Author’s response to reviews

Title: Prognostic factors for breast cancer patients with axillary lymph node dissection (pathological stage I-III) and the reversal of recurrence hazard rate between ER positive and negative breast cancer patients after long term survival

Authors:

Takayoshi Kiba (kiba@tri-kobe.org)
Tsutomu Nishimura (t246ra@kuhp.kyoto-u.ac.jp)
Masaya Ueno (Umasaya@aol.com)
Kiyotsugu Yoshikawa (yosikawa@kuhp.kyoto-u.ac.jp)
Kazuhiro Yanagihara (kazuhiro@kuhp.kyoto-u.ac.jp)
Satoshi Teramukai (steramu@kuhp.kyoto-u.ac.jp)
Masanori Fukushima (mfukushi@kuhp.kyoto-u.ac.jp)
Hironori Kato (hkato@kuhp.kyoto-u.ac.jp)
Masakazu Toi (toi@kuhp.kyoto-u.ac.jp)
Takashi Inamoto (t-inamoto@kitano-hp.or.jp)

Version: 2 Date: 26 June 2008

Author's response to reviews: see over
Dear the editor:

    Thank you for your kind review of our manuscript “Prognostic factors for breast cancer patients with axillary lymph node dissection (pathological stage I-III) and the reversal of recurrence hazard rate between ER positive and negative breast cancer patients after long term survival”. As suggested we are hereby sending a revised manuscript that has been altered in response to your comments.

    To reviewer 1
    Thank you very much for your comment. Regarding to the issues that you pointed, we have resubmitted the revised manuscript that has been altered in response to your comments.

1) We agreed your opinion that the best way to assess the effect of any individual variable on the outcome of breast cancer patients was to divide the patient cohort into different subgroups based on the time points. However, consistent with this, we have already reported this matter recently (Eur J Surg Oncol 2007; 33: 696).

2) In the survival, we did not censor death from any cause in overall and disease free survival. Also, we have changed our emphasis regarding the outcomes from “overall survival” to “disease free survival and annual hazard of recurrence”.

3) As suggested by you, we have deleted the unknown data of ER status. Consequently, we have investigated 742 breast cancer patients.

4) In the present study, we did not include histologic grade in the analysis. Histologic grade is not included in the recent revision of the TNM staging system of breast cancer. One of the main reasons for omitting grade in the staging criteria includes the interaction between tumor size and histologic grade and lack of clear evidence for the role of grade in small tumors (TNM stage pT1 and pT2) as a result of difficulties in comparisons among previous studies because of the variety of follow-up times, grading systems, patient sample, and measured outcomes (JCO 2002; 20: 3628). Moreover, studies that looked only at the smallest tumors (pT1a,
pT1b) tended to show somewhat smaller outcome differences between grade 1 and grade 3 than studies that included larger tumors (Eur J Cancer 1999; 35: 908; Cancer 1991; 68:1482). Therefore, we did not include histologic grade in the analysis.

5) As suggested by you, in the revised manuscript, we did not state that the prognosis for ER positive patients was worse than that for ER negative patients 10 years after surgery, in neither curve at 10 years was the ER positive survival lying below that of the ER negative group. According to the two waves (ER negative tumors versus ER positive tumors) of relapse pattern of breast cancer, we have discussed this matter, by looking at the data by Saphner et al. (JCO 1996; 14: 2738), as suggested by reviewer 3.

To reviewer 2

Thank you very much for your valuable comments. Regarding to the issues that you pointed, we have resubmitted the revised manuscript that has been altered in response to your comments.

1) As suggested by you, we have described the prognostic value of hormonal receptors on disease free survival in the revised manuscript. Moreover, we have deleted the unknown data of ER status. Moreover, we could not add the data of PgR status, because we did not have data base large enough to analyze.

2) We have selected the patient series, which of ER status could be investigated. Consequently, we have investigated 742 breast cancer patients. We have stated this matter in the Patients and Methods section. In addition, we have added the information regarding adjuvant hormone therapy, because the data have demonstrated the importance for understanding the annual hazard of recurrence of estrogen receptor status. In the present study, a special pathological review was not done. Therefore, to avoid confusion, we have changed the sentence to “Number of lymph node metastasis and ER status of the primary tumors were analyzed by staff members of the Department of Pathology at Kyoto University Hospital ”.

