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Monitoring Metastatic Breast Cancer with Serum HER-2/neu: Individual Patient Profiles

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Abstract

The Serum HER-2/neu assay from Siemens Healthcare Diagnostics measures the extracellular domain of the HER-2/neu oncoprotein in serum. Serum HER-2/neu levels are a useful aid in monitoring patients with metastatic breast cancer whose baseline levels are greater than 15 ng/mL. HER-2/neu values should be used in conjunction with information available from clinical and other diagnostic procedures in the management of breast cancer. Studies have shown that a lack of a significant decrease in levels is associated with lower overall survival, shorter duration of response, shorter time to progression, and lower response rates. Increasing levels are associated with disease progression, and decreasing levels are associated with response to therapy.¹⁻⁶ The patient profiles presented in this paper illustrate on an individual level how serum HER-2/neu levels reflect the patient's clinical course.

What is serum HER-2/neu?

Serum HER-2/neu, the cleaved extracellular domain of the HER-2/neu oncoprotein, circulates in the bloodstream. HER-2/neu is a growth factor receptor that belongs to the human epidermal receptor growth factor family, and its functions include driving cell growth. HER-2/neu is expressed on both normal and cancer cells; however, cancer cells exhibit gene amplification and/or protein overexpression.^{7,8} Excess HER-2/neu levels in breast cancer are associated with more aggressive disease and a poor prognosis. Patients with breast cancer that is tissue positive for excess HER-2/neu are eligible for treatment with HER-2-targeted therapies.^{1-6,9}

How do you use serum HER-2/neu?

Serum HER-2/neu levels can be used to monitor metastatic breast cancer patients whose status determined by tissue testing is either HER-2/neu positive or HER-2/neu negative. Serum HER-2/neu levels can be used to aid in monitoring metastatic breast cancer patients treated with chemotherapy, hormonal therapy, radiotherapy, and HER-2/neu-targeted therapies.^{1,4,5,10} If a baseline level is greater than 15 ng/mL, then the patient can be monitored on a regular basis using serum HER-2/neu (Figure 1). If the baseline level is less than 15 ng/mL, it may be useful to test periodically to monitor for levels that increase to greater than 15 ng/mL (Figure 1).

ADVIA Centaur Systems Serum HER-2/neu assay intended use

The Serum HER-2/neu assay is to be used in the quantitative determination of the HER-2/neu protein in human serum (HER-2/neu extracellular domain) using the ADVIA Centaur® Immunoassay System. Serum HER-2/neu values may be used in the follow-up and monitoring of patients with metastatic breast cancer whose initial serum HER-2/neu level is greater than 15 ng/mL. Serum HER-2/neu values should be used in conjunction with information available from clinical and other diagnostic procedures in the management of breast cancer. The clinical utility of the measurement of HER-2/neu in serum as a prognostic indicator for early recurrence and in the management of patients on immunotherapy has not been fully established.

What do changes in serum HER-2/neu levels indicate?

Increasing serum HER-2/neu levels are associated with disease progression, and decreasing levels are associated with response to therapy.¹⁻¹¹ A 2008 study by Ali et al. demonstrated that a lack of a significant (greater than 20%) decrease in levels was associated with lower overall survival, shorter duration of response, shorter time to progression, and lower response rates.¹ A 2004 study by Sandri et al. demonstrated that levels less than 15 ng/mL were associated with better overall survival.¹⁰ Similarly, a 2005 study by Lipton et al. demonstrated better survival in patients whose levels remained less than 15 ng/mL (median survival: 48 months), compared to patients whose levels exceeded 15 ng/mL consistently or at any point during the observation period (median survival: ~27 months and ~21 months, respectively).⁶

