MATHEWS

Review Article

Mathews Journal of Case Reports

Sensitivity and Specificity Improvement for Breast Cancer Detection by Tumor-Microenvironment Multimodality Molecular Imaging

Ramin Ghasemi Shayan[1], Fakhrosadat Sajjadian[2,*]

[1]*Radiology Department, Paramedical Faculty, Tabriz University of Medical Sciences, Iran*

[2]*Radiology Department, Paramedical Faculty, Tabriz University of Medical Sciences, Iran*

ABSTRACT

External factors in mutual cooperation with internal factors initiate and progress breast malignancies. One of those overwhelming major factors, affecting initiation, progression, therapy-resistance, recurrence and metastasis in cancer, is tumor microenvironment (TME). TME is described by hypoxia, vascular abnormal features, low extracellular pH (pHe), and increased interstitial fluid pressure which are to some extent unique to solid tumors (35). Breast cancer (BC) is the most universal fatal tumor and the second reason of death, after heart diseases, among women worldwide. External factors in mutual cooperation with internal factors initiates and progresses breast malignancies including mainly tumor micro environment. Tumor stroma is comprised of extracellular matrix (ECM), and stromal cells. In this article we extant a review on the main methods of breast cancer imaging that rely on molecular characteristics of solid tumor microenvironment for early and precise detection of breast cancer. There are 3 indispensable methods which have important role in detecting role of tumor microenvironment in progression of breast cancer. PET, MRI and Optical Imaging methods have been discussed through diverse detection of tumor microenvironment components using their numerous capabilities.

Keywords: Breast cancer, TME, PET scan, Optical imaging, MRI.

ABBREVIATIONS

BC: Breast Cancer; MRI: Magnetic Resonance Imaging; PET: Positron Emission Tomography; CT: Computed Tomography; MRA: Magnetic Resonance Angiography; TME: Tumor Microenvironment; OI: Optical Imaging; ECM: Extracellular Matrix; CAM: Cell Adhesion Molecule; VEGF: Vascular Endothelial Growth Factor; TNF: Tumor Necrosis Factor; NCPs: Nanoscale Coordination Polymers; FRET: Fluorescence Resonance Energy Transfer; BPCAs: Blood Pool Agents; ECF: Extracellular Fluid; MMPs: Matrix Metalloproteinases; DCE: Dynamic Contrast-Enhanced; OCAs: Oral Contrast Agents; SLNs: Sentinel Lymph Nodes; FDA: Food and Drug Administration; MEMRI: Manganese Enhanced MRI; SMA: Smooth Muscle Actin; FAP: Fibroblast-Activation Protein; TOLD: Tissue Oxygen Level Dependent; BOLD: Blood Oxygen Level Dependent.

Vol No: 08, Issue: 10

Received Date: October 14, 2023

Published Date: November 01, 2023

***Corresponding Author**

Fakhrossadat Sajjadian

Radiology Department, Paramedical Faculty, Tabriz University of Medical Sciences, Tabriz 51368, Iran, Tel: +989177140870, ORCID: 0000-0003-3478-1135

Email: mariasajjadian@yahoo.com

Citation: Shayan RG, et al. (2023). Sensitivity and Specificity Improvement for Breast Cancer Detection by Tumor-Microenvironment Multimodality Molecular Imaging. Mathews J Case Rep. 8(10):130.

