Evaluation of serum HER-2/neu in breast cancer patients: correlation with clinicopathological parameters and survival

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Introduction
HER-2/neu receptor is composed of a cytoplasmic domain with tyrosine kinase activity, a transmembrane domain and an extracellular domain (EC1). The HER-2/neu ECD may be cleaved and shed from the surface of breast cancer cells and serum HER-2/neu ECD levels can be detected by enzyme-linked immunosorbent assay (ELISA) without any significant cross-reactivity with other members of the HER family.4 Many reports have associated increased serum HER-2/neu concentration with earlier disease recurrence and shortened overall survival5,8,9, decreased response to chemotherapy and hormonal therapy, and prediction of response to trastuzumab based treatments.6

"The association between HER-2/neu status and serum HER-2/neu controversy, as some studies have identified a positive correlation, while others have not. The aims of the current study were to assess the correlation between serum HER-2/neu ECD and clinicopathologic factors. And we wanted to assess the effect of serum HER-2/neu on 3 year disease free survival rate.

Materials and Methods

Patients and Specimens
The study subjects, 167 women with breast cancer, were a subset of patients operated at OOO hospital from Jan 2005 to Dec 2006. This retrospective study was conducted in patients with a histological diagnosis of stage I-III breast cancer treated with conservative surgery or mastectomy.

Adapted from: serum HER-2/neu, breast cancer, DFS

초 록


결과: 평균제거량은 54명이었으며 평균증가량의 크기는 3.2 cm이었다. 고농도군에서 염증력으로 HER-2/neu가 양성인 경우는 많았 다. (p=0.03) 그리고 고농도군에서 야스프로게 호르몬 수용체가 양성인 경우가 많았다. (p=0.04) 형질의 HER-2/neu level이 무병 생존율에 영향을 미쳤으며 (p=0.01) 중앙의 고도의 무병생존율에 영향을 미쳤다. (p=0.07)

결론: 형질 HER-2/neu의 농도는 호르몬 수용체나 조직의 HER-2/neu의 농도와 연관이 없었지만 무병생존율과는 연관이 있었 다. 그러나 본 연구는 추적 기간이 짧아 환자가 많고 다양한 방식으로 후향 더 많은 수와 추적기간을 가지고 연구를 해야 할 것이다.
Tumor staging followed the tumor–node–metastasis (TNM–American Joint Committee on Cancer classification and the p–TNM was obtained after classical pathological examination. Patients with metastatic disease and with other previous tumors were excluded from this study. Estrogen receptors (ERs), progesterone receptors (PRs) and HER-2/neu status were assessed at the time of surgery on formalin–fixed paraffin embedded tissue blocks of the primary tumor in the Pathology Department of the University of OOO. Recorded clinical and pathological features for each patient include age, histology, grade, Ki–67, ER and PR status, AJCC stage, surgical treatment and medical adjuvant therapy. Follow–up, including clinical examination every 6 months for the first 2 years, every one year for the next 3 years and mammography, bone scan, chest X–ray was carried out in all patients. Recurrence was defined as the first documented evidence of new disease manifestation in the loco–regional area, in the contralateral breast, distant sites, or in a combination of these.

**serum HER-2/neu ECD assays**

Serum samples were collected from breast cancer patients before surgery. Five milliliters of peripheral blood were collected in a sterile tube without anticoagulant and centrifuged at 3000 g for 10 min at room temperature. Serum was stocked in 0.5–ml aliquots in cryovials and stored at 28.0°C until the time of HER-2/neu ECD automated analyses. Serum HER-2/neu ECD levels were measured using both HER-2/neu assays to compare the two ELISA methods. With the automated method, baseline serum HER–2/neu ECD levels were determined with the ADVIA Centaur HER–2/neu assay (Bayer Corporation, Tarrytown, NY), on the basis of two mAbs directed against the ECD of the HER2 antigen, using direct chemiluminescent technology. The measured chemiluminescence is directly proportional to the quantity of HER2/neu antigen in the sample. Quality control was ensured by assaying the two levels of control sera supplied with the kit in each series. Mean ± standard deviation (SD) and coefficient of variation (CV) for the controls were 15.7 ± 0.75 ng/ml (CV 4.5%) and 112.9 ± 4.99 ng/ml (CV 4.4%), respectively. This automated assay for HER2/neu ECD was demonstrated to be accurate, precise, resistant to interferences and reliable for longitudinal monitoring; the upper limit of normal was defined as 15 ng/ml.

**Other histopathological assays**

Histopathological features such as hormone receptor status and HER–2/neu status on immunohistochemistry (Dako, Copenhagen, Denmark) were all analyzed at the department of Pathology at the University of OOO. Expressions of p53, ERα, Ki–67 and HER–2/neu were determined immunohistochemically on paraffin sections using antibodies against ERα (Dako, Copenhagen, Denmark), Ki–67 (Dako, Copenhagen, Denmark), HER–2/neu (Dako, Copenhagen, Denmark), p53 (Dako, Copenhagen, Denmark). Histologic grading was performed using the criteria of Bloom and Richardson. Lymphatic vascular invasion (LVI) was defined as the presence of tumor emboli in peritumoral lymphatic spaces, capillaries or post capillary venules. ER status and PR status were taken as positive if more than 10% of tumor cells showed staining. Immunohistochemical score of 3+ for HER–2/neu was accepted as HER–2/neu positivity.

**Statistical Analysis**

DFS was defined as the time from surgery to first appearance of disease or death for any cause. Survival curves were estimated using the Kaplan–Meier method. Statistical tests were performed using the SPSS 12.0 statistical software package for Windows SPSS Inc, Chicago, IL. The survival function was calculated from the time of the onset of disease to the occurrence of death. Survival data were censored on December 31, 2009, which was the date on which the survival data were correlated with the death registry for the last time or 3 years after the onset of the disease. Kaplan–Meier estimates are presented for the survival function, and differences in survival were...