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Dr. Stefano La Rosa declares he has no conflict(s) of interest to disclose.
GEP neuroendocrine neoplasms are a heterogeneous group of neoplastic proliferations characterized by specific clinico-pathological and molecular features which mainly depend on the site of origin.

Stomach

Take home message:
Ki67 labeling index is a good prognostic marker but it should not be used alone to stratify patients in different prognostic categories; it should be considered together with clinico-pathologic tumor type and stage.
Duodenum

- Morphology: well differentiated (176 cases)
- Ki67: <2.5% (140 cases), 2.5-20% (31 cases)
- Mitoses: <2 (140 cases), 2-20 (16 cases)
- Grade: G1 (80%), G2 (20%)
- No WD-NET with Ki67>20%

Differences among NET subtypes

<table>
<thead>
<tr>
<th>Type</th>
<th>G1</th>
<th>G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>GP</td>
<td>92%</td>
<td>8%</td>
</tr>
<tr>
<td>Gastrinoma</td>
<td>85%</td>
<td>15%</td>
</tr>
<tr>
<td>D-cell tumor</td>
<td>65%</td>
<td>35%</td>
</tr>
<tr>
<td>NF-NET</td>
<td>82%</td>
<td>18%</td>
</tr>
</tbody>
</table>

Predictors of lymph node involvement

Proliferative grading, lymphovascular invasion and level of wall invasion can effectively predict LN metastases

Disease specific survival

Take home message:

- Ki67 labeling index is not useful to separate different tumor categories
- Ki67 labeling index is a predictor of lymph node involvement
- Although Ki67 labeling index is a predictor of disease free survival when considering duodenal NENs all together (G1, G2, G3), it does not discriminate alone the disease free survival between G1 and G2.
Upper jejunum

Lower jejunum and ileum (midgut)

In small bowel ileal NETs Ki67 labeling index does not predict metastatic disseminations

- Gonzales et al. Mod Pathol 27:1288-1295, 2014
- Clift et al. Endocr Connections 6:71-81, 2017
Take home message

Most ileal NETs are G1 and metastatic so Ki67 labeling index does not predict metastatic disseminations

However:
- Ki67 is an independent predictor for tumor progression
- 14% increased risk for tumor progression for each increasing unit
- Ki67 is an independent risk factor for decreased survival
- Ki67 cut-off at 5% seems better to discriminate between G1 and G2

Appendix

Most tumors are G1 NETs, infiltrate the muscular layer, but very rarely metastasize
Take home message:

- For appendiceal NETs reporting tumor grade is recommended by guidelines
- However, tumor grade is not statistically correlated with a different survival, which mainly depends on stage

<table>
<thead>
<tr>
<th>Reference</th>
<th>N°</th>
<th>G1</th>
<th>G2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jeremian, 2012</td>
<td>72</td>
<td>61</td>
<td>11</td>
</tr>
<tr>
<td>Hong, 2013</td>
<td>37</td>
<td>33</td>
<td>4</td>
</tr>
<tr>
<td>Tsukamoto, 2008</td>
<td>23</td>
<td>17</td>
<td>6</td>
</tr>
<tr>
<td>Kim, 2013</td>
<td>79</td>
<td>79</td>
<td>0</td>
</tr>
<tr>
<td>Sohn, 2015</td>
<td>972</td>
<td>906</td>
<td>66</td>
</tr>
<tr>
<td>Li, 2015</td>
<td>147</td>
<td>137</td>
<td>10</td>
</tr>
<tr>
<td>Nakamura, 2016</td>
<td>170</td>
<td>166</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>1500</td>
<td>1399</td>
<td>101</td>
</tr>
</tbody>
</table>

Ki67 has been generally used for grading evaluation because mitoses are extremely rare.

Rectum (hindgut)

![Image](https://via.placeholder.com/200)

Ki67 labeling index and lymphovascular permeation predict the metastatic potential of rectal neuroendocrine tumors.
Take home message:

- Most rectal NETs are G1
- Ki67 index is a prognostic marker
- The recently proposed cut-off of 3% seems the best one
- Ki67 index should not be used alone as a prognosticator, but in association with tumor size, lympho-vascular invasion, level of wall infiltration, and immunophenotype (L-cell versus EC-cell)

Concluding remarks

- Ki67 labeling index is a good prognostic marker for gastric, ileal, and rectal NETs
- For the best prognostic stratification of patients Ki67 should be considered with other prognosticators, depending on the tumor sites
- The cut-off of 2% used to discriminate between G1 and G2 NETs should be reconsidered and it may be different in relation to the tumor site

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