Original Study

Invasive Breast Cancer Preferably and Predominantly Occurs at the Interface Between Fibroglandular and Adipose Tissue

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Abstract

The position of invasive breast tumor in relation to fibroglandular and adipose tissue was assessed in this retrospective dynamic contrast-enhanced magnetic resonance imaging investigation of 294 patients. These tumors were found to occur predominantly at the interface between fibroglandular and adipose tissue.

Background: Increasing evidence suggests adipocyte involvement in malignant breast tumor invasive front or margin. The aim of this study was to evaluate the location of invasive breast tumors in relation to fibroglandular and adipose tissue by dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI). **Patients and Methods:** Pretreatment breast DCE-MRI images of 294 patients with biopsy-proven invasive breast cancer from 2008 to 2014 were studied. Invasive breast tumors were visualized as enhanced lesions in the postcontrast subtraction images. Positive identification of biopsy-confirmed invasive breast tumors on DCE-MRI images was achieved by correlation of findings from breast MRI and pathology reports. Tumor location in relation to fibroglandular and adipose tissue was investigated using precontrast T1-weighted MRI images. **Results:** Of 294 patients, 291 had DCE-MRI discernable invasive breast tumors located at the interface between fibroglandular and adipose tissues, regardless of the tumor size, type, receptor status, or breast composition. **Conclusion:** Invasive breast cancer preferably and predominantly occurs adjacent to breast adipose tissue.

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Introduction

The human breast is composed mainly of fibroglandular and adipose tissue. Although breast carcinoma is a type of cancer that arises from the epithelial cells that line the lobules and terminal ducts of breast glandular tissue,[1] it develops in a complex tissue environment and depends on bidirectional communication with other tissues for tumor initiation and progression.[2] Adipose tissue is of special interest because it is one of the major components in the breast. Increasing evidence suggests adipocyte involvement in the breast tumor invasive front, presumably due to the close proximity of adipose and glandular tissue.[3] An earlier histology study of 310 patients with invasive ductal carcinoma of the breast demonstrated that adipose tissue was present in the breast tumor margin of 245 patients.[4] While some studies have reported cross-talk between breast tumor cells and peritumoral adipocytes,[5,6] it is not known whether this cross-talk is incidental or obligatory in breast cancer initiation and development. The investigation into the breast tumor microenvironment has mainly been focused on nonadipocyte components.[7]

Overall adiposity plays an important role in many epithelial malignancies, including breast cancer, as manifested by increased breast cancer incidence rates in overweight/obese women.[8-10] Obesity is associated with systemic effects, including insulin resistance, altered hormone signaling, and high circulating levels of proinflammatory mediators that favor tumor initiation and progression.[11-13] However, the local effect of adipocytes in breast cancer has been less explored. In addition, the breast is a unique and

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dynamic organ. Breast density, a measurement of the fibroglandular/adipose tissue composition, fluctuates throughout an adult woman's life as a result of factors such as weight gain, pregnancy, lactation, and mammary- and age-related lobular involution. There has been a long-standing interest in the relationship between breast cancer and involution,[14-18] during which breast fibroglandular tissue is replaced by adipose tissue.

We aimed to evaluate the location of invasive breast tumors in relation to fibroglandular and adipose tissue using dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) in this retrospective study. DCE-MRI is an ideal tool with which to investigate the macroscopic interaction between adipose tissue and breast tumors. Malignant breast tumors are identified on postcontrast subtraction images by a rapid enhancement resulting from their increased vascularity, while adipose and fibroglandular tissue can be differentiated in the corresponding precontrast T1-weighted images.

Methods

Patient Selection

This retrospective DCE-MRI study of invasive breast cancer patients was approved by our institutional review board under the Health Insurance Portability and Accountability Act. The requirement for consent was waived. Breast MRI images and reports acquired from October 2008 to December 2014 at our outpatient center were reviewed consecutively using the Picture Archiving and Communication System (PACS) database. Those with a biopsy-proven unilateral invasive breast cancer diagnosis or suspicious lesions were identified from the MRI reports. These patients' electronic medical records were subsequently reviewed to confirm the presence of an invasive breast cancer diagnosis. Only those who had an MRI performed before any breast cancer–related therapeutic intervention were included in the current study. Women with a history of breast surgery and/or cancer of any organs were excluded. This study was limited to invasive breast cancer only. Women with a diagnosis of ductal carcinoma-in-situ were also excluded.

