Radiogenomic integration in Radiation therapy and its impact - Review of evidence in Medulloblastoma

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Radiogenomics - Pubmed Footprint

Radiogenomics | Brain | Medulloblastoma

Innovations in imaging transform nearly every aspect of healthcare - Horizons are just being known
The idea of being able to probe disease characteristics rapidly and non-invasively - tremendously exciting!

Radiomics and radiogenomics - vast potential to improve clinical decision support systems, aid diagnosis, prognostic assessment, and treatment selection

Especially true when radiomic and radiogenomic data are processed using machine learning techniques

Analyze the features of entire tumors or other volumes of interest at any location and provide a picture of tissue heterogeneity within and across multiple volumes at a single time point

Particularly important for oncology, because tumor heterogeneity has been identified as a prognostic determinant of survival in different types of cancer, and an obstacle to cancer control
Radiomics - “High-throughput extraction of quantitative features that result in the conversion of images into mineable data” and feature prominently in what is today called “quantitative imaging”

Radiogenomics - The integration of radiomics with clinical data and the molecular characterization of tissue, also known as “radiogenomics” for the building of predictive models

Hope of eventually contributing to clinical decision making, treatment management and through prognostic and predictive treatment response/toxicity prediction models
Radiomics | Radiogenomics
Principles | Rationale - Early insights from liver cancer

2007
The Use of Magnetic Resonance Imaging to Noninvasively Detect Genetic Signatures in Oligodendroglioma

Robert Brown,¹ Magdalena Zlatescu,²,⁷ Angelique Sijben,² Gloria Roldan,²,³ Jay Easaw,³,⁷ Peter Forsyth,³,⁷ Ian Parney,²,⁷ Robert Sevick,⁴,⁶,⁸ Elizabeth Yan,³ Douglas Demetrick,⁵ David Schiff,⁹ Gregory Cairncross,²,⁷,⁸ and Ross Mitchell¹,⁴,⁶,⁸

1p19q detection from MR images
Medulloblastomas epitomises the war against childhood cancer!

Overwhelming need for risk classification
- Minimize unnecessarily aggressive therapy for low-risk disease
- Maximize efficacious treatment for high-risk disease

Four separate studies dovetailed with previous work
- Crystallize a molecular classification of medulloblastoma
- Codified a new risk-stratification model based on molecular biology of these disease subtypes
Medulloblastoma Comprises Four Distinct Molecular Variants


A

Predicting Relapse in Patients With Medulloblastoma by Integrating Evidence From Clinical and Genomic Features

Model A
- Relapse
- Clinical attributes
  - Histology
  - Metastasis

Model B
- Disease subtype independent expression signature
  - c-Myc activated (v1) poor

Model C
- Disease subtype dependent expression signatures
  - mTOR induced c1 (poor)
  - Anti-CD44 regulated c2 (good)
  - c-Myc activated (v2) c3 (poor)
  - Histidine metabolism c4 (poor)
  - Gli1 downregulated c5 (good)
  - Ribavirin/RSV-induced response c6 (poor)

Model D
- DNA copy number gains or losses
  - amp (8q24.21) C-MYC
  - amp (12p24.3) N-MYC
  - del (8q) Monosomy 6
  - del (16q)
  - del (16q23.3)
  - amp (7q21.3)
  - amp (3q26.32)
QIN “Radiomics: The Process and the Challenges”

Virendra Kumar\textsuperscript{1}, Yuhua Gu\textsuperscript{1}, Satrajit Basu\textsuperscript{2}, Anders Berglund\textsuperscript{3}, Steven A. Eschrich\textsuperscript{3}, Matthew B. Schabath\textsuperscript{4}, Kenneth Forster\textsuperscript{5}, Hugo J.W.L. Aerts\textsuperscript{6,8}, Andre Dekker\textsuperscript{6}, David Fenstermacher\textsuperscript{3}, Dmitry B Goldgof\textsuperscript{2}, Lawrence O Hall\textsuperscript{2}, Philippe Lambin\textsuperscript{6}, Yoganand Balagurunathan\textsuperscript{1}, Robert A Gatenby\textsuperscript{7}, and Robert J Gillies\textsuperscript{4,1,7}
2012

Radiomics | Radiogenomics
Decoding numbers!

