Reviewer's report

Title: Combined immunohistochemistry of beta-catenin, cytokeratin 7, and cytokeratin 20 is useful for differential diagnosis of lung cancer

Version: 2 Date: 19 August 2005

Reviewer: Tibor Tot

Reviewer's report:

General

The manuscript has improved as revised, but there are still several points to correct, thus further revision is needed.

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Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

1. The title: it is now shortened, but misleading; "differential diagnosis of lung cancer" means to discriminate the different types of primary lung cancer, squamous from adeno etc. Suggestion: "Combined immunohistochemistry of beta-catenin, cytokeratin 7 and 20 is useful in discriminating primary lung adenocarcinomas from metastatic colorectal cancer".

2. The abstract has to be rewritten:
   - "differentiation" means either grade (e.g. poorly differentiated) or type (e.g. squamous differentiation) in relation to tumor pathology. Use the word separating or discriminating.
   - Please delete all the sentences focusing on the single needle biopsy; it may indicate a very limited experience in the field of lung pathology

3. Methods: It is clearly an improvement compared to the original manuscript that the authors use the WHO classification and states the frequency of the relevant thoracic operations on their institution. However, my criticism aimed to find a reason for the limited number of the studied cases. And this reason has not been found yet: 11 of the 38 primary acinar lung adenocarcinomas were studied, 19 of the 33 colorectal metastases and 10 of 725 primary colorectal tumors. Why not all 38 and 33 cases? How the 19, the 11 and the 10 cases were selected? Are they at least consecutive? The numbers tell the reader that this is not a prospective, planned study but a retrospective test of an idea.

4. The authors have, unfortunately, completely misunderstood my comment on cytokeratin phenotype of lung cancer. The comment was "It would be of value to describe shortly the other types of lung adenocarcinoma and their beta-catenin - CK20/7 phenotype, as there are considerable differences between them. Especially, primary lung adenocarcinomas similar in their CK phenotype to colorectal cancer, have to be discussed."

It means that, as both the authors and this reviewer know, most of the lung adenocarcinomas are CK20-/CK7+. However, there are CK20+ primary lung adenocarcinomas, especially among the mucinous bronchioloalveolar lung cancers (see Saad RS et al. Am J Clin Pathol 2004:122(3):421-7). The present study was focused on the acinar lung adenocarcinomas (of for us unknown reason !) thus escaping the real challenge of comparing bronchioloalveolar cancers to colorectal cancers.
Further, in a study like this, which is focused on a very selected segment of immunohistopathology (one subtype of primary compared to a single source of metastasis) the reader would expect that the authors are familiar with and make comment on “pulmonary intestinal-type adenocarcinoma”, a very infrequent type of primary lung adenocarcinomas but representing the real diagnostic problem in this field.

Otherwise, choosing lung acinar adenocarcinomas to compare to colorectal cancers is the easiest way of getting significant results; if you have chosen all kinds of the lung primary adenocarcinomas to compare to all kinds of metastatic adenocarcinomas (as in the real clinical practice), the study would become much more complex and the results much less straightforward.

5. A thorough language editing is still a must before the manuscript could be properly understood and accepted.

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Minor Essential Revisions (such as missing labels on figures, or the wrong use of a term, which the author can be trusted to correct).

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Discretionary Revisions (which the author can choose to ignore)

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What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Not suitable for publication unless extensively edited

Statistical review: No