

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

A. Rinke¹, S. Maasberg², N. Begum³, R. P. Baum⁴, P. Goretzki⁵, M. Anlauf⁶,
M. M. Weber⁷, S. Ezzidin⁸, B. Wiedenmann², U.-F. Pape²

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

¹ Dept. of Gastroenterology, Endocrinology & Metabolism, University Hospital Marburg, Germany, ²Med. Dept. of Hepatology & Gastroenterology, Charité Campus Virchow Clinic, Berlin, Germany, ³Dept of Surgery, University Hospital Schleswig-Holstein, Campus Lübeck, Germany, ⁵Dept. of Surgery, Lukashospital, Neuss, Germany, ⁶Institute of Pathology, University Hospital Düsseldorf, Germany, ⁷Dept. of Endocrinology and Metabolism, University Hospital Mainz, Germany, ⁸Dep. of Nuclear Medicine, University Hospital Bonn, Germany

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 value¹⁻³. 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 to 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 importance⁴.

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:

Figure 1: Participating centers within the German NET-registry



Table 1: Basic data in the German NET-registry

number of included cases :	2009
female: male pts	964:1045
mean age at initial diagnosis:	56.5 yrs
median age:	58 yrs (14-93 yrs)
mean follow-up:	34.5 months
median follow-up:	25 months

Figure 2: Primary tumour localizations

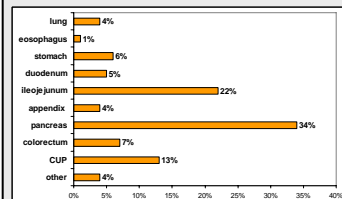
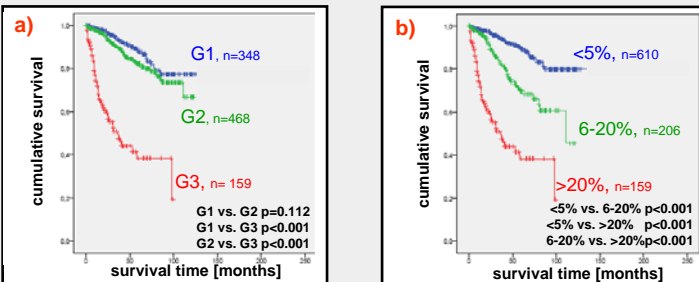


Figure 3: Overall survival influenced by Ki-67grading according to ENETS (a) and new cut off values (<5%, 6-20% and >20%, b)



References:

1 Jann H et al. *Cancer* 2011
3 Panzutto et al. *Endocr Rel Cancer* 2005

2 Pape UF et al. *Cancer* 2008
4 Scarpa A Mod. *Pathol* 2010

Acknowledgements:

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

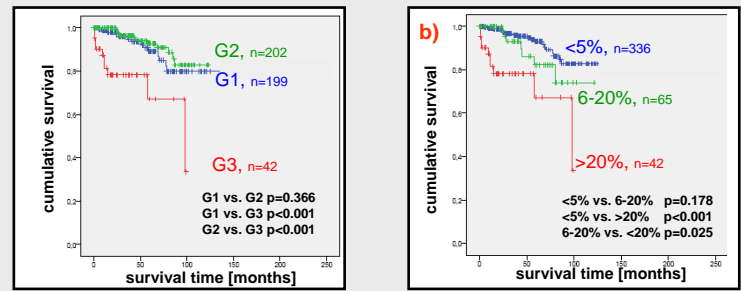


Figure 5: Analysis of prognostic value of Ki-67 grading (a) and new cut off values (b) in pts. with metastases at initial diagnosis (extensive disease, ED)

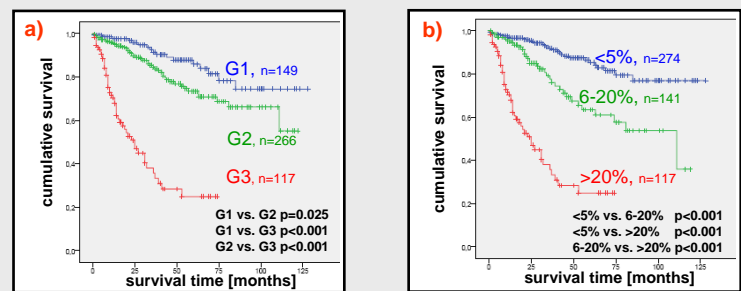
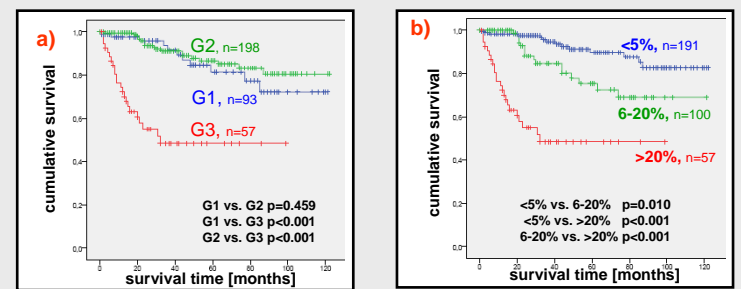


Figure 6: Influence of (a) Ki-67 grading according to ENETS and (b) new cut off values (<5%, 6-20%, >20%) on survival in pancreatic NETs.



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.

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 (Microsoft Access) after informed consent had been obtained. Data analysis was performed after structured data extraction and statistical assessment using SPSS Version 15.0.