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The relationship between MMP9 and tumor microenvironment and survival in patients with invasive ductal breast cancer

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Background: The role of tumor microenvironment including tumor cells, surrounding stroma and vasculature in determining breast cancer outcome is increasingly recognized. Components of tumor microenvironment and matrix metalloproteinase 9 (MMP9) are associated with worse survival. However, the interrelationship between these components and MMP9 are not clear in clinical sittings. The aim of the present study was to examine the relationship between these factors, clinic-pathological characteristics and survival in patients with invasive ductal breast cancer.

Methods: 456 patients who had primary operable invasive ductal breast cancer between1995-1998 were included. MMP9 was assessed at the tumor stroma (MMP9-S), cell cytoplasm (MMP9-C) and cell membrane (MMP9-M) using immunohistochemical (IHC) staining on tissue microarrays. Tumor stroma percentage (TSP) and necrosis were assessed on H&E sections and graded as low or high. Local inflammatory response was assessed at the invasive margin using the Klintrup-Makinen (K-M) score. Lymphatic (LVI) and blood vessel invasion (BVI) and angiogenesis were assessed using IHC staining of D2-40, Factor VIII and CD34 respectively.

Results: 233 patients (51%) had high MMP9-S, 229 patients had high (51%) MMP9-C and 218 patients (48%) had high MMP9-M. High MMP9-S and MMP9-C were associated with increased tumor size and angiogenesis (both P<0.05), LVI and high TSP (both P<0.01). High MMP9-C was associated with increased tumor size, Her-2 positivity (both P<0.05), LVI (P<0.001), BVI and high TSP (all P<0.01). High MMP9-M was associated with increased tumor necrosis, Her-2 positivity (both P<0.05), LVI, BVI, and high TSP (all P<0.01). There was no association between MMP9 at any location with local inflammatory infiltrate. MMP9-C and MMP9-M were associated with increased tumor recurrence (P=0.001 and P=0.002 respectively). MMP9-S only showed a trend towards increased incidence of tumor recurrence (P=0.059). The median follow-up of survivors was 164 months, with 21 cancer deaths. On univariate analysis a high MMP9 at different locations was associated with shorter cancer-specific survival (CSS) (MMP9 –S (P=0.006), MMP9-C and MMP9-M (both P<0.001). On multivariate analysis, MMP9-C was strongly associated with poorer CSS (HR 2.54, 95% CI 1.54-4.21, <P=0.001), independent of tumor size, nodal status, PR status (all <0.01), LVI and BVI (<0.01) and TSP (P=0.001). In chemotherapy untreated patients (n=207), MMP9-C remained significantly associated with poor CSS (HR 2.28, 95% CI 1.14-4.57, P=0.020) independent of tumor size and grade. In triple negative patients (n=107), MMP9-S (HR 4.29, 95% CI 1.48-12.49, P=0.007) and BVI (HR 4.64, 95% CI 2.13-10.11, P=0.001) were the only predictors of poor CSS.

Conclusion: MMP9 was associated with the presence of high risk pathological characteristics such as lympho-vascular invasion, angiogenesis and increased amount of tumor stroma and was independently associated with poorer cancer survival. The increased expression of MMP9 is an important factor in the nature of extracellular matrix and the tumor microenvironment as a whole and in determining outcome in breast cancer patients. Compared to standard pathological characteristics, the present results suggest that assessment of both tumor microenvironment and MMP9 may have superior prognostic value compared with TNM staging particularly in patients with triple negative breast cancer.

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