Digital immunohistochemical evaluation of PDL1 in lung carcinomas

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Programmed Death-Ligand 1

- Immune checkpoints (e.g. PD(L)1, CTLA4)
- The ligand is a molecule on the surface of ACP cells
- Its receptor is the CD279 molecule on the surface of T-cells
- Effects of the interaction
  - Inhibition of activity
  - Proliferation of antigen-specific T-cells

Immunotherapeutic products

- PD-1 inhibitors
  - **Pembrolizumab** (2014): metastatic NSCLC, without EGFR/ALK mutation
    - 1st line monotherapy >50% TPS (Tumor proportion score)
    - 2nd line monotherapy >1%
  - **Nivolumab** (2014): metastatic NSCLC, in case of EGFR/ALK mutation in combination with their inhibitors
- PDL-1 inhibitors
  - **Atezolizumab** (2016): 1st line metastatic nsqNSCLC, without EGFR/ALK mutation
  - **Durvalumab** (2018): metastatic, ireresectable, beside radio- and platinum-based chemotherapy non-progrediating NSCLC
Background & objectives

- PDL1 IHC conventional evaluation
  - can be difficult in some cases
  - can depend on the proficiency of the pathologist
  - can depend on the workload of the pathologist
  - inter- and intraobserver variability

- PDL1 IHC Digital Image Analysis (DIA)
  - standardized
  - reduces the problems caused by the above mentioned
  - more precise choice of targeted therapy
  - several parameters about millions of cells
1. Evaluation of immunopositivity by using digital methods (novelty)

2. Comparison of conventional and digital evaluation of IHC

3. Are there any data left in digital slides for prognostic and predictive use?
Methods

• 156 patients’ PDL1 IHC (DAKO 22C3)
  – 10% squamous cell carcinoma
  – 90% adenocarcinoma

• 26 cases (16.6%) excluded: during the conventional process the pathologist could not evaluate the staining

• **130 cases** were given a percent in immunopositivity (TPS)
1. Pannoramic 250 (3DHistech) scanner
2. **3DHistech** image analysis softwares (PatternQuant, MembraneQuant) have to be set for proper data processing
3. DIA results have to be collected and compared to conventional methods (TPS)
1. Teaching using 50 random slides
2. 3 algorythms have been created. In the case of each slide the correct one can be chosen within a standard of 10 seconds

➢ The evaluation of each slide takes between 1-20 minutes depending on the computer’s processing power and the size of the slide
PatternQuant
Measured parameters

• Differentiation of cell populations:
  – Tumor cells
  – Macrophages
  – Tumor infiltrating lymphocytes
  – Peritumoral lymphocytes

• In each group numerised data about the following:
  – Number of cells, their density
  – Nucleus size
  – Nucleus/cytoplasm ratio
  – Nucleus roundness
Objective measurement of the nucleus/membrane/cytoplasm staining:

- **Positivity score (can be fine-tuned)**
  - Weak%
  - Medium%
  - Strong%

- **H-score (histo-score)**
  
  \[ 1 \times \text{Weak\%} + 2 \times \text{Medium\%} + 3 \times \text{Strong\%} \]

  a number between 0-300
# Results

## Tumor cells vs. TPS:

<table>
<thead>
<tr>
<th></th>
<th>adenocarcinoma</th>
<th>squamous cell carcinoma</th>
<th>overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H-score</strong></td>
<td>0.88</td>
<td>0.92</td>
<td>0.89</td>
</tr>
<tr>
<td><strong>Medium positive</strong></td>
<td>0.74</td>
<td>0.91</td>
<td>0.75</td>
</tr>
<tr>
<td><strong>Strong positive</strong></td>
<td>0.86</td>
<td>0.94</td>
<td>0.86</td>
</tr>
<tr>
<td><strong>Medium + strong positive</strong></td>
<td>0.87</td>
<td>0.91</td>
<td>0.88</td>
</tr>
</tbody>
</table>
### Results

**Peritumoral lymphocytes vs. TPS:**

<table>
<thead>
<tr>
<th></th>
<th>adenocarcinoma</th>
<th>squamous cell carcinoma</th>
<th>overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H-score</strong></td>
<td>0.57</td>
<td>0.62</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Medium positive</strong></td>
<td>0.68</td>
<td>0.72</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Medium + strong positive</strong></td>
<td>0.68</td>
<td>0.73</td>
<td>0.68</td>
</tr>
</tbody>
</table>
### Results

**Tumor infiltrating lymphocytes vs. TPS:**

<table>
<thead>
<tr>
<th></th>
<th>adenocarcinoma</th>
<th>squamous cell carcinoma</th>
<th>overall</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>H-score</strong></td>
<td>0.29</td>
<td>0.34</td>
<td>0.31</td>
</tr>
<tr>
<td><strong>Medium positive</strong></td>
<td>0.26</td>
<td>0.08</td>
<td>0.27</td>
</tr>
<tr>
<td><strong>Medium + strong positive</strong></td>
<td>0.28</td>
<td>0.09</td>
<td>0.28</td>
</tr>
</tbody>
</table>
## Machine vs. Conventional Category

C0: <1%, C1: 1-50%, C2: 50-100%

<table>
<thead>
<tr>
<th>MC vs CC</th>
<th>CC0</th>
<th>CC1</th>
<th>CC2</th>
<th>overall</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>MC0</td>
<td>14</td>
<td>8</td>
<td>0</td>
<td>22</td>
<td>16.92%</td>
</tr>
<tr>
<td>MC1</td>
<td>27</td>
<td>32</td>
<td>5</td>
<td>64</td>
<td>49.23%</td>
</tr>
<tr>
<td>MC2</td>
<td>2</td>
<td>8</td>
<td>34</td>
<td>44</td>
<td>33.85%</td>
</tr>
<tr>
<td>overall</td>
<td>44</td>
<td>48</td>
<td>39</td>
<td>130</td>
<td>100%</td>
</tr>
<tr>
<td>%</td>
<td>33.08%</td>
<td>36.92%</td>
<td>30.00%</td>
<td></td>
<td>100%</td>
</tr>
</tbody>
</table>

Different: 50 (38.46%)  
Same: 80 (61.53%)  
Machine gave higher category: 37 (28.26%)  
Machine gave lower category: 13 (10%)

Clinical response?
Summary

• 3DHistech softwares successfully recognise certain cell populations
• Machine evaluation correlates well (0,89) with the conventional method
• There were differences in categories
• Clinical follow-up in progress to analyse clinical response regarding CC and MC
Remercies

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