INTRODUCTION

Breast cancer (BC) is the most common malignant tumor and the second cause of death, after heart diseases, among women worldwide [1-3]. More than one million women are affected by BC globally, and also it is the cause of more than 400,000 deaths yearly [4]. Premature diagnosis and screening of breast cancer improve survival rate and result in decreased mortality rate [5]. Due to inter and intra heterogeneity of BC which is detectable by high level of phenotype and genotype diversity in tumor components like as cells and microenvironment, treatment plan decision is proving to become more complicated and prognosis can vary among patients [6,7]. It is proven that tumor diversity and aggressiveness are strongly linked with the nature of microenvironmental properties [8]. Therefore, in order to select appropriate therapy, not only requires the clinical and historical status of the patient but also the molecular features of the tumor components. BC has been categorized into four subtypes including luminal A, luminal B, HER2 (human epidermal growth factor receptor 2) positive and basal (known as, triple negative) [9,10]. The etiology of BC is complicated and several factors are involved in causation of tumor evolution [11,12]. Vast majority studies are evidence of involving two risk factors in BC including intrinsic and non-intrinsic factors. The former refers to randomly unavoidable driver mutations in DNA replication causing genetic diversity in different individuals at various rates. The letter is divided into two subgroups classifying to endogenous and exogenous factors. Endogenous factors such as immune response, hormones, genetic susceptibility and blood supply could be considered as tumor microenvironment/ tumor cells niche which actively participate in fate of cells. Lifestyle, radiation, viruses and chemical carcinogens play exogenous factors role in this category [13-15]. Therefore, external factors in mutual cooperation with internal factors initiate and progress breast malignancies. One of those overwhelming major factors, affecting initiation, progression, therapy-resistance, recurrence and metastasis in cancer, is tumor microenvironment (TME). Mechanisms of the tumor microenvironment, comprising cellular (macrophage, fibroblast, endothelial, mesenchymal, immune cells), and cellular (extra-cellular matrix (ECM) molecules, vascular and lymphatic vessel) are increasingly recognized as a hallmark in cancer biology [16-18]. The ECM of TME with abundant effective biomarkers on tumor growth and invasion like as ECM proteins and proteases [19], physiological microenvironment comprising hypoxia (oxygen tension), acidity (PH potential), interstitial pressure and also tumor vascular biomarkers such as cell adhesion molecule (CAM) [20], vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF) [21] could be targeted on molecular imaging [22]. In some solid tumors, comprising the breast and pancreas, up to 90% of the tumor mass is TME [22]. Participation of complex and heterogeneous TME in cancer progression came out from pioneering researches that described the 'seed' (cancer cell) link to its 'soil' (TME) [19]. Actually, molecular imaging technologies integrate molecular biology and anatomical information and conventional imaging method. Therefore, it is able to state a fundamental role in clinical diagnosis and treatment of cancer [23]. Surprisingly, molecular imaging not only detects cancer, even if it is too small, but it also destroys the cancer micro foci during surgery, resulting in no cancer tissue remains [21]. In spite of various treatment options such as surgery, chemotherapy, radiation, endocrine and targeted therapy, several recurrence and failure exist in breast cancer, leading to metastasis and death [24]. Using imaging tools and understanding the molecular mechanisms that drive tumor resistance are absolutely vital to prevent invasion and metastasis in breast cancer [25,26]. Cancer molecular imaging has been categorized as imaging modalities and imaging probes or contrast agents, which are applied to target, detect and cancer biomarkers [27,28]. Regarding to importance of imaging agents which are crucial for exact molecular imaging, their design and development such as specificity, high sensitivity, and low toxicity must be considered [29]. Currently, in order to designing novel therapies, targeted cancer therapy main focuses are on the biomarkers of either TME or cancer cells that reciprocal interactions fuel the developmental process of tumor [30,31]. Hence, molecular imaging of the TME might improve efficiency of novel therapies and facilitate the recognition of pre-metastatic niche [32,33]. Regarding the key role of TME in breast cancer advancement and the limitation of imaging modalities, multimodality imaging combining both macro- and microscopic changes to study TME is needed for tumor masses imaging and successful treatment of cancer [34]. Heterogeneity property is recognized as a hallmark of breast tumor, so there is an urgent need to understand the molecular mechanism and pathways that take part in the diversity for personalized medicine in BC patients. In this article we extant a short review on the main methods of breast cancer imaging that rely on molecular characteristics of solid tumor microenvironment for early and precise detection of breast cancer.

TME and Imaging details of TME through three different modality

TME

TME is described by hypoxia, vascular abnormal features, low extracellular pH (pHe), and increased interstitial fluid pressure which are to some extent unique to solid tumors

[35]. Tumor stroma is composed of extracellular matrix (ECM), and stromal cells. Tumor stromal cells comprising fibroblasts, endothelial cells, pericytes, and numerous immune cells, such as macrophages, neutrophils, mast cells, myeloid progenitors, and lymphocytes, in neighborhood of cancer cells which have significant accomplishment in reprogramming of stromal cells [36] and remodeling of ECM [37]. Compelling evidence extensively suggests that the tumor stroma itself transforms in the course of tumor advancement. On the other hand, tumor stroma is able to reform tumor metabolism, progression, treatment response, and even can affect cell signaling pathways and cellular differentiation process [38,39]. For visualizing and estimating detailed characteristics of the TME as inseparable part of tumor, non-invasive multimodal imaging methods have been developed in preclinical cancer [40].

Imaging modalities contrast agents

PET imaging needs use of radioactive contrast agents to achieve images. Some agents applied for PET imaging prepare data about tissue metabolism or some other accurate molecular activity. The emitted positron strikes with a neighboring electron to produce two 511 KeV gamma rays coarsely 180 apart. PET contrast agents and their details including chemical name and application are shown in the Tab1 below.

