HABITATS IN PROSTATE CANCER

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Learners Objective

- Current Prostate Cancer Clinical Care
- Concepts of Habitat Imaging
- Quantification of Imaging Habitat and predictive risk assessment for active surveillance.
- Potential of quantitative histology and future research direction
Motivation

• Prostate cancer continues to be the most common cancer among men (estimated to affect ~160, 000 men, yearly) and second largest cause of cancer death among men in the US*.
• About 80% of the prostate cancers are diagnosed in men $\geq 65$ years of age.
• Prostate cancer is an heterogeneous disease with over 20 different cell lines available for laboratory purpose.
• About 90% of Prostate cancers are Adenocarcinomas originating in the gland and ducts. About 75% of the tumors appear in the peripheral zone.
• Current standard of care: involves DRE (digital rectal examination) and PSA (prostate specific antigen) for surveillance and diagnosis of the disease.

• Siegal et.al, Ca Cancer J Clin, Cancer statistics 2016
Current Impediment


• “Nowhere is the issue of overtreatment of indolent tumor's and under-treatment of high-risk disease with the potential to metastasize more pertinent than in prostate cancer”

• “Controversy is to divide the population into High risk needing active treatment and low risk individuals that needs active surveillance”
Clinical Risk Assessment

The National Comprehensive Cancer Network (NCCN) defines:

- ‘High-risk’ as T3a, Gleason $\geq 8$, or PSA $\geq 20$ng/ml
- ‘Very high risk’ as T3b or T4 disease, the prognostication of which was improved by recording the proportion of biopsies with $\leq 50\%$ versus $>50\%$ tumor involvement

Our Focus: **Active Surveillance**: Availability of advanced Imaging (mpMRI) opens avenues for quantitative risk assessment.

- NCCN guidelines
- Chang, A et al, Nat.Reviews 2014
Why Targeted Therapies Fail?

*(one reason): Tumors have Ecology! (Heterogeneous)*

Tumors are not homogeneous well-mixed systems: they are complete ecosystems comprised of habitats; each with their own local selection pressures and phenotypes.
What are Habitats?

• **Definition:** Is an **ecological or environmental area that is naturally inhabited by particular species of plant or animal.**

• Each species have preferred Habitats for its natural living.

• **INFERENCE:** If we can find the species (tumor), we can guess its Habitats (tumor-region). And vice-versa is true.

* Gatenby Radiology, 2013

Dr. Joel Brown
Imaging Habitats: Scene

Inference: What information can Habitats Provide us?
- Localization of Region of Interest (Tumor)
- Identification of Broad area of interest (Micro-environment)
Prostate Habitats: Example

T2

T1 (Phase 3)

ADC

Whole Prostate

OTSU (Distribution)

ROI

Fuzzy Functions

Region Identification

Tumor (extreme)

Tumor

T (DCE, Phase 3) Prostate

ADC
Can Habitats Predict Cancer Aggressiveness?

Data:

1. Surveillance Cohort
(Accrual at Univ. Miami, expected accrual ~165 patient by 2019)
- 54 MAST Patients
- Biopsy locations available
- Pathology for MAST patients

Imaging: mpMRI
- T2w, DCE (T1w), ADC
- Registered/ Resampled to T2.

<table>
<thead>
<tr>
<th>Class</th>
<th>Benign (GS ≤6)</th>
<th>Cancer</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>GS ≤6 Vs ≥7</td>
<td>74</td>
<td>37</td>
<td>111</td>
</tr>
<tr>
<td>GS ≤6 Vs ≥8</td>
<td>74</td>
<td>14</td>
<td>88</td>
</tr>
</tbody>
</table>

2. Data: SPIE Prostate X Challenge
- Training: ~203 patients (T2, ADC, DWI,K-Trans)
- Testing: ~140 patients
Habitat Identification ( Low T2, Low in ADC ), which is “Habitat-Tumor” region (most probably tumor region).