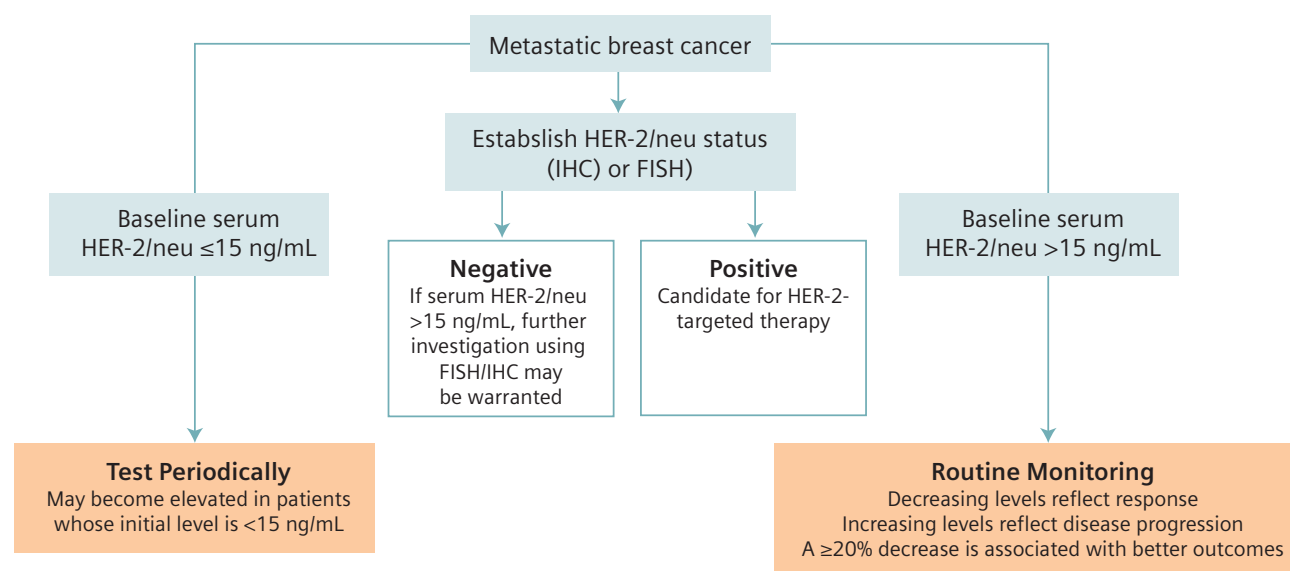


Figure 1. A Serum HER-2/neu testing algorithm for metastatic breast cancer.

Patient profiles

The individual case studies in this paper are presented courtesy of Professor Ivan Brandslund, MD, DMSc, Vejle Sygehus Hospital, Denmark, from a project initiated in 2004. These six profiles are representative of the changes in serum HER-2/neu levels that are associated with response to therapy (decreasing levels) and with progressive disease (increasing levels). During a 5-year period (January 2004 to January 2009), 862 breast cancer patients were enrolled at the Vejle Sygehus Hospital for serum HER-2/neu monitoring; accrual is still ongoing.¹¹

Profile 1: 44-year-old female patient

This 44-year-old patient was diagnosed in April 2006 with inoperable poorly differentiated invasive ductal carcinoma (T4 N2 M1). At diagnosis, the patient had both liver and lymph node metastases. The tumor size, nodal involvement, distant metastases, and HER-2/neu status are all indicative of poor prognosis. The primary tumor was estrogen receptor (ER), progesterone receptor (PR), and HER2-neu (3+) positive. Liver metastases (Figure 2), however, were ER and PR negative. Her baseline serum HER-2/neu level in April 2006 was 146.5 ng/mL (Figure 3). This patient's clinical course was reflected by changes in her serum HER-2/neu levels. Increases were associated with progression of disease and decreases were associated with response to therapy (Figure 3).

From May to November of 2006, she was treated with neoadjuvant vinorelbine and trastuzumab (nine cycles). She had an initial response, demonstrated by X-ray computed tomography (CT) regression of liver metastases in July 2006. In September 2006, the CT remained unchanged from July. Her serum HER-2/neu levels measured in October 2006 decreased to 91.4 ng/mL. In November 2006, consistent with progression, her serum HER-2/neu levels increased to 132.6 ng/mL (Figure 3). Due to progression in November, vinorelbine was discontinued and docetaxel started. This combination therapy continued through May 2007.

