Overexpression of Eukaryotic Initiation Factor 4E Is Correlated with Increased Risk for Systemic Dissemination in Node-Positive Breast Cancer Patients

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BACKGROUND: Molecular events impact systemic dissemination. Overexpression of eukaryotic initiation factor 4E (eIF4E) has been shown to predict worse clinical outcomes in breast cancer. Node-positive breast cancer patients were specifically studied to determine if eIF4E elevation increases risk for systemic dissemination.

STUDY DESIGN: Two hundred two node-positive breast cancer patients were prospectively accrued and treated with standardized treatment and surveillance protocol. Tumor eIF4E protein level was quantified by Western blots as x-fold over benign samples from noncancer patients. Primary end point was systemic metastasis.

RESULTS: Systemic recurrence was detected in 22.2% of the low eIF4E group, 27.3% of the intermediate group, and 49% of the high group, at a median follow-up of 47 months. A greater risk for systemic metastasis was seen in the high eIF4E group compared with the low group (log-rank test, $p = 0.0084$). Patients in the high eIF4E group had a 1.5-fold (hazard ratio = 1.52; 95% CI, 1.07−2.17; $p = 0.0206$) higher risk for systemic metastasis than the low group. Sixty percent of the patients with high eIF4E were observed to have metastasis to multiple sites, compared with 50% in the intermediate group, and 14.5% in the low group ($p = 0.02$, Fisher's exact test). When patients were segregated based on nodal classification (N1, N2, and N3), eIF4E overexpression continued to be a predictor for systemic dissemination in patients with N1 disease.

CONCLUSIONS: High eIF4E is correlated with an increased risk for systemic metastasis in node-positive breast cancer patients. High eIF4E overexpression was associated with a higher incidence of metastasis to multiple sites. Therefore, high eIF4E overexpression appears to be a marker for molecular events that increases risk for systemic dissemination. (J Am Coll Surg 2014;218: 663−673. © 2014 by the American College of Surgeons)

Breast cancer has become the number one cause for cancer-related morbidity and mortality in women.[1] In the United States, breast cancer remains the most common malignancy among women of all races and ethnicities, and the second leading cause of cancer death.[2] Although long-term locoregional control can be achieved with surgery and adjuvant therapy in >90% of patients, cancer death due to disseminated disease remains high. Lymph node involvement remains a critical component in staging breast cancer, although it appears that it is molecular events in malignant cells that will ultimately determine a patient's clinical outcomes.[3-5]

Tumor metastasis is a multistep process, and dysregulation of many factors, such as tumor-associated microenvironment and multiple gene overexpression, can lead to systemic metastasis. One such molecular event might be the dysregulation of protein translation. An important regulatory element in protein translation is the eukaryotic initiation factor 4E (eIF4E). This is a

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Abbreviations and Acronyms

eIF4E = eukaryotic initiation factor 4E
EMT = epithelial mesenchymal transition
mRNA = messenger RNA
UTR = untranslated region
VEGF = vascular endothelial growth factor

25-kD translation-initiating factor that regulates genes expression as a subunit of the eIF4F helicase complex. The helicase complex helps unwind messenger RNAs (mRNAs) with long 5′ untranslated region (UTR) structures, and reduces the steric hindrance inhibiting protein synthesis of such mRNA.[6,7]

Eukaryotic initiation factor 4E is a rate-limiting factor in the formation of the helicase complex. Therefore, in an environment with excess eIF4E, there is upregulation of protein translation of mRNAs with long 5′UTRs.[8] Overexpression of eIF4E overexpression has been correlated with upregulation of gene products important in cell functions. These have included cyclin D1, important in cell cycle regulation,[9] angiogenic factors, such as vascular endothelial growth factor (VEGF)[10] and fibroblast growth factor,[11] as well as TLK1B, a threonine kinase that is important in chemoresistance in cancer cells.[12]

Overexpression of eIF4E has been associated with malignant transformation in vitro.[13] Additionally, the clinical significance of eIF4E in cancer is evidenced by the discovery of eIF4E overexpression in human malignancies, including breast cancer,[14] head and neck squamous cell cancer,[15] and colon cancer,[16] among others.

In 1995, Kerekatte and colleagues first reported the overexpression eIF4E in varying degrees in breast cancer specimens from patients, but not in benign breast tissue.[14] Subsequently, it was found that eIF4E was overexpressed in varying degrees in the specimens of breast cancer patients. Comparing patients with high eIF4E overexpression in their tumor specimens with patients with low eIF4E overexpression, it was found that the high eIF4E patients had worse clinical outcomes than patients with low eI4E, as determined by a higher cancer recurrence and a higher cancer-related death. The degree of eIF4E overexpression was not correlated with whether patient had nodal involvement. In addition, patients with high overexpression of eIF4E had recurrence from their breast cancer and died from their disease more frequently than patients with low eIF4E overexpression, whether they had nodal disease or not.[17,18]

Two separate prospective trials confirmed that eIF4E overexpression is predictive of worse breast cancer outcomes, independent of nodal status. In a node-positive breast cancer patient—only prospective trial, high 4E overexpression was associated with a 2.4-fold increase in relative risk for cancer recurrence, and a 2.3-fold increase in relative risk for cancer-related death.[19] A second study was carried out specifically in pathologically node-negative only breast cancer patients. In this study, high 4E overexpression was again associated with an increased risk for cancer recurrence and cancer-related death.[20]

Breast cancer can disseminate by means other than via the lymphatic, and because eIF4E overexpression has been reported to upregulate VEGF in vitro, eIF4E and VEGF were studied in human breast cancer specimens. Byrnes and colleagues reported that VEGF elevation was correlated with eIF4E overexpression.[21] Additionally, increasing eIF4E overexpression was also correlated with a higher microvessel density count in the tumor. In turn, breast cancer patients were observed to have a higher risk for both cancer recurrence and cancer-related death when their eIF4E was highly overexpressed. This report, together with the observation that worse clinical outcomes for patients with high eIf4E overexpression that is independent of nodal disease, suggests a nonlymphatic means for metastasis, such as hematogeneous dissemination.

These observations led us to ponder this hypothesis: eIF4E overexpression is a marker of molecular events that portend systemic dissemination independent of lymphatic involvement. We designed our current study to answer the question: In patients with node-positive disease already, does high eIF4E overexpression predict a higher risk for systemic dissemination?

METHODS

The study design was to accrue 202 patients with pathologically proven node-positive breast cancer. Patients were counseled and consented to participate in this IRB-approved study. Exclusion criteria included earlier malignancy, local recurrence, and development of a second primary malignancy.

Patients' treatment and surveillance protocol were standardized to ensure study homogeneity. Compliance with protocol was measured. Standardized treatment for the primary breast cancer was provided based on their stage of disease. Surgical treatment included breast conservation therapy or mastectomy. Axillary node staging was accomplished with either SLNB or a complete axillary node dissection, when appropriate. Adjuvant radiation therapy was provided routinely when breast conservation therapy was performed, and after mastectomy when it was indicated. Adjuvant systemic chemotherapy, anti-estrogen therapy, and anti-HER2 therapy were offered and administered as per current standard of care.

A standardized surveillance protocol for detecting systemic metastasis was followed for all study patients.