- Image data
  - Image modality
  - Acquisition
  - Reconstruction
  - Image data storage

- Image segmentation
  - Ground truth
  - Automate
  - Reproducible
  - Validate

- Features extraction & qualification
  - Features space
  - Automatic extraction
  - Informative
  - Reproducible
  - Low redundancy

- Analysis and database
  - Clinical and research PACS
  - Storage & sharing of reports & annotations
  - Integrations of clinical, imaging and genomics databases
  - Informatics analyses
Radiomics | Radiogenomics

Decoding Molecular Phenotypes & Radiogenomics!

Behind the Numbers:
Decoding Molecular Phenotypes with Radiogenomics—Guiding Principles and Technical Considerations

- Understanding biological correlates behind imaging phenotypes
- Understanding how a biological process is reflected in imaging
- Defining clinical biomarkers or biological surrogates
Radiogenomics - The Radiobiology Face!

Radiogenomics

- Study of the link between germ line genotypic variations and the large clinical variability observed in response to radiation therapy

Hypothesis

- Proportion of the variance in the phenotype of interest—radiation toxicity—is explained by genotypic variation

Published in final edited form as:
2016, Annual Doppman Memorial Lecture, NIH
Professor Michael Kuo

Kuo and his team have pioneered the field of Radiogenomics
Help guide patient outcomes, and to predict treatment response
<table>
<thead>
<tr>
<th>Location features</th>
<th>Diffusion features</th>
<th>MRI-based nomograms for prediction of subgroups</th>
</tr>
</thead>
</table>

Medulloblastoma landscape - Correlates of imaging & molecular groups
### Medulloblastoma landscape - Correlates of imaging & molecular groups

|-------------------|----------------------------------------------------------------------------------------------------------------------------------|

**Location (horizontal axis)**
- Location (vertical axis)
- Relation with dorsal brainstem
- Contrast-enhancement
- T2-weighted characteristics
- Peri-tumoral edema
- Intra-tumoral hemorrhage
- Cyst (size and location)
- Hydrocephalus
- Metastases (incidence, location, and pattern)

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**Review**


*Archya Dasgupta, Tejpal Gupta*
<table>
<thead>
<tr>
<th></th>
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</thead>
<tbody>
<tr>
<td>Location (horizontal axis)</td>
<td>Midline, CP/CPA</td>
</tr>
<tr>
<td>Location (vertical axis)</td>
<td>Central, inferior</td>
</tr>
<tr>
<td>Relation with dorsal brainstem</td>
<td>Infiltrate</td>
</tr>
<tr>
<td>Contrast-enhancement</td>
<td>homogeneous, bright</td>
</tr>
<tr>
<td>T2-weighted characteristics</td>
<td>Isointense, homogeneous</td>
</tr>
<tr>
<td>Peri-tumoral edema</td>
<td>Mild/ absent</td>
</tr>
<tr>
<td>Intra-tumoral hemorrhage</td>
<td>+/-</td>
</tr>
<tr>
<td>Cyst (size and location)</td>
<td>Intra-tumoral microcysts</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Absent/ mild</td>
</tr>
<tr>
<td>Metastases (incidence, location,</td>
<td>Rare</td>
</tr>
<tr>
<td>and pattern)</td>
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</tbody>
</table>
Radiomics | Radiogenomics

SHH-MB landscape - Correlates of imaging & molecular groups

<table>
<thead>
<tr>
<th>Location features</th>
</tr>
</thead>
</table>

Location (horizontal axis) - Lateralised/ midline in infants
Location (vertical axis) - Superior abutting tentorium
Relation with dorsal brainstem - >50% away
Contrast-enhancement - Variable, moderate
T2-weighted characteristics - Isointense, heterogeneous
Peri-tumoral edema - Significant
Intra-tumoral hemorrhage - Absent
Cyst (size and location) - Intra- and peri-tumoral microcysts and macro
Hydrocephalus - Seldom
Metastases (incidence, location, and pattern) - Variable incidence
Radiomics | Radiogenomics

