ETHIOPIAN INTERNATIONAL JOURNAL OF MULTIDISCIPLINARY RESEARCH

eISSN: 2349-5715 pISSN: 2349-5707

Volume: 11, Issue 01, Jan-2024 SJIF 2019: 4.702 2020: 4.737 2021: 5.071 2022: 4.919 2023: 6.980

MRI DETECTION OF BREAST CANCER

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Abstract: Breast cancer has a high rate of metastasis; one-third of the patients diagnosed with breast cancer eventually develop metastases in distant organs, with an increased risk of mortality [1]. Breast cancer primarily metastasizes to the bone, lung, liver, lymph nodes and brain [2]. Breast cancer metastasis can occur years after apparently successful treatment, underscoring the importance of efficient clinical management of the disease, including prompt treatment response and monitoring for possible relapse. Early and accurate detection and differential diagnosis of breast cancer with metastatic potential and micrometastasis (<2 mm) may facilitate the design of more effective and time-sensitive patient-specific therapies[4,5]. Current clinical imaging modalities demonstrate limited potential in the detection and differential diagnosis of small high-risk breast cancer (<2 mm) and micrometastasis. Magnetic resonance imaging (MRI) is a powerful technique for high-resolution visualization of the anatomic structure and function of soft tissues, including tumours[6]. Small molecular Gd(III) chelates are routinely used for clinical cancer imaging to enhance image contrast by shortening the relaxation times of the surrounding water protons[7]. However, these chelates are non-specific contrast agents and cannot differentiate tumour aggressiveness or provide efficient detectable contrast in small tumours and micrometastases. Consequently, molecular imaging using a biomarker that is specifically associated with tumour aggressiveness and metastasis is an effective approach towards the early detection and differential diagnosis of high-risk breast cancer.

Key words :MRI, breast cancer, metastasizes, extracellular matrix.

Metastasis is the primary cause of death in breast cancer patients. Early detection of high-risk breast cancer, including micrometastasis, is critical in tailoring appropriate and effective interventional therapies. Increased fibronectin expression, a hallmark of epithelial-to-mesenchymal transition, is associated with high-risk breast cancer and metastasis. We have previously developed a penta-peptide CREKA (Cys-Arg-Glu-Lys-Ala)-targeted gadolinium-based magnetic resonance imaging (MRI) contrast agent, CREKA-Tris(Gd-DOTA)$_3$ (Gd-DOTA (4,7,10-tris(carboxymethyl)-1,4,7,10-tetraazacyclododecyl gadolinium), which binds to fibrin–fibronectin complexes that are abundant in the tumour microenvironment of fast-growing breast cancer. Here we assess the capability of CREKA-Tris(Gd-DOTA)$_3$ to detect micrometastasis with MRI in co-registration with high-resolution fluorescence cryo-imaging in female mice bearing metastatic 4T1 breast tumours. We find that CREKA-Tris(Gd-DOTA)$_3$ provides robust contrast enhancement in the metastatic tumours and enables the detection of micrometastases of size <0.5 mm, extending the detection limit of the current clinical imaging modalities. These results demonstrate that molecular MRI with CREKA-Tris(Gd-DOTA)$_3$ may facilitate early detection of high-risk breast cancer and micrometastasis in the clinic.[2]

Tumour microenvironment plays an essential role in tumour progression and metastasis [8,9]. A major component of the microenvironment is the extracellular matrix (ECM), which is composed of distinct components including collagen, proteoglycans, laminins and fibronectin. Compared with normal tissue, the tumour ECM is highly deregulated, with fundamentally different composition, architecture, biochemistry and physical properties10. Fibronectin is abundantly expressed in several

