Reviewer's report

Title: Evaluation of DNA ploidy in relation with established prognostic factors in patients with locally advanced (Unresectable) or metastatic pancreatic adenocarcinoma: A retrospective analysis

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Reviewer: Peter Buchler

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In the presented study, the authors evaluated the prognostic significance of DNA ploidy (content) in patients with pancreatic cancer. Overall the authors examined twenty two potential prognostic variables in 226 patients with proven pancreatic cancer diagnosed between 1997 and 2003. The authors reported a mean survival time of 9.6 month (median survival 6.75 month) and found ten factors by multivariant analysis with an independent effect on survival (performance status, local extension of tumor, distant metastasis, ploidy score, anemia under epoetin therapy, weight loss, pain, steatorrhoea, CEA and treatment modality (surgery plus chemotherapy). Furthermore the authors report that patients, who were treated with palliative surgery and chemotherapy had a 6.7 times lower probability of death in comparison with patients without any treatment. The probability of death was 5 times higher for patients with a ploidy score > 3.6 and 6.3 times higher with a ploidy score 2.2-3.6 compared to patients with a ploidy score <2.2. From these data, the authors concluded, that survival was improved by surgery and chemotherapy and the presence of a low DNS ploidy score.

Without any doubt this is an interesting study with a topic of highest clinical relevance: identification of prognostic factors in pancreatic cancer. This study, however, has several major drawbacks. It is an entire retrospective study and patients were recruited from 5 different institutions. Nothing is mentioned on the treatment algorithms used by these 5 institutions during the trial period. For example, it is highly unlikely that erythropoietin therapy was given to a relevant number of patients. In this overall small and highly heterogeneous collective the authors aimed to analyze 22 parameters which may impact survival. In summary this study is interesting but based on the retrospective character of the trial and the minimal clinical information available this manuscript appears too speculative and too preliminary with regard to any conclusions to be drawn.

Comments

1. The authors state that all patients had unresectable disease in this study but palliative surgery was done in 52.7% of these patients. First the authors have to define what kind of palliative procedures were performed. Based on the assumption that palliative surgery consisted of a hepatico-jejunostomy and a gastro-jejunostomy it is likely that these patients had resectable disease in the preoperative CT-scans, otherwise the indication for surgery would be unusual. On the other hand this procedure is risky if the patients have extensive liver
metastases and sometimes can not be done in the case of severe peritoneal spread. Therefore, there are likely two populations in this study which simply can not be compared based on tumor load. One population is the primary metastatic collective on primary imaging precluding them from surgery and the other collective, that appeared resectable on pre-operative imaging but turned out to be not resectable intraoperatively. The authors have to invest more accuracy to better characterize the collective in this study.

2. Since all patients had nonresectable disease, why did only 62.9% receive chemotherapy? What was the rationale for indicating chemotherapy? This number likely reflects heterogenous therapy approaches.

3. Regarding the determination of DNA content it seems likely that the authors analyzed DNA ploidy in metastatic lesions and primary tumors as well, since pancreatic cancer is difficult to diagnose with FNA derived from the primary tumor. The authors have to demonstrate the numbers of metastatic lesions and primary tumors. It is likely that metastatic lesions had different DNA ploidy scores when compared to primary lesions. What was the scientific evidence to choose the cut-off levels for ploidy scoring.

4. Tumor sampling using FNA usually does not result in large tissue samples. To obtain 100-200 tumor nuclei one requires a different sampling approach rather than FNA.

5. It is hard to believe that DNA ploidy is homogeneous within a tumor sample. The author should provide the degree of variation found within single tumor specimens. What was the method used to grade a sample as poly-ploid. How did the authors differentiate mitotic figures from ploidy per se.

6. The survival cures of patients demonstrating surgery and chemotherapy compared to the other treatment modalities appears statistical significant. Once again, this is scientifically not valid since these are two entire different populations. The authors should provide detailed numbers of patients in each of the groups.

**Level of interest:** An article of limited interest

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.