The January 2007 CT was unchanged, and serum HER-2/neu levels decreased to 41.6 ng/mL. In April 2007, the CT was still unchanged, but serum HER-2/neu levels increased to 63.1 ng/mL (Figure 3). Her May 2007 CT showed progression of liver metastases, a finding consistent with the previous month's serum HER-2/neu levels. Serum HER-2/neu levels in this month continued to increase to 74.9 ng/mL and then to 90.2 ng/mL. In June 2007, she had further progression of liver metastases (Figure 3). During August to October 2007, therapy was changed to cyclophosphamide and epirubicin (three cycles) (Figure 3). Her serum HER-2/neu levels increased in August 2007 to 383.7 ng/mL and continued to increase in November 2007 to 884.1 ng/mL and in December 2007 to 1068 ng/mL (Figure 3). Her October 2007 CT showed progression of liver metastases (Figure 4).

In 2008, her disease continued to progress despite a single cycle of carboplatin. By February 2008, her CT showed (Figure 5) extensive progression of her liver metastases, and her serum HER-2/neu levels had increased to 3329.9 ng/mL (Figure 3).



Figure 2. Liver metastases at diagnosis shown on the May 23, 2006 CT.



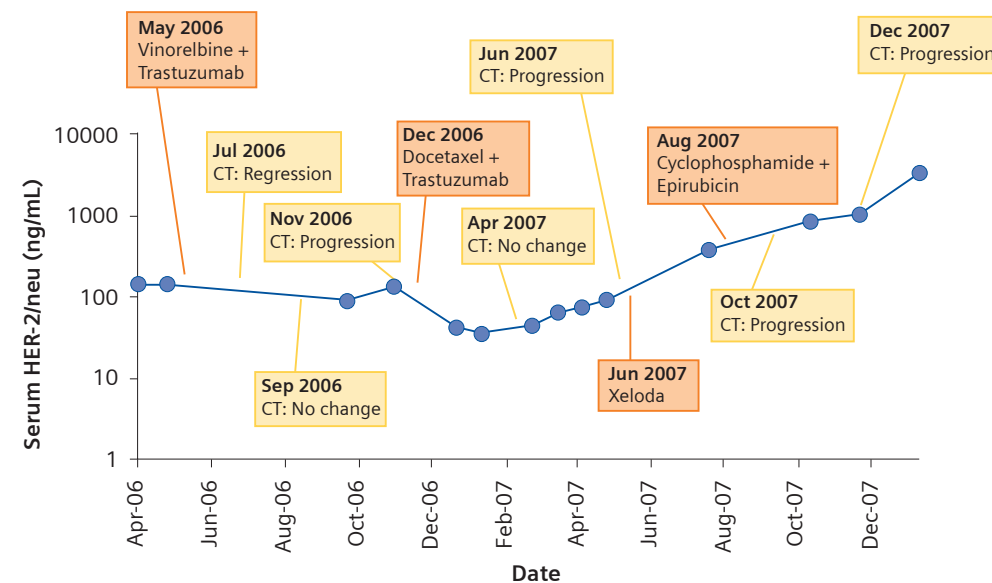


Figure 3. Clinical course and serum HER-2/neu levels (logarithmic scale).



Figure 4. October 23, 2007 CT showing progression of liver metastases.



Figure 5. February 7, 2008 CT showing extensive progression of liver metastases.

Profile 2: 34-year-old female patient

This 34-year-old patient was diagnosed with ER- and HER-2/neu-positive, PR-negative metastatic breast cancer. The tumor size, nodal involvement, distant metastases, and HER-2/neu status are all indicative of poor prognosis. She was treated with surgery on May 6, 2008. Prior to surgery, she was treated with epirubicin and cyclophosphamide for three cycles. After this, she was also started on palliative docetaxel, cyclophosphamide, and trastuzumab for 15 cycles, with the last cycle in June 2010. This patient's serum HER-2/neu levels reflected her clinical course (Figure 6). Progression was associated with increasing levels and response with decreasing levels.

There was no change on CT in December 2009, but her serum HER-2/neu declined to 7.8 ng/mL, consistent with response (Figure 6). In February 2010, her serum HER-2/neu level was 8.9 ng/mL. The April 2010 CT showed partial regression of liver metastases, consistent with her decreased serum HER-2/neu levels in December and February (Figure 6). Two serum HER-2/neu levels taken in

April 2010 were 20.4 ng/mL and 20.1 ng/mL, increases (more than double the February measurement) that were indicative of progression. In July 2010, there was no change in the liver and bone metastases; but she had brain metastases, which were treated with radiotherapy, and letrozole was also started. During July 2010, her serum HER-2/neu levels continued to increase: 80.1 ng/mL for the first measurement and 112.8 ng/mL for the second. In September 2010, she was switched to lapatinib and capecitabine because of CT progression of her liver and lymph node metastases, and serum HER-2/neu levels peaked at 119.4 ng/mL. In November 2010, she showed partial CT regression of liver metastases, and her serum HER-2/neu levels had declined to 36.3 ng/mL (Figure 6).

