Author’s response to reviews

Title: Does Colon Cancer Ever Metastasize to Bone First? A Temporal Analysis of Colorectal Cancer Progression.

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Version: 2 Date: 6 July 2009

Author’s response to reviews: see over
Dear Dr. Alam,

Thank you very much for the constructive comments from your reviewers and yourself, which we believe will substantially improve the manuscript. We appreciate the opportunity to address the comments in a revised manuscript. We have made the changes described below and await your decision on the revised manuscript. Thank you for your consideration.

Sincerely,

David Q. Wan, MD

Comments from the Associate Editor:
This manuscript concerns a retrospective analysis in 252 colon cancer patients who had PET and CT, or PET/CT to determine the time interval of bone metastasis from hepatic and pulmonary involvement. The topic is interesting. However, there are several limitations which need to be addressed before the paper can be considered for publication. For instance, it was not clear whether patients received adjuvant chemotherapy or received treatment for metastatic disease?

Response: Most of the patients initially received adjuvant therapy, and those are the therapies listed in Table 1. Patients with metastases also received therapy directed at the metastases, and those treatments are listed on page 5.
How was the time to development of metastatic disease determined? Was it based on time from initial diagnosis?

**Response:** Time to development of metastatic disease was defined as time from initial diagnosis to the appearance of metastasis in imaging studies. We added this explanation to the manuscript on page 5.

What fraction of patients had PET scans?

**Response:** In our clinic, PET or CT is recommended for all colon cancer patients for staging/restaging or monitoring therapy. Some of our patients do not have PET or CT scans because of conflicting clinical issues or (more commonly) insurance status, and these patients were not included in this study.

I assume Kaplan Meier statistics was performed; this should be detailed in the statistical analysis section.

**Response:** We did not perform Kaplan Meier analyses because we were not examining survival.

The manuscript also needs to be revised for language corrections and clarity before publication.

**Response:** The revised manuscript was reviewed by two scientific editors, who made suggestions to improve its language and clarity.
Reviewer’s report # 1  
Version: 1 Date: 15 April 2009  
Reviewer: J E Tepper

Reviewer’s report:
This is an inherently flawed analysis. Using a database of patients who had PET scans produces an enormous bias in the results, so that the conclusions are probably not justified. If patients are referred for a PET scan there was probably a reason. It is not generally accepted practice to do routine screening PET scans in followup for a colon or rectal cancer. Thus, for example, if there were clear evidence of bone disease from clinical and standard X-ray criteria there would likely not have been a reason to obtain a PET scan. Valid information on the incidence of specific types of metastatic disease simply cannot be obtained with this type of database and analysis.

Response: In our clinic, PET or CT is recommended for all colon cancer patients for staging/restaging or monitoring therapy. Some of our patients do not have PET or CT scans because of conflicting clinical issues or (more commonly) insurance status, and these patients were not included in this study. This is stated on page 4 of the manuscript. Our clinicians prefer to perform PET scans even of patients with clear clinical or X-ray evidence of metastasis because PET scans are better for monitoring the effects of therapy.

The data on therapy (and some other issues) is very unclear. Did most of these patients receive adjuvant therapy or was the therapy listed for metastatic disease?

Response: Most of the patients initially received adjuvant therapy, and those are the therapies listed in Table 1. Patients with metastases also received therapy directed at the metastases, and those treatments are listed on page 5.

When time to development of metastatic disease (and similar) are listed, is that from the initial diagnosis, time of therapy initiation, time of PET scan or when?
The standard would be from time of diagnosis, but that is not stated and the time
to liver metastases seems very short compared to other data.

**Response:** Time to development of metastatic disease was defined as time
from initial diagnosis to the appearance of metastasis in imaging studies. We
added this explanation to the manuscript on page 5 and page 8.

Much of the information presented contradicts other information in the literature.
There is good evidence that surgical resection of isolated lung mets produces
results as good as resection of isolated liver mets, and that this event is relatively
common.

**Response:** The percentages of lung and bone metastases are in line with the
literature. The percentage of liver metastasis is lower than in early studies,
probably because of most of our patients were eligible for surgery. Most of our
patients with lung and liver metastases had multiple lesions (solitary liver lesions
were more common than solitary lung lesions).

It really was not very clear what the authors were trying to determine. The stated
purpose cannot be learned from this analysis

**Response:** We tried to determine that lung metastasis has the shorter time
span and is more concurrent with bone metastasis than liver metastasis does.
We revised the results section, Table 2, and Table 3 in order to be more specific
in results.