Group 3 MB landscape - Correlates of imaging & molecular groups

<table>
<thead>
<tr>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Location (horizontal axis)</td>
<td>Midline, 4th ventricle, vermis</td>
</tr>
<tr>
<td>Location (vertical axis)</td>
<td>Central</td>
</tr>
<tr>
<td>Relation with dorsal brainstem</td>
<td>Abuts</td>
</tr>
<tr>
<td>Contrast-enhancement</td>
<td>Heterogeneous, fluffy</td>
</tr>
<tr>
<td>T2-weighted characteristics</td>
<td>Hypointense, homogeneous</td>
</tr>
<tr>
<td>Peri-tumoral edema</td>
<td>Absent/ mild</td>
</tr>
<tr>
<td>Intra-tumoral hemorrhage</td>
<td>Absent</td>
</tr>
<tr>
<td>Cyst (size and location)</td>
<td>Peri-tumoral macrocysts</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>Moderate to severe</td>
</tr>
<tr>
<td>Metastases (incidence, location, and pattern)</td>
<td>Highest</td>
</tr>
</tbody>
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A | B | C
<table>
<thead>
<tr>
<th>Location features</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Location (horizontal axis)</strong></td>
<td>Midline, 4th ventricle, vermis</td>
</tr>
<tr>
<td><strong>Location (vertical axis)</strong></td>
<td>Inferior</td>
</tr>
<tr>
<td><strong>Relation with dorsal brainstem</strong></td>
<td>Abuts</td>
</tr>
<tr>
<td><strong>Contrast-enhancement</strong></td>
<td>Heterogeneous, patchy</td>
</tr>
<tr>
<td><strong>T2-weighted characteristics</strong></td>
<td>Hyperintense, homogeneous</td>
</tr>
<tr>
<td><strong>Peri-tumoral edema</strong></td>
<td>Absent/ mild</td>
</tr>
<tr>
<td><strong>Intra-tumoral hemorrhage</strong></td>
<td>Absent</td>
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<td><strong>Cyst (size and location)</strong></td>
<td>Intra-tumoral microcysts</td>
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<td><strong>Hydrocephalus</strong></td>
<td>Moderate to severe</td>
</tr>
<tr>
<td><strong>Metastases (incidence, location, and pattern)</strong></td>
<td>Moderate</td>
</tr>
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Images: A, B, C, D
<table>
<thead>
<tr>
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<tbody>
<tr>
<td>Group 4 MB</td>
<td>Ependymal metastasis with restricted diffusion but no enhancement “Mismatch pattern” Particularly if located in the infundibular recess</td>
</tr>
</tbody>
</table>
Medulloblastoma - MRI based nomograms, predictive models, prognosticators for subgroups

Models: Dasgupta (2018), Chang (2021)

Table 3: Area under the curve (AUC) with 95% CI of receiver operating characteristics (ROC) curves for subgroup-specific nomograms in the training cohort and validation cohort

<table>
<thead>
<tr>
<th>Molecular Subgroup</th>
<th>AUC (95% CI) in Training Cohort (n = 76)</th>
<th>AUC (95% CI) in Validation Cohort (n = 35)</th>
</tr>
</thead>
<tbody>
<tr>
<td>WNT</td>
<td>0.754 (0.624–0.885)</td>
<td>0.693 (0.416–0.970)</td>
</tr>
<tr>
<td>SHH</td>
<td>0.939 (0.887–0.991)</td>
<td>0.991 (0.971–1.000)</td>
</tr>
<tr>
<td>Group 3</td>
<td>0.726 (0.582–0.870)</td>
<td>0.600 (0.380–0.820)</td>
</tr>
<tr>
<td>Group 4</td>
<td>0.851 (0.733–0.969)</td>
<td>0.788 (0.632–0.945)</td>
</tr>
</tbody>
</table>
Medulloblastoma - MRI based nomograms, predictive models, prognosticators for subgroups

Models | Dasgupta (2018), Chang (2021)

- 8 contrast-enhanced T1-weighted texture features were significantly different between 4 molecular subgroups
- Together with prediction models, the radiomics features may provide suggestions for stratifying patients with MB into different risk groups
Radiomics | Radiogenomics

Medulloblastoma - Quest for non invasive markers & the essentials to build a radiogenomics model

- Discover non-invasive biomarkers that mirror the molecular properties of these tumors
- Most clinically used biomarkers use a piece of tissue and apply genomics
- Subtyping of medulloblastoma is often based on gene expression of 22 genes - nanostring
- Knowing the subtype of informs on the biology of the disease and what treatment is likely to help
- Main disadvantage is that surgical sampling - invasive
- Biomarkers on imaging - potentially more easy to implement?
- Quantitative imaging is a great candidate to investigate whether feature(s) can serve as a biomarker for the underlying biological type
- Add to this - toxicity prediction
- Becomes a heady cocktail of personalised treatment with some knowledge of outcomes & toxicity
- Essentials to build the model - coordination of experts to integrate
  - The genomics strategy
  - Quantitative imaging strategy
  - The integration strategy
Radiogenomic integration in Radiation therapy and its impact
Review of evidence in Medulloblastoma

Summary