Biologic Predictors of Pathologic Fracture in Metastatic Breast Cancer

Rahul Jain, Guston G. Zervoudakis, Thomas Leonidas Karadimas, David Joyce, G Douglas Letson, Odion T Binitie, Alexander Leandros Lazarides

INTRODUCTION:

Current fracture-risk models in metastatic disease to the appendicular skeleton, such as Mirels' criteria, rely heavily on radiographic criteria but omit tumor biology. Breast cancer carries a variety of receptor subtypes and varying histologic grades which may influence risk of pathologic fracture beyond what is seen radiographically.

METHODS:

In a cohort of breast cancer patients with metastases to the appendicular skeleton (n=189), we retrospectively examined those with biopsy-proven receptor subtype statuses and Nottingham grades. Firth logistic regression estimated associations for receptor subtype status alone, grade alone, and combined phenotypes with pathologic fracture. We performed analyses without adjustment and adjustment for Mirels' score and bisphosphonate use. Findings are reported as odds ratios (OR) with 95% confidence intervals (CI).

RESULTS:

In unadjusted analyses, estrogen-receptor (ER) negativity was associated with higher odds of pathologic fracture (OR 4.06, 95% CI 1.22–12.42), while progesterone-receptor and HER2 status alone were not associated with fracture risk. Nottingham grade 3 cancers showed greater fracture odds than grade 2 (OR 7.94, 1.72–76.24), and no fractures occurred among grade 1 cases. After adjusting for confounders, fracture risk was associated with increasing Nottingham grade (OR 5.70, 1.12–57.00) and ER-negative status (OR = 2.15). ER-negative grade 3 patients had the highest fracture frequency (37.5%), followed by ER-positive grade 3 (15%), whereas ER-positive grade 2 patients demonstrated a very low fracture rate (2.1%). Relative to ER-positive grade 2, ER-positive grade 3 patients had heightened odds of fracture (OR 5.97, 1.18–59.15); ER-negative grade 3 patients showed even higher odds of fracture (OR 20.15, 2.75–239.28). After adjustment, this association remained statistically significant only for ER-negative grade 3 (OR 17.67, 1.91–262.58).

DISCUSSION AND CONCLUSION:

In breast cancer that is metastatic to the appendicular skeleton, Nottingham grade and receptor subtypes may implicate pathologic fracture risk beyond what is known through radiographic risk-analysis alone. Incorporating these biologic markers alongside Mirels' scoring may improve individualized fracture□risk stratification. Given the markedly elevated odds of pathologic long-bone fracture in ER-negative grade 3 disease, these patients should be referred early for orthopedic evaluation.