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 neoplasms[1-7]. Prediction of prognosis is difficult due to a lack of reliable and widely accepted markers. Recently some clinical and histopathological factors proved to be of significant prognostic value[6,7]. Among them Ki-67 grading according to ENETS was shown to be a useful parameter for outcome stratification[1-10]. In some studies[11,12] Ki-67 failed to differ significantly between G1 and G2 tumors, thereby aggravating prognosis prediction especially in NEN with low proliferative index. Thus, some authors[11,12] claim that a cut off value of ≤2% for G1 tumours 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 importance[11,12].

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[9].

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 (Lohmann & 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 intervall of initial diagnosis:	1999 - 2010
female: male pts	964:1045
mean age @ inital diagnosis :	56.5 yrs
median age @ inital diagnosis:	58 yrs (14-93 yrs)
mean follow-up:	34.5 months
median follow-up:	25 months

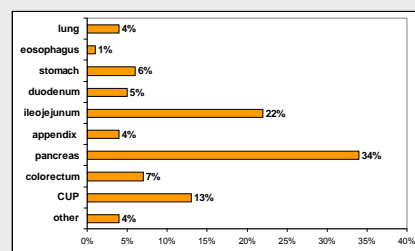### Figure 1:
Primary tumour localizations

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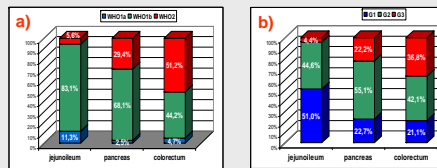

Figure 3:
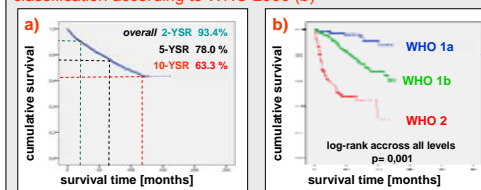Results of overall survival (a) and survival of histopathological classification according to WHO 2000 (b)

a) overall 2-YSR 93.4%
5-YSR 78.0 %
10-YSR 63.3 %

b) WHO 1a, WHO 1b, WHO 2
log-rank accross all levels p= 0,001

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

a) G1, n=348; G2, n=468; G3, n= 159
b) ≤5%, n=610; 6-20%, n=206; >20%, n=159

G1: ≤2%	G1 vs. G2 p=0.112	≤5% vs. 6-20% p<0.001
G2: 3-20%	G1 vs. G3 p<0.001	≤5% vs. >20% p<0.001
G3: >20%	G2 vs. G3 p<0.001	6-20% vs. >20% p<0.001

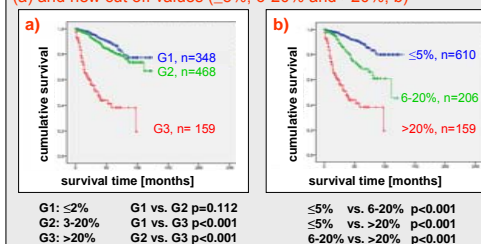### Figure 5:
Analysis of prognostic value of Ki-67 grading (a,c) and new cut off values (b,d) in pts. with or without metastases (LD: a,b; ED: c,d)

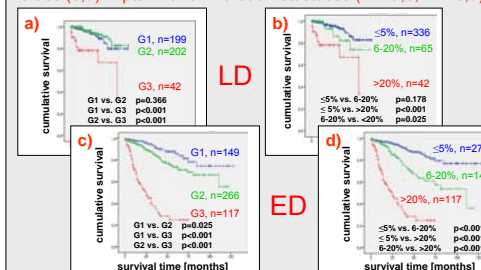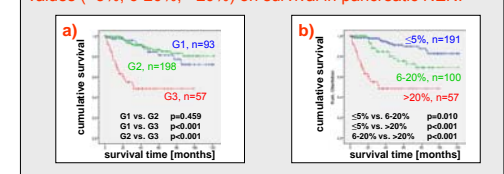a) G1, n=199; G2, n=202; G3, n=42   LD
b) ≤5%, n=336; 6-20%, n=65; >20%, n=42

G1 vs. G2 p=0.366	≤5% vs. 6-20% p=0.178
G1 vs. G3 p<0.001	≤ 5% vs. >20% p<0.001
G2 vs. G3 p<0.001	6-20% vs. <20% p=0.025

c) G1, n=149; G2, n=266; G3, n=117   ED
d) ≤5%, n=274; 6-20%, n=141; >20%, n=117

G1 vs. G2 p=0.025	≤5% vs. 6-20% p<0.001
G1 vs. G3 p<0.001	≤ 5% vs. >20% p<0.001
G2 vs. G3 p<0.001	6-20% vs. >20% p<0.001

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.

a) G1, n=93; G2, n=198; G3, n=57
b) ≤5%, n=191; 6-20%, n=100; >20%, n=57

G1 vs. G2 p=0.459	≤5% vs. 6-20% p=0.010
G1 vs. G3 p<0.001	≤5% vs. >20% p<0.001
G2 vs. G3 p<0.001	6-20% vs. >20% p<0.001

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 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 tumors.
➤ These multicentric results confirm a suggested modification of the cut-off-value for G1 NETs not only from the pancreas[11,12] but from all primary localizations.
➤ Especially for tumors with low proliferative rate additional reliable markers for prognostic stratification are needed.

References:

1 Rindi et al. *Virchows Arch* 2006   2 Rindi et al. *Virchows Arch* 2007
3 Heitz et al. *WHO* 2004   4 Klimstra et al. *WHO* 2010
5 Sobin et al. *UICC* 2009   6 Pape et al. *Endocr Rel Cancer* 2008
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