Avoiding major surgery and improving quality of life in patients with early rectal cancer

Early Rectal Cancer
Translational Research Opportunities
The strength of this trial

- Distinctive cohort
- Untreated
- Close follow up
- Internal control: TME surgery arm vs local excision

Question to ask

Why are these tumours (still) early stage?

Which are high risk cancers at an early stage?
The consensus molecular subtypes of CRC

Right sided

<table>
<thead>
<tr>
<th>CMS1</th>
<th>CMS2</th>
<th>CMS3</th>
<th>CMS4</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSI immune</td>
<td>Canonical</td>
<td>Metabolic</td>
<td>Mesenchymal</td>
</tr>
<tr>
<td>37%</td>
<td>13%</td>
<td></td>
<td>23%</td>
</tr>
<tr>
<td>SCNA high</td>
<td>Mixed MSI status, SCNA low, CIMP low</td>
<td></td>
<td>SCNA high</td>
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<tr>
<td>KRAS mutations</td>
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<tr>
<td>WNT and MYC activation</td>
<td>Metabolic deregulation</td>
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<td>Worse relapse-free and overall survival</td>
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</tbody>
</table>

Guinney et al., Nature Medicine 2015

Translational approach to ERC

Next generation sequencing
Gene expression signatures
Liquid biopsy?
Results from TRACC study

Tracking mutations in ctDNA to predict relapse in early CRC

- Assess whether ctDNA is detectable with ddPCR in patients with stage II/III CRC
- 37/38 (97%) patients have at least 1 mutation in one of the genes of interest in tissue

Translational approach to ERC

Next generation sequencing  
Gene expression signatures  
ctDNA – negative correlation
Immunoprofiling

Immunoscore as prognostic marker for rectal cancer

Early rectal cancers with higher CD8 infiltrate lower LN involvement

Anitei et al., Clin Cancer Research 2014
Däster et al., Disease Markers 2014
Immunoprofiling

Immune infiltrate predictive?? for chemoradiotherapy in rectal cancer?

Lower ratios of

\[
\begin{array}{c|c|c}
\text{CD4} & \text{CD8} & \text{FOXP3} \\
\text{PD-1} & \text{PD-1} & \text{PD-L1} \\
\end{array}
\]

in tumour regression than in residual disease group

Immunoprofiling

Define new prognostic marker panel: e.g. CD3, CD8, FOXP3, Ki-67, PD-L1, Cytokeratin

Spatial Analysis of immune infiltrate

Park et al., Oncotarget 2017
Translational approach to ERC

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Morphology and Microenvironment Analysis

Correlation with Radiology
- Diameter
- Depth and width of invasion
- Gross morphology
- Lymph node involvement
- Further assessment
  - Tumour budding
  - Lymphovascular invasion
  - Grading
- Tumour/Stroma Ratio
Morphology and Microenvironment Analysis

Translational approach to ERC

- Next generation sequencing
- Gene expression signatures
- ctDNA – negative correlation
- Methylation based molecular clocks
- Immunoprofiling
- Morphological/Radiological
More ideas…?