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Letter to the Editor

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

To the Editor,

First of all the authors would like to thank Dr. Petersen for his comments on our study on neuroendocrine tumors [1,2]. We are of course aware of some shortcomings, that is to say, the limited number of patients, its retrospective nature, and finally the Soga/Tazawa classification we used. The Soga/Tazawa class "D" that comprise the poorly differentiated (or high grade) cases had a worse prognosis. To identify these cases we strictly adhered to the criteria described [3]. Although we did not perform a kappa analysis (there were only 7 cases within this category) we felt that there was no problem in detecting them. Today I would classify these tumors as well differentiated neuroendocrine carcinomas simply due to their mitotic activity and invasion. The explanation that histological differentiation (e.g. type "D") is the only independent risk factor refers to Table 3 of the paper. Two parameters were remaining within the model that had higher p-values than the type of tumor: (i) the state of the surgical margins, and (ii) recurrent disease. In both cases we did not need any further information because an incomplete resection will almost always be associated with recurring disease, and whenever that occurred we already knew that we were dealing with a progressive disease. What we meant is that tumortype is the single independent morphological parameter (with a $p = 0.009$ and a RR of 35.24).

I agree that it would have been interesting to calculate the correlation between morphometric, DNA-cytometric and clinicopathological data. Though we have looked for associations between every single parameter (morphometry; DNA-cytometry) and clinicopathological data we feel that our clinical data are – apart from survival – also the most unreliable parameters. Though we made an effort to gather as much information about our subjects as possible one needs to be aware that the widely varying clinical course the tumour can take is also strongly reflected in the varying and broad spectrum of clinical investigations which were undertaken – or not – after diagnosis. Given this very diverse follow-up with tumours from varying locations trying to establish correlations in this small study population one wonders whether such a link can truely be found given the design of the study. Looking at our data with hindsight we feel that our assertions regarding associations would stand on much firmer grounds if we had used a different statistical test though. As you can see in Table 2. The numbers are sometimes very low in the 2×2 tables and really one should use the Fisher-Exact-Test in these cases as the Pearson Chi-Square-Test is unreliable. Given that context it would have been even more interesting if we had looked for correlations. The finding of a "dose-response-effect" would have done even more to strengthen our suppositions. The Tarone-Ware-Test on the other hand gives a conservative estimate of association so that we were more likely to underestimate associations found in the survival curves than overestimate them. Given that survival was also the most unambiguous clinical parameter these results are the most reliable and important from our point of view. Another question was on the impact of factor combination to increase prognostic information. There are plenty of examples in literature showing that factor combination might be of value in certain tumor entities. In our study the most important DNA parameter was 5cEE. All these cases with 5cEE > 3 had a type III DNA histogram and a 2cDI > 0.4, and were, therefore, interrelated. Finally, the ambiguity in distinction of DNA histograms was questioned. Well, that was certainly justified since interpretation and classification of histograms will always bring some subjectivity into an otherwise objective field. But this is a problem of DNA cytometry in general and so the classification scheme proposed by the 4t ESACP consensus conference is a good compromise. Our histogram types could easily be translated into the ESACP categories and a definite classification was possible in all our cases.

Taken together, the aim of our study was to investigate whether an objective method like DNA image cytometry could be of help assessing prognosis in patients with neuroendocrine tumors. The answer is: yes, though at the moment only as supplement, because the tumors with worse prognosis belong to the group of

well differentiated neuroendocrine carcinomas. However, as already mentioned, the number of cases in this study was small. It may well be that this method holds the potential to be helpful even in tumors we would currently classify as well differentiated neuroendocrine tumors. A prospective study, or a confirmation of our results by a much larger retrospective trail would be desirable.

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