Distinct cut off values of Ki-67-index for NET-grading in a large German multicentre cohort


on behalf of all the members of the German Registry of Neuroendocrine Gastrointestinal Tumours (NET-Registry)

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Background:
Neuroendocrine tumours (NET) are a rare and heterogeneous group of epithelial neoplasm. Prediction of prognosis is often difficult due to a lack of reliable and widely accepted markers. Recently some clinical and histopathological factors proved to be of significant prognostic value. Among them Ki-67 grading according to ENETS was shown to be a useful parameter for outcome stratification. In most studies however it failed to differ significantly between G1 and G2 tumors, thus aggravating prognosis prediction especially in tumours with low proliferation rate. Therefore some authors claimed that a cut off value of <2% for G1 tumours might be too low to accurately divide G1 from G2 tumours. They hence suggested a cut of value of <5% for G1 tumours as a better cut off margin with greater prognostic importance.

Aim of the study:
Analysis of the prognostic significance of different cut-off values of the proliferation marker Ki-67 (G1= <2% vs. <5%) in a large multicentre cohort of the German NET registry (figure 1 and table1).

Results:
Table 1: Basic data in the German NET-registry

<table>
<thead>
<tr>
<th>number of included cases</th>
<th>female: male pts</th>
<th>mean age at initial diagnosis</th>
<th>median age</th>
<th>mean follow-up</th>
<th>median follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>2009</td>
<td>604:1045</td>
<td>56.5 yrs</td>
<td>50 yrs</td>
<td>34.5 months</td>
<td>25 months</td>
</tr>
</tbody>
</table>

Figure 1: Participating centers within the German NET-registry

Figure 2: Primary tumour localizations

Figure 3: Overall survival influenced by Ki-67 grading according to ENETS (a) and new cut off values (<5%, 6-20% and >20%, b)

Figure 4: Analysis of prognostic value of Ki-67 grading (a) and new cut off values (b) in pts. without metastases (limited disease, LD)

Figure 5: Analysis of prognostic value of Ki-67 grading (a) and new cut off values (b) in pts. with metastases at initial diagnosis (extensive disease, ED)

Figure 6: Influence of (a) Ki-67 grading according to ENETS and (b) new cut off values (<5%, 6-20%, >20%) on survival in pancreatic NETs.

Conclusions:
- Outcome of grade 1 and 2 NETs according to ENETS classification is often difficult to predict especially in low proliferative G2-NETs.
- Raising the cut off value for G1 tumours from a Ki-67 index <2% to <5% leads to a significant increase in prognostic value of Ki-67 grading between G1 and G2 tumours.
- These results suggest a modification of the cut off of value for G1 NETs.
- Especially for tumours with low proliferation rate additional reliable markers for prognostic stratification are needed.

References:
1 Jann H et al. Cancer 2011
2 Pape UF et al. Cancer 2008
3 Panazutto et al. Endocr Rel Cancer 2005
4 Scarpa A Mod. Pathol 2010

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