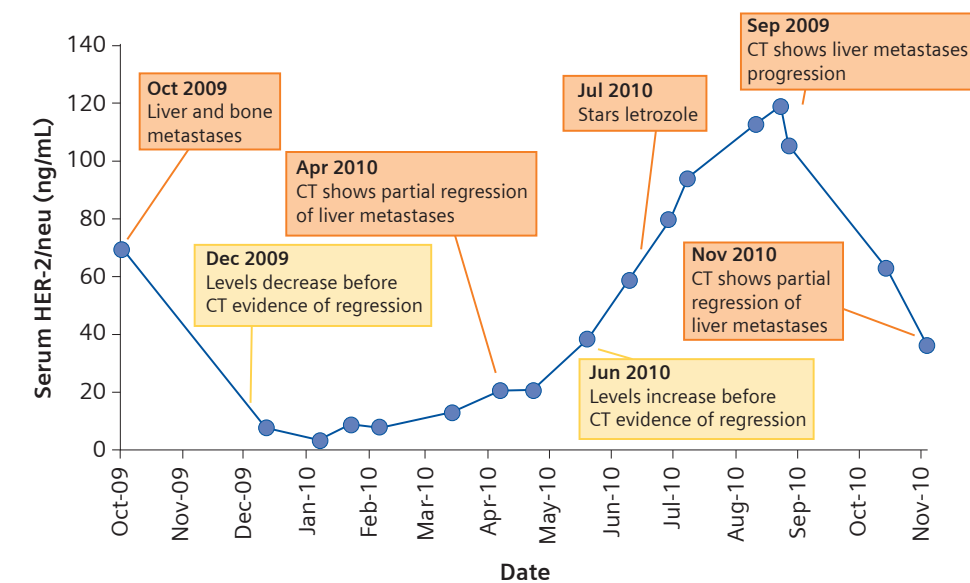
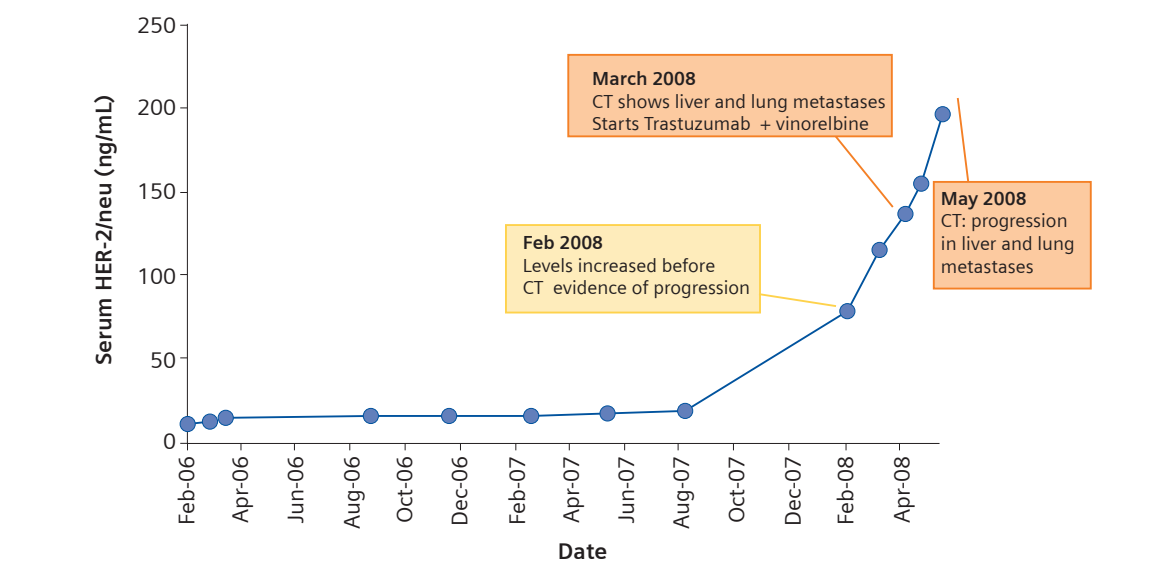
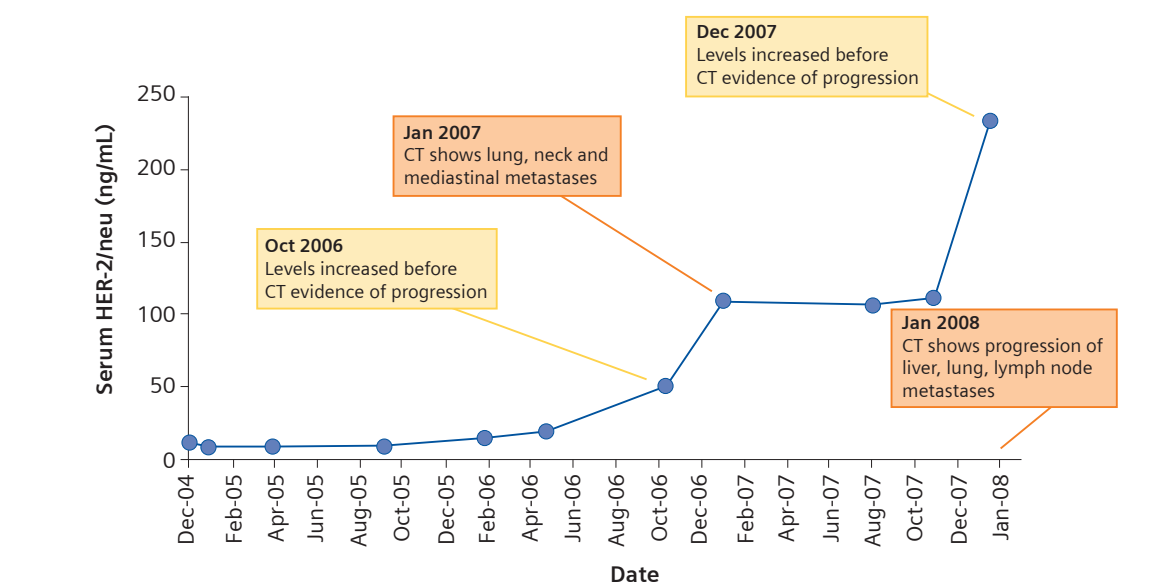