It is based on this physical chief and the positron equivalent signals that the point source of the gamma rays can be expected, by using a coincident circuit for detectors 180 apart [41,42]. In other words, PET imaging uses radioactive isotopes that release positrons, such as 18F, 15O, 13N, or 11C; whereas SPECT imaging uses isotopes that emit gamma photons, such as 99mTc, 123I, or 125I. Positrons travel short expanses in tissues, in the order of milli meters, and strike with surrounding electrons (annihilation), producing two high energy gamma rays that travel in opposite directions to one another and are detected by the PET camera [43]. Currently, most of the clinical imaging agents encompassing MRI and CT contrast agents, and PET tracers are small molecules which are used because of their low cost, well-defined structure, and good safety profiles. Specificity and sensitivity are the noteworthy parameters in designing the imaging agents for molecular imaging of TME biomarkers [22]. Both PET and SPECT provide data about physiological activity, such as glucose metabolism, blood flow, perfusion, and oxygen consumption. However, they shortage anatomical detail, which has led to the development of hybrid systems that syndicate PET and SPECT with other image modalities such as CT and MRI [43]. The first type of *optical imaging agents* is *endogenous optical contrast* which researches in biomedical optics have long due to the fact used spectroscopy and imaging methods to scrutinize the absorption, scattering, fluorescence, and polarization consequences of everyday and neoplastic tissues. Both morphological and biochemical discrepancies due to cancer enhancement have been proven to have an effect on the optical houses of the host tissue, inspiring the improvement of imaging structures to realize disorder using light-based measurements which is known as endogenous optical contrast. The second type is *Non-specific exogenous contrast agents* in which developing optical distinction with exogenous retailers has conservatively relied on non-specific small molecules in order to both existing extraordinary absorbing and fluorescent properties, or to set off detectable modifications in native tissue effects. A vary of fundamental dyes with absorbing or fluorescent homes comprising fluorescein, indocyanine green, cresyl violet acetate, toluidine blue, and Lugol's iodine are presently used in scientific screening [44]. *Non-specific fluorochromes* or phosphorescent nanoscale coordination polymers (NCPs) with unprecedentedly high dye loadings were coated with thin silica shells to tune the dye launch kinetics. Supplementary functionalization of the NCP/silica particles with poly ethylene glycol (PEG) and PEG-anisamide heightened their biocompatibility and concentrated on capability, enabling cancer-specific imaging of human lung most cancers H460 cells [45]. *Phosphorescent Nanoscale Coordination Polymers* (NCPs) with unprecedentedly high dye loadings were coated with thin silica shells to tune the dye release kinetics. Supplementary functionalization of the NCP/silica particles with poly ethylene glycol (PEG) and PEG-anisamide heightened their biocompatibility and targeting capability, permitting cancer-specific imaging of human lung cancer H460 cells [46]. *Bright fluorescent nanoparticles* or Fluorescent cross-linked nanoparticles with mutable fluorophore loading amounts, locations, and particle sizes have been manufactured from sequential one-pot functionalization/cross-linking of block copolymer micelles with amine-terminated dye and cross-linker molecules, by reductive amination and amidation. The fluorescence quantum yield and brightness of these nanoparticles had been assessed with the aid of steady-state and dynamic fluorescence methods. The consequences validate that the quantum yield and brightness of the fluorescent nanoparticles correlated straight with the range of dyes/nanoparticle and the nanoparticle size. A strategy to amplify the fluorescence brightness of nanoparticles with fluorescein and near-infrared dyes is proposed [47]. *Molecular-specific exogenous contrast agents* has allowed imaging of reporter gene expression at macroscopic and microscopic scales, with good sized impact on mobile phone lifestyle and animal research [48,49]. Cancer biomarkers are continuously being recognized by using molecular

