Reviewer's report

Title: Eukaryotic Initiation Factor 4E (eIF4E) and Angiogenesis: Prognostic Markers for Breast Cancer

Version: 1 Date: 30 August 2006

Reviewer: Quyen Chu

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General

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

1. The authors wrote in the abstract that "when eIF4E, histological grade, and tumor stage were included in a multivariate Cox regression analysis, eIF4E emerged as an independent prognostic factor (p=0.03) along with grade and stage, but lost its independent prognostic value after the inclusion of angiogenic factors in the model". However, in the body (pg. 11) as well as in Table 5, this was not the case.


3. Authors need to state whether these patients had received adjuvant therapy (i.e. chemo, hormonal, XRT)

4. Authors need to show the median survival and the estimated 5-year survival for the entire group as a whole as well as for each individual prognostic markers. In this manner, it will allow the readers to compare the authors' patient cohorts with the readers' own cohorts of patients to make sure that outcomes are what would be expected for treated patients.

5. Authors included a significant proportion of stage IV patients (almost 20%. This may likely skew the data and this needs to be addressed. Would you still reach the same conclusions had these been excluded. In multiple prospective trials conducted by Dr. Benjamin Li's group at Louisiana State University Health Sciences Center-Shreveport (Ann Surg 2002;235:732-9, Ann Surg 2005;242:584-92, Surgery 2006;140:161-9, Ann Surg 2006;243:684-92), stage IV patients were specifically excluded. Their papers need to be included in the discussion and the authors' data need to reflect theirs with these.

6. Authors included a cohort of DCIS, LCIS and the more uncommon invasive subtypes such as invasive lobular carcinomas, medullary carcinomas, tubular carcinomas. These generally behave differently and given the fact that they make up almost a third of the studied population (35%), it makes one wonders whether the same conclusions can be arrived at if they were excluded. Although the authors may not want to redo the calculations, this weakness needs to be acknowledged.

7. Authors have almost 64% of patients with nodal disease. This is higher than expected and therefore needs to be addressed. Is it due to the inclusion of stage IV patients? Although Cox proportional hazard ratio demonstrated that eIF4E was an independent predictor, despite nodal status, this still needs to be stressed to make the paper stronger.

8. We know that, despite all molecular, clinicopathologic parameters evaluated, nodal status remains the most important prognosticator (Silverstein et al, World J Surg 2001;25:767-72, Jatoi et al, J Clin Onc 1999;17:2334-40). Yet, the authors demonstrated a "borderline significance for overall survival" and no significance for disease-free survival. Needs to explain why this was the case

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

1. Authors need to review p-value numbers. There are discrepancies between what was quoted in the abstract and in the body and table. Under the abstract results section, the authors write,
   a. "A significant relationship was found between the level of eIF4E and histological grade (p=0.008)", yet the body text on page 9 quoted a p=0.016.
   b. "VEGF, IL-8, and MVD were closely related to tumor grade (p=0.005 -vs- 0.003 , p=0.015 -vs- 0.011, and p<0.001, respectively) and clinical stage (p=0.04 -vs- 0.007, p=0.02 -vs- 0.034, and p<0.001) (The second p-values following the above p-values are what were quoted in the body/table).

2. page 6 at the bottom has the following typos: " Staining was graded in a four grade classification as follows: -, for those).

3. On page 9, under Correlation of eIF4E, VEGF, IL-8 and MVD with clinicopathologic parameters section, the second to the last sentence, the p-values were not consistent with what was written in the table (e.g.
"We also found that VEGF and IL-8,... (p=0.003 and p=0.001 vs 0.002 in table) and (p=0.007 and p=0.034 vs p=0.048 in the table, respectively).
4. Table 5. the p-value for eIF4E was written as 0.000. Need to either state <0.001 or include another number at the end.
5. Figure 4B, need to write (months) in the x-axis, following the title Disease-Free Survival

What next?: Accept after minor essential 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