Author's response to reviews

Title: Association Between Delayed Initiation of Adjuvant Chemotherapy and Survival in Breast Cancer: A Systematic Review and Meta-analysis

Authors:

Ke-Da Yu (yukeda@163.com)
Sheng Huang (coldfish1222@163.com)
Guang-Yu Liu (liugy1975@yahoo.com.cn)
Zhi-Ming Shao (zhiminshao@yahoo.com.cn)

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Author's response to reviews: see over
Dear Senior Editor,

Please re-consider our manuscript "Association Between Delayed Initiation of Adjuvant Chemotherapy and Survival in Breast Cancer: A Systematic Review and Meta-analysis" for publication in *BMC Med.*

We have removed the single-institution study from the manuscript according to the editor's suggestion.

On June 4, 2011, JAMA published a review by Biagi et al titled as “Association Between Time to Initiation of Adjuvant Chemotherapy and Survival in Colorectal Cancer: A Systematic Review and Meta-analysis” (JAMA. 2011;305(22):2335-2342). The question of time to initiation of adjuvant chemotherapy is also unclear in breast cancer. Notably, the use of adjuvant chemotherapy is even more prevalent in patients with breast cancer than those with colorectal cancer. Clinically, breast cancer patients with tumor larger than 1 cm or with involved lymph nodes are recommended to receive adjuvant chemotherapy, and 60-80% of patients with breast cancer would ultimately receive adjuvant chemotherapy. However, the optimal time from surgery to the start of chemotherapy is unclear albeit clinicians have used chemotherapy in breast cancer for more than a half century.

In this study, we determined the relationship between time to adjuvant chemotherapy and survival outcomes in breast cancer via a systematic review and meta-analysis. The overall meta-analysis demonstrated that a 4-week increase in time to AC was associated with a significant decrease in both OS (HR=1.15; 95% confidence interval [CI], 1.03-1.28; random-effects model) and DFS (HR=1.16; 95% CI, 1.01-1.33; fixed-effects model), suggesting that longer time to adjuvant chemotherapy was associated with worse survival in breast cancer patients.

Our meta-analysis is limited by the nonrandomized and retrospective nature of the included studies. However, it is unrealistic to expect that a randomized trial of time to adjuvant chemotherapy will ever be done due to its low operability, poor patient compliance, and potential ethical problems; rather, analyses such as ours are likely to provide the only evidence of such an effect. Therefore, we must rely on the data as reviewed in this study. We believe that our results, coupled with preclinical models and relevant clinical evidence, have provided sufficient proof of a substantial reverse
relationship between prolonged waiting times to initiation of adjuvant chemotherapy and reduced survival. We also believe our results have a great and universal influence on the clinical practice, and could help to modify protocols for those agencies that carry breast cancer cares and services.

All authors of this research paper have directly participated in the planning, execution, or analysis of the study. All authors of this paper have read and approved the final version submitted. The contents of this manuscript have not been copyrighted or published previously. The contents of this manuscript are not now under consideration for publication elsewhere. The contents of this manuscript will not be copyrighted, submitted, or published elsewhere while acceptance by the Journal is under consideration. There are no directly related manuscripts or abstracts, published or unpublished, by any author(s) of this paper.

Thank you for your consideration.

Sincerely yours,

Ke-Da Yu, MD PhD and Zhi-Ming Shao, MD PhD
Department of Breast Surgery, Cancer Center and Cancer Institute, Shanghai Medical College, Fudan University
399 Ling-Ling Road, Shanghai, 200032, P.R.China
Email: yu kd@shca.org.cn