**Habitat Tumor:**
- Low T2
- Low ADC
- High DWI
Feature Based Model

308 Features

- **Features Computed on the Habitat Region**

<table>
<thead>
<tr>
<th>Category</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size</td>
<td>9</td>
</tr>
<tr>
<td>Shape</td>
<td>18</td>
</tr>
<tr>
<td>Location</td>
<td>10</td>
</tr>
<tr>
<td>Intensity</td>
<td>42</td>
</tr>
<tr>
<td>RunLength</td>
<td>16</td>
</tr>
<tr>
<td>GraySizeZone</td>
<td>16</td>
</tr>
<tr>
<td>Cooccurrence</td>
<td>25</td>
</tr>
<tr>
<td>GrayTone</td>
<td>5</td>
</tr>
<tr>
<td>Laws</td>
<td>125</td>
</tr>
<tr>
<td>Wavelet</td>
<td>30</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>~307</td>
</tr>
</tbody>
</table>

Malignancy Risk Predictor

mpMRI

Dynamics (on DCE)
Discriminate Low Vs High Risk: (GS ≥ 7) Vs Benign (GS ≤ 6)

**ADC (Raw): GS ≤ 6 Vs ≥ 7**

<table>
<thead>
<tr>
<th>Features</th>
<th>Error</th>
<th>AUC: μ (σ), CI</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiomics-ADC</td>
<td>0.205</td>
<td>0.854 (0.083), [0.678,0.98]</td>
<td>0.613</td>
<td>0.926</td>
</tr>
</tbody>
</table>

**T2 (Raw): GS ≤ 6 Vs ≥ 7**

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<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Radiomics-T2</td>
<td>0.218</td>
<td>0.788 (0.123), [0.335,0.965]</td>
<td>0.585</td>
<td>0.886</td>
</tr>
</tbody>
</table>

**Combined (ADC & T2)**
AUC = 0.89

**ADC (Radiomics)**
AUC = 0.854 [0.68,0.98]

**T2 (Radiomics)**
AUC = 0.788 [0.34,0.97]
b. Low Vs Aggressive: GS ≤ 6 Vs GS ≥ 8

ADC (Raw): GS ≤ 6 Vs GS ≥ 8

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<th>AUC: µ (σ), CI</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiomics-ADC (Stat-Quart-coef-; Least-axis-length;COM-shift)</td>
<td>0.079</td>
<td>0.858 (0.15), [0.438,0.969]</td>
<td>0.63</td>
<td>1</td>
</tr>
</tbody>
</table>

ADC (Radiomics) AUC = 0.858 [0.44,0.97]

ADC (Raw): GS ≤ 6 Vs GS ≥ 8

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<th>AUC: µ (σ), CI</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiomics-T2 (Vol-density-;F75:Area-density-AvgCooc_)</td>
<td>0.163</td>
<td>0.91 (0.105), [0.62,0.979]</td>
<td>0.389</td>
<td>0.984</td>
</tr>
</tbody>
</table>

T2 (Radiomics) AUC = 0.91 [0.62,0.97]

Combined (ADC & T2) AUC = 0.94
Clinical Benefit

- Radiomic Predictors shows wide range of benefit to predict true disease (Higher grade Gleason).
Digital Pathology Challenges

Quantification of H&E slides

- Each Cell: ~99 Features Extracted
- Slide: ~93,684 segmented cells
  (~52308 Tumor ~41374 Stroma)

C1: Stain-Intensity-Based  11
C2: Cell-Size/Shape  ~25
C3: Texture (Co-Occurrence, Gray level)  ~63

• Morphology of the cells will characterize the tumor at the lowest resolution.
Future Goal: Multi-modality Integration

MRI Image

Resolution: mm

T1 (DCE)

T2

ADC

MR Image

Digital Pathology

Risk of Disease Progression

Genomics

HE Stain

IHC Stain: Digital Path

Area=1201.6 mm²
Perimeter=152.4 mm
Volumen=2615 mm³
Surf. area=1099.33 mm²
Surf. Area/Volumen=0.42 mm⁻¹

Density, Necrosis
Mean = 19.33 HU
SD = 76.59 HU
Min = -249 HU
Max = 118 HU

Spiculations
Slope at margin =133.5±31.3 HU/mm
Low density inclusions
Rel. vol.= 0.21 mm³
Number=10
Volume=4.89±8.35 mm³

Future Goal: Multi-modality Integration

Risk of Disease Progression
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References

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- Chang, A et al, Nat.Reviews 2014
- Litwin, JAMA, 317 (24), 2017;