Distinct cut off values of Ki-67 index for NET-grading predict long-term outcome in gastrointestinal neuroendocrine (carcinoid) neoplasms

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Background:
Neuroendocrine neoplasms (NEN, formerly termed “carcinoid tumors”) form a rare and heterogeneous group of epithelial neoplasms1-7. Prediction of prognosis is difficult due to lack of reliable and widely accepted markers. Recently some clinical and histopathological factors proved to be of significant prognostic value8-7. Among them Ki-67 grading according to ENETS was shown to be a useful parameter for outcome stratification8-10. In some studies11,12 Ki-67 failed to differ significantly between G1 and G2 tumors, thereby aggravating prognosis prediction especially in NEN with low proliferative index. Thus, some authors11,12 claim that a cut off value of <2% for G1 tumors might be to low to accurately divide G1 from G2 tumors. They, hence, suggest a Ki-67 value of ≤5% for G1 tumors as a better cut off with greater prognostic importance11,12.

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).

Methods:
The German NET registry is a nationwide survey for gastrointestinal NETs which comprises data from patients (pts) with histologically proven NET diagnosed since 1999. Histopathological and clinical data as well as information on outcome results of 2009 patients with NET were collected by specifically trained study nurses by structured extraction from clinical source documents and entered into a data base (Lothmann & Birkner, Berlin, Germany) after informed consent had been obtained. Data analysis was performed after structured data extraction and statistical assessment using SPSS Version 15.0.

Results:

Table: Basic data in the German NET-registry
- number of cases: 2009
- time interval of initial diagnosis: 1999 - 2010
- female: male pts 964:1045
- mean age at initial diagnosis: 58.5 yrs
- median age at initial diagnosis: 58 yrs (14-93 yrs)
- mean follow-up: 34.5 months
- median follow-up: 25 months

Figure 1: Primary tumour localizations

Figure 2: Distribution of tumor classes in most frequent primary tumour localizations acc. to WHO 2000 (a) and ENETS/WHO 2010 (b)

Figure 3: Results of overall survival (a) and survival of histopathological classification according to WHO 2000 (b)

Figure 4: Overall survival influenced by Ki-67 grading according to ENETS (a,c) and new cut off values (<5%, 6-20% and >20%) (b)

Figure 5: Analysis of prognostic value of Ki-67 grading (a,c) and new cut off values (b,d) in pts with or without metastases (LD, a,b; ED, c,d)

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

Conclusions:
- Prognosis of NENs is based on histopathological classification according to WHO 2000/2010, grading according to Ki-67 index, and the extent of tumor load (staging, LD/ED) at initial diagnosis.
- Outcome of grade 1 and 2 NETs according to the ENETS classification is often difficult to predict especially in low proliferative G2-NETs.
- Raising the cut-off value for G1 tumors from a Ki-67 index ≤2% to ≤5% leads to a significant increase in prognostic value of Ki-67 grading between G1 and G2 tumors.
- These multicentric results confirm a suggested modification of the cut-off value for G1 NETs not only from the pancreas11,12 but from all primary localizations.
- Especially for tumors with low proliferative rate additional reliable markers for prognostic stratification are needed.

References:
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