Breast DCE-MRI Image Acquisition Techniques

Clinical breast DCE-MRI acquisition techniques have evolved over the years at our institution. Early images were acquired with relatively thicker slices and without fat saturation in order to achieve a high temporal resolution. New techniques that allowed thinner slices with fat saturation were gradually adapted after 2014.

Three-dimensional axial DCE-MRI images without fat saturation that covered both breasts entirely were acquired with the following parameters: TR/TE, 4.2/2.1 ms; flip angle, 10°; slice thickness, 2.5 to 2.7 mm; and in-plane resolution of 0.33 mm × 0.33 mm to 0.67 mm × 0.67 mm at a temporal resolution of 15 seconds per acquisition. Gadobenate dimeglumine (MultiHance, Bracco Imaging) was administered intravenously at a dose of 0.1 mmol/kg and an injection rate of 2 mL/s using a power injector (Spectris Solaris MR Injection System, Medrad). DCE-MRI was performed on one of the 1.5 T Achieva (Philips Medical System), 3 T Intera (Philips Medical System), or 3 T TrioTim (Siemens) MRI scanners using bilateral phased-array breast coils with patients lying in the prone position.

Three-dimensional axial DCE-MRI images with fat saturation that covered both breasts entirely were acquired with the following parameters: TR 4.9 to 7.8 ms, TE 2.5 to 4.8 ms; flip angle, 12°; slice thickness, 0.5 to 1.5 mm; and in-plane resolution 0.66 mm × 0.66 mm to 0.91 mm × 0.91 mm at a temporal resolution of 16 to 93 seconds per acquisition on the 3 T Intera (Philips Medical System), or 3 T TrioTim (Siemens) MRI scanners using bilateral phased-array breast coils with patients lying in the prone position. Gadobenate dimeglumine (MultiHance, Bracco Imaging) was administered intravenously at a dose of 0.1 mmol/kg and an injection rate of 2 mL/, using a power injector (Spectris Solaris MR Injection System, Medrad).

Breast Tumor Identification

Enhanced breast lesions were visually identified on the postcontrast subtraction images after the contrast enhancement reached a plateau, which occurred about 1 to 2 minutes after the administration of the contrast agent. Findings from the official breast MRI reports and pathology reports were used to confirm whether these enhanced lesions were indeed the pathology-proven invasive breast tumors.

Location of the Breast Tumor in Relation to Adipose Tissue

Breast fibroglandular and adipose tissues were differentiated by their strong intensity difference on the precontrast T1-weighted images. Adipose tissue appeared bright and fibroglandular tissue appeared dark on the T1-weighted images without fat saturation. The contrast between adipose and fibroglandular tissue is reversed on T1-weighted images with fat saturation. The breast tumor position in relation to adipose tissue was visually assessed by overlaying the contrast-enhanced MRI images on the corresponding T1-weighted precontrast images. Image analysis and visualization were performed in Fiji/ImageJ.[19,20]

Breast Density Assessment and the Thickness of the Upper Abdominal Adipose Layer

Three-dimensional MRI breast density was calculated from the contralateral breast with no tumor from the precontrast T1-weighted images without fat saturation as described elsewhere.[21] Briefly, bright fatty tissue and the entire breast were segmented by thresholding separately after the correction of image intensity bias artifacts due to magnetic field heterogeneity. Total voxel counts of the fatty tissue and the entire breast were calculated by an automated macro. The percentage of fatty tissue density was calculated as the percentage of total voxel counts occupied by the fatty tissues divided by that of the entire breast. The MRI percent breast density was calculated as the remaining percentage of the fatty tissue.[21]

The thickness of the upper abdominal adipose layer (UAAL) was measured on the T1-weighted precontrast axial images immediately below the breasts. This thickness was used as a surrogate marker for body adiposity because of a lack of body mass index information in this retrospective study.[21]

Results

Patient Selection Characteristics

Breast DCE-MRI was performed in our institution for high-risk screening,[22] evaluation of a suspicious lesion/lump, and treatment

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