Reviewer's report

Title: Angiogenesis in Cancer of Unknown Primary: Clinicopathological study of CD34, VEGF and TSP-1.

Version: 1 Date: 13 January 2005

Reviewer: frank A greco

Reviewer's report:

MAJOR COMMENTS:

The authors have studied the paraffin section biopsies on patients with unknown primary cancer looking at the tissue expression of VEGF and TSP-1 as well as determining the MVD. This has been correlated to whether the patients fell within a more prognostically favorable or unfavorable group. The authors have definitively demonstrated that VEGF expression is universal in these patients and was strong in a large majority of patients (83%). They also showed that TSP-1 was frequently expressed, although strong in only 20%. There was no clinical or pathologic association with these protein expressions. However, tumor MVD was higher in the tumors of patients classified with unfavorable prognosis versus those with a more favorable prognosis. Although the authors conclude in the first sentence in their Abstract (in Conclusions) that their findings indicate that angiogenesis has a central role in the biology of cancer of unknown primary site, I believe that they should be more conservative by rephrasing this by deleting the word "central". In the last paragraph of their Discussion, the second sentence should be deleted ("This data add up to the understanding of biology of these tumors"). Their data do not support this conclusion. Certainly, their findings are of interest and would support VEGF targeted therapy in this clinical setting. Their data, however, do not address nor prove that this is a central feature in the biology of these cancers compared to other cancers, and does not really address specific genetic changes unique to these tumors. The authors need to add a brief paragraph in the Discussion section discussing the extreme heterogeneity of patients with unknown primary cancer. Although it is certainly important to group these patients in reference to biological and therapeutic studies, there are certain subsets of patients that clearly are different than others. Many of the patients in their "favorable" prognostic group are now known to have a distinct clinical biology and are relatively unique compared to others who are also classified as unknown primary cancer. These include young patients with midline tumors, women with peritoneal carcinomatosis or isolated axillary adenocarcinoma, and those with neuroendocrine tumors. The first 3 groups contain patients with extragonadal germ cell tumors, primary peritoneal carcinoma, and occult breast cancer. All these patients are now known to be distinct compared to the usual patients with unknown primary cancer. The authors need to address this issue. The inclusion of these subsets of favorable patients, many with known lineage and clinical biology, make the whole series less homogenous and therefore the results and conclusions could be quite variable.

MINOR COMMENT:

Reference 16 is incomplete and needs a citation.
Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)

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

Discretionary Revisions (which the author can choose to ignore)

What next?: Accept after minor essential revisions

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being published

Statistical review: No

Declaration of competing interests:

"I declare that I have no competing interests"