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types of malignant tumours and is associated with an invasive and metastatic phenotype10. Tumour fibronectin has been used as a biomarker to develop antibody-targeted vehicles for specific and effective delivery of imaging agents and therapeutic drugs to metastatic sites. Changes in the production and organization of fibronectin in the ECM contribute to the 'pre-metastatic niche', which dictates the pattern of metastatic spread. The expression of fibronectin is highly upregulated by transforming growth factor-beta (TGF-β) during epithelial-to-mesenchymal transition (EMT), and is a hallmark of EMT. According to The Cancer Genome Atlas (TCGA)-National Cancer Institute (NCI), invasive ductal breast carcinoma and breast carcinoma exhibit a six to sevenfold increase in the fibronectin expression, compared with normal breast. Thus, the highly expressed fibronectin and its complex with other matrix proteins such as fibrin are attractive biomarkers in molecular imaging for the early detection and differential diagnosis of high-risk breast cancer and micrometastasis. Tumour metastases labelled with green fluorescent protein (GFP) appear green in various organs and tissues, including brain, liver, lung, lymph node and spleen. Strong red fluorescence from CREKA-Cy5.0 was observed in the metastases, while the normal tissues showed little fluorescence. Immunostaining of the metastatic tumour sections with an antibody against fibronectin showed abundant fibronectin expression in the tumour ECM. The fluorescence from CREKA-Cy5.0 co-localized with the fibronectin immunostaining in the metastatic tumours, while the non-specific peptide probe showed little binding in the tumour sections and no co-localization with the fibronectin staining. Contrast-enhanced MRI with small molecular Gd(III) chelates generally demonstrates low sensitivity of molecular imaging of cancer-related cell surface biomarkers. Unlike the biomarkers expressed on the cancer cell surface [4], fibronectin and its complexes with other ECM proteins are highly expressed in high-risk breast cancer and distant metastases as compared with normal tissues. In this study, we have demonstrated that abundant fibrin–fibronectin complexes in the ECM of micrometastatic tumours facilitate the binding of a sufficient amount of a small molecular, targeted MRI contrast agent, CREKA-Tris(Gd-DOTA)$_3$, to generate robust enhancement for effective molecular MRI of micrometastasis[8]. By targeting the cancer-associated ECM, we were able to effectively image metastases, including micrometastases, distributed in different distant organs such as the lung, liver, lymph node, adrenal gland and bone. The effectiveness of molecular MRI with CREKA-Tris(Gd-DOTA)$_3$ in detecting breast cancer micrometastases was validated by high-resolution fluorescence cryo-imaging of GFP-labelled 4T1 breast cancer cells and the binding of a CREKA-targeted fluorescence probe. Fluorescence cryo-imaging has the ability to detect single GFP-labelled cancer cells[6], and is a new gold standard in validating the effectiveness and sensitivity of imaging probes and contrast agents for cancer molecular imaging in preclinical development. Three-dimensional, whole-body co-registration of high-resolution MRI images and fluorescence cryo-images in mice enabled us to determine the effectiveness and sensitivity of molecular MRI in detecting micrometastases.

The effectiveness of molecular MRI with CREKA-Tris(Gd-DOTA)$_3$ was demonstrated in two different breast cancer metastasis models with both mouse and human carcinoma cells, including intracardiac implant and orthotopic spontaneous models. The former tumour model is relatively convenient to develop reproducible metastases with relatively controlled sizes. The latter model encompasses all aspects of the metastatic cascade initiated from a primary tumour, which closely resembles clinically relevant metastasis, including the biochemical composition of the tumour ECM. Increased expression of fibronectin and its complexes with fibrin was demonstrated using binding of CREKA-Cy5.0 in both the tumour models, in comparison to the non-binding observed in healthy tissues . CREKA-Tris(Gd-DOTA)$_3$ was able to produce strong signal enhancement to delineate

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metastatic tumours in both the tumour models during molecular MRI with high spatial resolution, which correlated well with both bioluminescence imaging and fluorescence cryo-imaging.

Currently, X-ray mammography, [8]F-2-deoxy-D-glucose (FDG)-positron emission tomography–computed tomography, ultrasound and contrast-enhanced MRI are commonly used in the detection and clinical management of breast cancer. However, these imaging techniques are not cancer specific and fail to detect micrometastases. Molecular MRI with CREKA-Tris(Gd-DOTA)$_3$ shows high specificity and sensitivity in detecting micrometastasis in the mouse tumour models when compared with fluorescence cryo-imaging with CREKA-Cy5.0 in correlation with fluorescence cryo-imaging of GFP-labelled cancer cells. This technique has shown comparable sensitivity (91%) to fluorescence imaging in detecting breast cancer micrometastases with volumes as small as 0.5 mm^3, with a potential to detect even smaller micrometastases . For example, bone is the most common site (90%) of breast cancer metastasis and also the most frequent site of relapse after treatment for primary breast cancer [9]. Molecular MRI with CREKA-Tris(Gd-DOTA)$_3$ was able to detect bone micrometastasis with a diameter <0.5 mm, demonstrating that this technique has the potential to address the limitations of the current clinical imaging modalities. Non-invasive, high resolution and specific detection of micrometastases and other high-risk cancer in the whole body. The goal of cancer molecular imaging is to provide physicians a tool for early detection and differential diagnosis of high-risk tumours with confidence. The preliminary FROC blind analysis has shown 83% overall sensitivity in detecting metastatic tumours by molecular MRI with CREKA-Tris(Gd-DOTA)$_3$. The FROC blind analysis had no apparent criteria and the results might be affected by the experience of the reader. Further comprehensive work is needed to optimize the imaging protocols and to establish the imaging analysis criteria with a larger sample size for accurate early detection and diagnosis of very small aggressive tumours with molecular MRI.

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