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Letter to the Editor

Prognostic impact of DNA-image-cytometry in neuroendocrine (carcinoid) tumours

To the Editor,

The report of Raatz, Böcking and Hauptmann [1] represents an excellent example of an in depth retrospective study on the influence of different clinicopathological parameters including static DNA cytometry on tumour prognosis illustrating the power but also some limitations of a comprehensive survival analysis in surgical pathology.

The authors studied in total 44 neuroendocrine (carcinoid) tumours of different localizations including in particular gastrointestinal neuroendocrine tumors from the middlegut (6 small intestine, 1 Meckel's diverticulum, 1 valvula Bauhini, 10 appendix, 4 appendix plus coecum, 2 colon ascendens), foregut (5 stomach, 3 papilla Vateri, 3 pancreas) and hindgut (1 colon transv./desc., 5 rectum) and few pulmonary carcinoids (3 bronchus). The H&E sections of all tumours were reviewed, classified according to the Soga and Tazawa classification (Soga and Tazawa 1971) defining 5 different growth pattern types (A solid/nodular, B trabecular, C tubular/acinar, D atypical, E mixed), immunohistochemically analyzed for NSE, Chromogranin, S-100 and peptide hormones somatostatin, serotonin, glucagons, gastrin and pancreatic polypeptide, assessed by the morphometric parameters mean nuclear area and form factor and finally DNA cytometry. In the latter analysis the parameters DNA stemlines (first and second), the 5c exceeding events (5cEE), the 5c exceeding rate (5cER), the 2c deviation index (2cDI), the DNA entropy, malignancy grade and mean content were evaluated. Finally the survival of each patient was assessed by review of the hospital files, sending questionnaires to the referring doctors and contracting the registrars' office. Thus, a plethora of information was collected for a large collective of this rare tumour type, the investigations were carefully performed and thoroughly analyzed and therefore the authors first of all need to be congratulated for their very comprehensive study.

This is particularly true considering the important finding that the DNA cytometry parameters 2cDI, the 5cER, the DNA malignancy grade and entropy (each with at least $p < 0.005$), the pattern type of the DNA histogram as well as the form factor and an increased mean nuclear area were significantly associated with a higher mortality in the univariate analysis. The importance can not be overemphasized considering the fact that previous ploidy studies being well reviewed in the paper have shown conflicting results regarding the impact of DNA measurement on the prognosis of neuroendocrine tumours. In addition, other clinicopathological parameters like poor differentiation or globlet cell type ($p < 0.00001$), histological type, infiltrative growth, local recurrence, type of operation (curative/endoscopic versus palliative), localization in the jejunum or ileum and age over 55 years were each significant parameters for a higher mortality.

On the one hand, the high number of significant findings underscores the importance of the study. On the other hand, it also represents its main dilemma because not all parameters can be simultaneously incorporated into the multivariate analysis due to the limited number of cases. This limitation being inherent to many similar retrospective studies is clearly expressed by the authors. Still, it represents the only shortcoming of the report because in the abstract the quite broad and in the result section not sufficiently well documented statement is made that the only independent risk factor was the histological differentiation. This is probably due to the high probability value attributed to poor differentiation. However, neither the criteria for defining the differentiation grade were well documented in the paper neither the authors' experience in its reproducibility were adequately discussed. Similarly, it would have been very interesting to investigate the correlations between the different DNA cytometry and morphometry parameters on the one side and the clinical parameters on the other side to potentially reduce the number of parameters to be entered into the Cox-model. For instance, one might speculate that the cases with higher 5cEE/5cER correlate with those which carry an increased nuclear area. If this is true this might have the practical consequence to incorporate the increase or variability of nuclear size as a

parameter for histological differentiation. Furthermore it would be very interesting to know whether the combination of the different significant DNA cytometry parameters would increase the prognostic impact. In principle, one might expect that DNA ploidy as a quantitative measure should be superior to the semiquantitative evaluation of histological differentiation. In this regard, a statement of the authors with regard to a potential ambiguity in the distinction of cases with pattern 1 DNA histograms (i.e. those with a single DNA stemline near 2c and "only few values at 4c") and pattern 2 ("smaller" stemline around 4c) DNA histograms would be desirable. Finally, a precise statement is missing which of the Soga & Tazawa subtypes correlated with poor prognosis.

Overall, this is a very interesting and important study that underscores the power of DNA measurement in tumor characterization, the complexity of the detection of aneuploidy and the need to define stringent criteria for specific tumor types.

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[2] J. Soga and K. Tazawa, Pathologic analysis of carcinoids. Histologic reevaluation of 62 cases, *Cancer* **28** (1971), 990–998.