Reviewer's report

Title: COX-2 overexpression in resected pancreatic head adenocarcinomas correlates with favourable prognosis

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Reviewer: Claudio Avellini

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The paper “COX-2 overexpression in resected pancreatic head adenocarcinomas correlates with favourable prognosis” offers an absolutely well-defined question, concerning the relationship between COX-2 expression and the biological behaviour of neoplasia at pancreatic head level. The methods are appropriate and accurately described, both from the technical and from the statistical analysis point of view. Title and abstract are exhaustive (and the title is somewhat rightly provocative).

There are two main issues in this paper: the first concerns the role of COX-2 as a putative prognostic marker; the second is based upon the different topographical and histological types of adenocarcinoma in this site. The concept of contrasting results in the Literature about COX-2 expression and prognosis is well underlined, the Literature has been extensively reviewed and technical issues about different results are correctly analyzed, both in methods section and in discussion.

In particular, the microarrays used in the study by Matsubayashi are not comparable with this paper’s methods. The kind of variability in COX-2 reactivity throughout the same neoplasia does not allow an adequate evaluation with tissue microarrays. Probably, 5 HPF carefully chosen on the basis of an adequate neoplastic component are hardly enough to obtain reliable data; on the other hand, the criteria to define the overexpression of COX-2 are strict and reliable.

Other positive elements are the significant dimension of the series, the relatively recent material (which guarantee a good antigenic preservation), and chiefly the absence of lost patients to follow up.

All these considerations underline the adequacy of data and the adherence of the manuscript to the relevant standards for reporting and data deposition.

It is interesting to argue about the role of COX-2 in the initiation of neoplastic process, with following disappearance or reduced expression, with a possibly strict relationship with the differentiation grading.

As far as the site of tumor origin is concerned, the review of data and of slides for ampulla, distal bile duct and pancreas (ductal origin) and for differentiation of histological subtypes has been described in methods section. Probably, some
more detail about morphological parameters to define these two data group could be useful.

Nevertheless, it is interesting the relationship between COX-2 expression and these groups of lesions: similar percentages of COX-2 reactivity in the three topographical groups and more frequent reactivity in cases with intestinal type differentiation suggest a complex relation between COX-2 and histological grading: ampullary cancers with intestinal differentiation show significantly favourable prognosis. It is intriguing the absence of significant correlation between COX-2 expression and intestinal type of differentiation. The question is: is COX-2 associated with specific cellular type or environmental molecular factors induce its expression at the beginning of tumor development? Furthermore, could COX-2 expression be simply a marker of good differentiation without a real role from the prognostic point of view?

Recent evidences, cited and discussed in this paper, show a complex role for COX-2, which can exert an indirect role favouring tumor initiation and progression, can be replaced by other pathways activating PI3K/Akt, can be epigenetically silenced, disappearing from neoplastic cells (or from some of them).

These and other observations could be a source of ideas to answer some questions about conflicting data in the Literature and the relation between COX-2 expression, grading and prognosis. The good balance of the discussion is evident: probably some more considerations could be useful concerning COX-2 +/poor differentiation and COX-2 -/ high differentiation, showing an “intermediate behaviour with respect to survival”.

Finally, further studies could shed light on an hypothesis of progressive disappearance of COX-2 expression parallel to tumor dedifferentiation.

In conclusion, this paper is very interesting and well performed, acceptable for publication. My observations fall in the category of discretionary revisions.

There are some typing errors and a small inaccuracy:

- page 3, row 15# COX-2
- page 4, row 2# “pancreatic parenchyma ductal structure” (better than “pancreatic tissue”)
- page 6, row 5# pancreatobiliary
- page 12, row 14#... an intrinsic....
- page 13, row 15# ...explain....
- page 21, table 2# Multivariate

**Level of interest:** An article of importance in its field
Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:

'I declare that I have no competing interests'