No information is specifically given on followup. The implication is that they had
100% followup on all patients, but this seems extraordinarily unlikely

**Response:** We surveyed the colon cancer patients from diagnosis to serial
imaging time periods. The average follow-up time after diagnosis was 38
months with average 3.04 imaging reports per patient. We focused on the
temporal pattern of organ metastasis. We only collected the survival data for
patients with osseous metastasis.
The English is poor, making it seem like the authors never read the paper prior to Submission.

**Response:** The revised manuscript was reviewed by two scientific editors, who made suggestions to improve its language and clarity.
Reviewer’s report # 2

Title: Does Colon Cancer Ever Metastasize to Bone First? A Temporal Analysis of Colorectal Cancer Progression.

Version: 1 Date: 15 April 2009

Reviewer: Tzu-Chen Yen

Reviewer’s report:
The enormous potential of FDG PET in oncology has become evident in recent years, though it started as a diagnostic tool. The present study further expands the possible roles of FDG PET in cancers progression and may benefit for clinicians from an equivocal or an unusual lesion observed by FDG PET. My overall impression is that the study is carefully thought out and that the manuscript is well written and prepared thoroughly, especially for a medical student. Therefore, my comment is no need for revision.

Response: Thank you for your kind comments.
Reviewer’s report # 3
Version: 1 Date: 27 April 2009
Reviewer: Simona Ben-Haim

I have the following remarks for the discussion:

1) Page 11 last sentence: is the entire brain routinely imaged in your institution? Otherwise, you may want to rephrase this sentence.

Response: Our PET/CT imaging protocol does not include the brain, because PET has low sensitivity for detecting brain tumors. So, we did not assess brain metastases. We clarified this sentence on page 11.

2) A major limitation is the retrospective nature of the study. This should be added to the discussion

Response: We agree that the retrospective nature of the study is a limitation of the study because the imaging modality at each time point varied among patients and the patients were only followed during the imaging periods, but we feel that the information available from the existing data is useful to the clinician and so worth publishing. In the revised manuscript, we have stated this on page 13 to 14.
Reviewer's report # 4
Version: 1 Date: 11 May 2009
Reviewer: Bert H O'Neil

Major compulsory revisions
Overall, this was a good project for a medical student, but the quality of the manuscript suggests insufficient mentoring on this project. The paper is interesting, but requires extensive revision for clarity.

Response: We revised the manuscript according to the reviewers' comments. The revised manuscript was also reviewed by two scientific editors, who made suggestions to improve its language and clarity.

I have difficulty understanding the meaning of the times to development of lung and bone mets stated in the results. This is partly due to the fact that the fraction of patients who had serial PET scans is never noted. Also the group appears to be heterogeneous in terms of when in their disease course they were referred for PET. If all times were based on ascertainment of the initial time of diagnosis, this needs to be stated in the methods.

Response: We revised most parts of results section to be clear that all time calculations were based on the initial time of diagnosis (page 8). We stated the patient's data from serial PET scans in section of Methods (page 4). We added staging information in Table 1.

A large number of patients included in the ‘n’ are non-informative because they never experienced recurrence at all. What is the point of including this mix of patient stages? I would suggest calling the denominator the number of patients who presented with or subsequently developed metastatic disease.

Response: We agree that including patients without metastases is not useful for determining the order and timing of metastasis to specific organs. However, to evaluate the incidence of bone metastasis, we had to include all the patients.

Minor essential revisions
Abstract- The results section does not make sense and needs to be revised
Response: We apologize and have made the Results section of the abstract clearer.

Beginning with the abstract, the use of the term “pure” throughout the paper is inaccurate and should be changed to a better descriptor such as “isolated”
Response: We replaced “pure” bone metastasis and the like with “isolated” and “metastasis to bone only.”

Methods- statistical methods need to be more detailed, for example do not account for Kaplan-Meier statistics.
Response: We have added more detail on the statistical methods used. We did not perform Kaplan-Meier survival analysis because we were not studying survival.

Also, stage at presentation and surgical therapy needs to be presented in table form in the results.
Response: Stage at presentation and surgical therapy were added, in Table 1.

On page 7, beginning on the 7th line from the bottom, sentence beginning “Lung to bone took…” Please revise this sentence for clarity.
Response: We change the sentence (now on page 8) to read: “The average time from liver to bone involvement was 8.3 months (+13.4, CI 0.6-15.9), and the average time from lung to bone involvement was 3.3 months (+4.2, CI 0.7-5.9).”