) to 82 Gy (median dose to IPL)
  2 other (TCP, MC)
SIB planning (FMISO)

Ca oropharynx, regular IMRT (a-1) and FMISO-guided IMRT with boost (a-2), delineation based planning

Lee et al. 2008
Intensity \rightarrow \text{biological property} \rightarrow \text{dose}

Base dose of 60 Gy
Mean dose of 90 Gy
$^{61}\text{Cu-ATSM}\ PET$-guided boost

$$D_i = 60Gy + 30Gy \times PET / <PET>$$

Korreman et al. 2010
Clinical trials

• We need evidence that SIB (or sequential boost) to high risk volumes changes outcomes
  – Lung
  – Prostate
  – Brain
  – Head & Neck
Clinical trials

- Arm A: 66Gy in 24 fractions of 2.75 Gy with an integrated boost to the primary tumor as a whole
- Arm B: 66Gy) in 24 fractions of 2.75Gy with an integrated boost to the 50% SUVmax area of the primary tumor (pre-treatment FDG-PET-CT)
- Boost to at least 72 Gy if can be accommodated without violating normal tissue constraints
Clinical trials

Dose escalation was possible in 15 of the first 20 patients enrolled.
For the boost region dose level of 86.9±14.9Gy was reached.
Prostate cancer RT: SIB for IPL

Fonteyne et al. 2008, MRI/MRS - defined IPL, boost to IPL using fixed gantry IMRT

Housri et al. 2011, MRI/MRS - defined IPL
Prostate cancer RT: SIB for IPL

- 37 Fx
- NTCP (rectum) < 7%
- Max DIL control

Nahum and Uzan, 2012
Phase II trial for glioma: SRS+60Gy/30

Clinical Investigation: Central Nervous System Tumor

Phase II Trial of Radiosurgery to Magnetic Resonance Spectroscopy-Defined High-Risk Tumor Volumes in Patients With Glioblastoma Multiforme

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Phase II trial for glioma: SRS+60Gy/30

- Surgery (Day 0)
- MRS by day 35
- SRS by day 35
- CRT 60Gy/30 fx by day 49 (46Gy+14 Gy)

- 35 patients
  - Median age 62 y (21-84)
  - Median KPS 90 (60-100)
  - 29 pts RPA class 4 or 5
  - 16/35 concurrent chemo
Phase II trial for glioma: SRS+60Gy/30

Table 4  Summary of patient survival time by prognostic classification

<table>
<thead>
<tr>
<th>Classification</th>
<th>No. of patients</th>
<th>GK MRS median survival</th>
<th>RTOG historical control, XRT alone</th>
<th>Survival difference of GK MRS patients vs. historical control</th>
<th>EORTC historical control, XRT + temodar</th>
<th>Survival difference of GK MRS patients vs. historical control</th>
</tr>
</thead>
<tbody>
<tr>
<td>RTOG RPA Class 3</td>
<td>4</td>
<td>&gt;22*</td>
<td>17.9</td>
<td>4.1†</td>
<td>21.4</td>
<td>0.6†</td>
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<tr>
<td>RTOG RPA Class 4</td>
<td>13</td>
<td>18.7</td>
<td>11.1</td>
<td>7.6†</td>
<td>16.3</td>
<td>2.4†</td>
</tr>
<tr>
<td>RTOG RPA Class 5</td>
<td>16</td>
<td>12.9</td>
<td>8.9</td>
<td>4.0†</td>
<td>10.3</td>
<td>2.6†</td>
</tr>
<tr>
<td>Concurrent temozolomide</td>
<td>16</td>
<td>20.8</td>
<td>NA</td>
<td>NA</td>
<td>14.6</td>
<td>6.2†</td>
</tr>
</tbody>
</table>

Abbreviations: GK = Gamma Knife; MRS = magnetic resonance spectroscopy; RTOG = Radiation Therapy Oncology Group; XRT = radiotherapy; EORTC = European Organization for Research and Treatment of Cancer; NA = Not applicable. Other abbreviation as in Table 2.

* Median survival not yet reached at time of analysis.
† Statistically significant.
Conclusions

• Validation of FI needed
• Correlation with outcomes established
• Sufficient proof from planning studies that boost is feasible
• Need trials which are likely to provide conclusive evidence