Reviewer's report

Title: Chance mechanisms affecting the burden of metastases

Version: 1 Date: 1 August 2005

Reviewer: Steven Frank

Reviewer's report:

General:

As far as I understand the paper, the following describes the main point. Biologically similar tumors may give rise to highly variable numbers of metastases or a highly variable volume of metastatic burden. Therefore, metastatic burden may not provide a good measure of the biological characteristics of a tumor, including future potential metastatic development. This is important because metastatic burden is often used to classify tumors and determine the course of clinical treatment.

I have a mixed opinion. On the one hand, it is likely that replicates of an identical tumor would give rise to variable metastatic burden, as has been shown in animal experiments. Thus, metastatic burden is not a precise measure of future metastatic potential. On the other hand, it is also likely that some tumors do differ in both observed metastatic burden and in future metastatic potential, and that observed burden is positively correlated with potential.

The real issue is that metastatic burden is partly explained by biological properties of the tumor and partly explained by chance events. To understand how to use observed metastatic burden in treatment, one must understand the relative importance of the deterministic and stochastic components.

The author makes this point about how deterministic and stochastic components contribute to metastatic burden. However, the paper is devoted to showing that stochastic processes alone could in theory explain the observed distribution of metastatic burden.

The distributions of many biological outcomes can often be fit to purely stochastic distributions, because the aggregation of several deterministic processes operating at different scales leads to a limiting stochastic distribution. That is why, for example, height and weight often follow the normal distribution, even though individual genotypes may determine a significant fraction of the variation. So, the fact that a stochastic distribution can be fit to the observed distribution of metastatic burden, as shown in the paper, does not by itself provide much insight.

In the end, the paper makes an important point that is likely to be true: metastatic burden has a significant stochastic component. However, the analysis and presentation does not provide any insight into how we can estimate the fraction of the observed variation ascribed to stochastic processes and the fraction of the variation ascribed to biological properties of the tumor. So, the paper provides a useful warning about stochasticity in metastatic burden, but the actual analyses could be made more useful and be explained more clearly.

---------------------------------------------------------------------------------

Major Compulsory Revisions (that the author must respond to before a decision on publication can be reached)
The author should address the points above either by appropriate revision or by providing a counter-argument in defense of the current approach.

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

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** No

**Declaration of competing interests:**

I declare that I have no competing interests