Figure 6. Clinical course and serum HER-2/neu levels.

Profiles 3 and 4: 59-year-old and 57-year-old females with disease progression
 These patients showed disease progression on CT that was associated with increasing serum HER-2/neu levels (Figure 7).



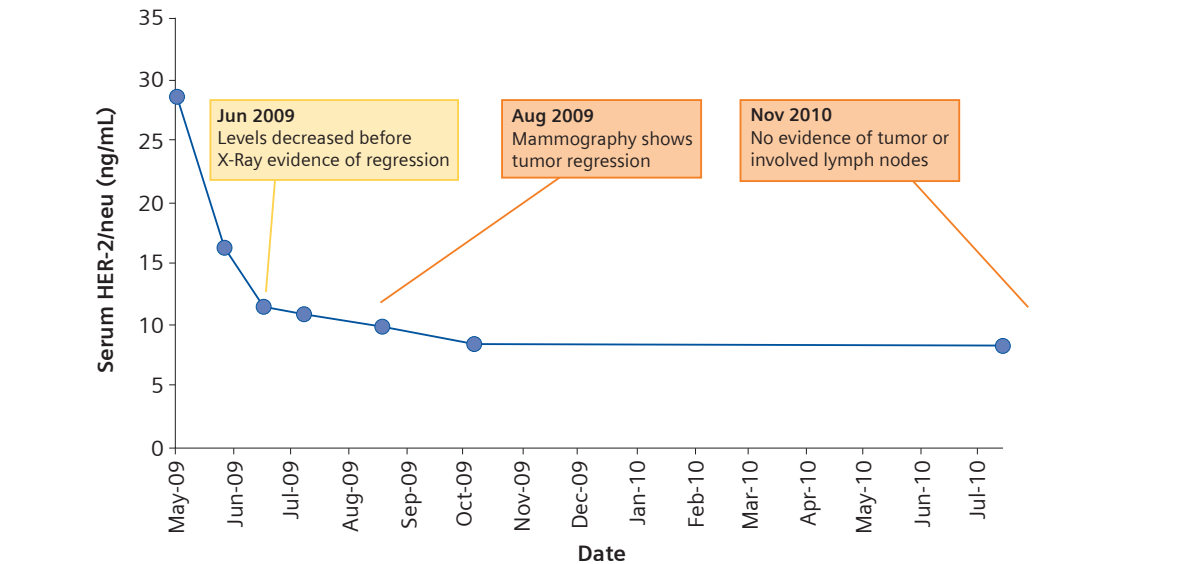
a) 59-year-old female with disease progression.