3) In the Method section, we have described the evaluation of ER in more detail.

4) In the present study, the median follow up time was 5.7 years and conclusions were drawn at 10 and 20 years. As suggested by you, this is a big difference. Therefore, we have not described the 20-year survival rates after operation in the revised manuscript.
5) To establish the interesting point, according to the two waves (ER negative tumors versus ER positive tumors) of relapse pattern of breast cancer, we have discussed this matter, by looking at the data by Saphner et al. (JCO 1996; 14: 2738), as suggested by reviewer 3.

To reviewer 3
Thank you very much for your kind and valuable comments. Regarding to the issues that you pointed, we have resubmitted the revised manuscript that has been altered in response to your comments.

1) As suggested by you, in the revised manuscript, we did not state that the prognosis for ER positive patients was worse than that for ER negative patients 10 years after surgery, in neither curve at 10 years was the ER positive survival lying below that of the ER negative group. Consequently, we have changed the title “Prognostic factors for breast cancer patients with axillary lymph node dissection (pathological stage I-III) and the reversal of recurrence hazard rate between ER positive and negative breast cancer patients after long term survival”.

2) As suggested by you, we have reassessed this paper, looking at the data by Saphner et al (JCO 1996; 14: 2738). Saphner et al. showed the annual rate of events in patients with ER positive and negative cancers. Because beyond 10 years hazard had increased statistical errors, we investigated the annual hazard of recurrence until 10 years after operation. In the present study, a positive ER status was associated with a lower hazard of recurrence in the first 2 years after surgery, but a higher hazard of recurrence from years 3 to 10. The EBCTCG performed a meta-analysis of systemic treatment of early breast cancer by hormone, cytotoxic, or biologic therapy methods in randomized trials involving 144,939 women (Lancet 2005; 365: 1687). Allocation to approximately 5 years of adjuvant tamoxifen reduces the annual breast cancer death rate by 31% (Lancet 2005; 365: 1687). Results from the EBCTCG meta-analysis show a highly significant advantage of 5 years versus 1 to 2 years of tamoxifen with respect to the risk of recurrence and a less significant advantage with respect to mortality (Lancet 2005; 365: 1687). Consistent with this, the present study may indicate the importance of adjuvant hormone therapy for ER positive cancer patients beyond 3 years after operation. In fact, among ER-positive patients of the present study, 26.3 % (21/59) used adjuvant hormone therapy in patients with recurrence cancer by 5 years, but 48.5% (16/33) used it in patients with recurrence cancer beyond 6 years, and 42.8% (145/339) used it in patients without recurrence cancer. Moreover, the approximate 10-year disease-free survival between ER
positive and negative patients was reversed (Figure 2). However, the current recommendation is that adjuvant tamoxifen be discontinued after 5 years in all patients as current standard therapy, because there was a trend toward a worse outcome associated with a longer duration of treatment (J Natl Cancer Inst 1996; 88: 1510). Further analyses may be needed to clarify the importance of adjuvant hormone therapy in operated breast cancer patients. We have discussed this matter in the Discussion section of the revised manuscript.

Thank you very much for your consideration. I am looking forward to your reply, hopefully saying this manuscript is accepted in your journal, *BMC cancer*.

Sincerely yours,

Takayoshi Kiba, M.D., Ph.D.
Translational Research Informatics Center, 1-5-4 Minatojima-minamimachi, Chuo-ku, Kobe, 650-0047, Japan
Takashi Inamoto, M.D., Ph.D.
Department of Breast Surgery, Kitano Hospital, The Tazuke Kofukai, Medical Research Institute, 2-4-20 Ohgimachi, Kita-ku, Osaka, 530-8480, Japan
Phone: +81-6-6312-1221
FAX: +81-6-6361-0588
E-mail: t-inamoto@kitano-hp.or.jp