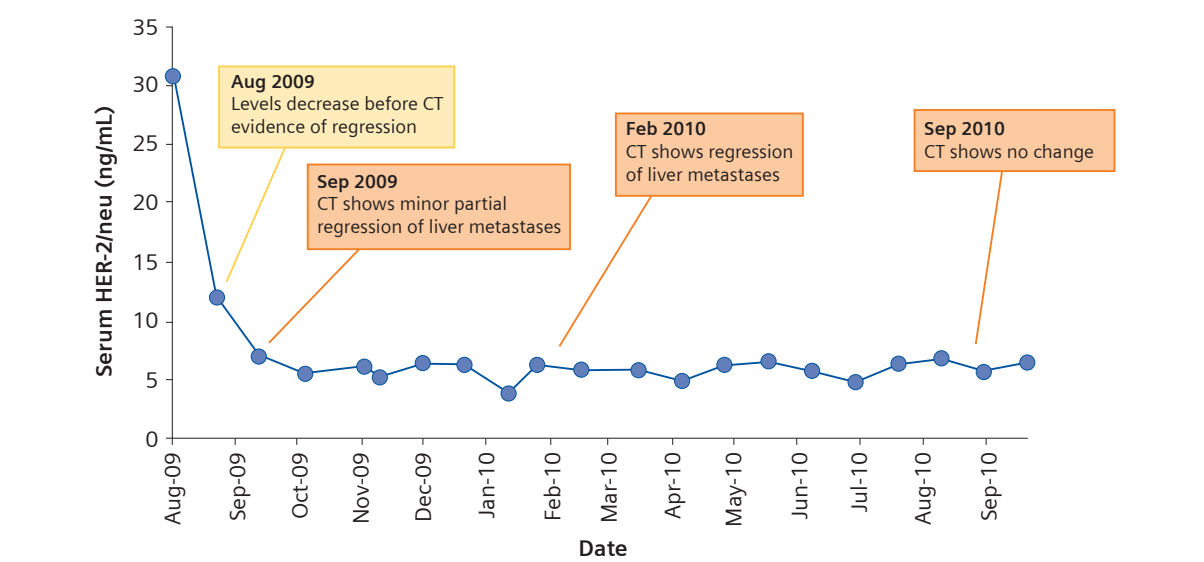
(b) 57-year-old female with disease progression.

Figure 7. Two patient profiles (a, b) demonstrating serum HER-2/neu level increases in patients with progressive disease.

Profiles 5 and 6: Two 54-year-old females with treatment response
 These patients showed response on CT that was associated with decreasing serum HER-2/neu levels as the disease regressed / responded to therapy (Figure 8).



(a) A 54-year-old female with response to treatment.



(b) Another 54-year-old female with response to treatment.

Figure 8. Two patient profiles (a, b) demonstrating serum HER-2/neu level decreases in patients with response to therapy.

Conclusion

The individual patient profiles presented in the paper, from a larger population of patients, demonstrated that serum HER-2/neu levels reflected the clinical course of disease in patients with metastatic breast cancer whose baseline levels were greater than 15 ng/mL. These individual profiles were consistent with larger studies that demonstrated that changes in serum HER-2/neu levels reflected clinical course and provided useful information for the clinician monitoring patients with metastatic breast cancer.

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