profiling studies, and embody particular proteins, cell surface receptors, and enzymes. Organic fluorophores, steel nanoparticles, and semiconductor quantum dots have all been inspected as optical reporters, either encompassing direct conjugation to the probe ligand, or indirect binding via a linker area [44]. *MRI contrast agents* are contrast agents who have been progressed to visualize the body structures internally in magnetic resonance imaging (MRI) and lead to increasing the contrast difference between normal and abnormal tissues. The route of administration, depends on the subject of interest, may be intravenously or orally. The first is suitable for GI tract scans and the second is more useful for most other scans. Also they omit through the kidneys in the body [50]. MRI contrast agents have been classified according to the magnetic properties into paramagnetic and super paramagnetic contrast agents. The paramagnetic contrast agents consist of dysprosium (Dy3+), the lanthanide metal gadolinium (Gd3+) and the transition metal manganese (Mn2+). The lanthanide ion gadolinium (III) is the most commonly used contrast agent in MRI [51]. The super paramagnetic contrast agents contain iron oxide and iron platinum particles [52,53]. *Gadolinium-based contrast agents: paramagnetic* are chemical substances that are used in MRI scans and do not contain iodine, so they are mostly safe and rarely cause an adverse effect or allergic reaction. Using gadolinium-based contrast agents, the quality of MR images are enhanced for diagnosing more accurately disease or abnormality by improving the visualization of specific organs, tissues, and blood vessels [54,55]. Gadolinium is the most usually used for enhancement of vessels in magnetic resonance angiography (MRA) and brain tumor enhancement related to the degradation of the blood–brain barrier [56]. Gadolinium contrast agents can be categorized by body compartment as extracellular fluid (ECF) agents, blood pool contrast agents (BPCAs) and organ-specific agents [54,55,57,58]. Moreover, *Extracellular fluid agents (intravenous contrast agents*) are small molecular weight composites with nonspecific distribution in blood and extracellular space of the body. These compounds are designed to discriminate tumors, inflammation in imaging and also used for magnetic resonance angiography (MRA). A list of the ECF agents is presented in Table 2. *Also Blood Pool Agents* (BPCAS) are divided into macromolecular and low-molecular-weight agents and are used almost in MRA. A list of the BPCAS is presented in Table 3. Finally, Targeted/ organ-specific agents mostly improve the discrimination and diagnosis of hepatic lesions. A list of such compounds is presented in Table 4.

Table 1. PET scan contrast agents and their applications.

PET Contrast Agents	Chemical Name	Application
^{64}Cu-ATSM	N^4-methylthiosemicarbazone	Hypoxic Detection (tissue with low oxygen)
FDG	^{18}F-fluorodeoxyglucose	Metabolic activity of tissues Study tumor response to treatment
^{18}F-fluoride	-	Modifications both in normal bone as well as bone tumors Measure response to treatment
FLT	3'-deoxy-3'-[^{18}F]fluorothymidine	Identify growth in a primary tumor Perceive tumor response to treatment
FMISO	^{18}F-fluoromisonidazole	Hypoxia (low oxygen) in tissues
Gallium	-	Inflammation, such as infection Rapid cell division
Technetium-99m	-	Radiolabel many distinct regular radiopharmaceuticals in bone and heart scans

Table 2. ECF agents. ECF, extracellular fluid; Gd-DTPA, gadolinium (III) diethylene triamine pentaacetate; Gd-DOTA, gadoterate dotarem; Gd-DTPA-BMA, gadolinium 3-diethylenetriamine pentaacetate-bis (methylamide).

Short Name	Generic Name	Trade Name
Gd-DTPA	Gadopentate dimeglumine	Magnevist
Gd-DOTA	Gadoterate meglumine	Dotarem
Gd-DTPA-BMA	Gadodiamide injection	Omniscan
Gd-HP-DO3A	Gadoteridol injection	ProHance
Gd-DTPA-BMEA	Gadoversetamide	OptiMARK
Gd-DO3A-butrol	Gadobutrol	Gadovist
Gd-BOPTA	Gadobenate dimeglumine	MultiHance

Table 3. BPCAs. BPCAs, blood pool contrast agents; USPIO, ultrasmall super paramagnetic iron oxide.

Short Name	Generic Name	Trade Name
NC-100150	PEG-feron (USPIO)	Clariscan
SH U 555 C	Ferucarbotran (USPIO)	Supravist
MS-325	Gadofosveset	AngioMARK
Gadomer-17	-	-
Gabofluorine-M	-	-
P792	Gadomelitol	Vistarem
AMI-227	Ferumoxtran-10 (USPIO)	Combidex
Gd-BOPTA	Gadobenate dimeglumine	MultiHance

Table 4. Targeted/organ-specific agents. Gd-DTPA, gadolinium (III) diethylenetriamine pentaacetate; Mn-DPDP, manganese dipyridoxyl diphosphate; SPIO, superparamagnetic iron oxide; USPIO, ultrasmall superparamagnetic iron oxide; Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriamine pentaacetate.

Short Name	Generic Name	Trade Name
Mn-DPDP	Mangafodipir trisodium	Treslascan
Gd-EOB-DTPA	Gadoxetate	Primovist
Gd-BOPT	Gadobenate dimeglumine	-
AMI-25	Ferumoxides (SPIO)	Eovist
SH U 555 A	Ferucarbotran (SPIO)	MultiHance
AMI-227	Ferumoxtran-10 (USPIO)	Endorem
Gadofluorine-M	-	-
Mn-DPDP	Mangafodipir trisodium	Feridex
Dy-DTPA-BMA	Sprodiamide injection	Resovist
Gd-DTPA-mesoporphyrin	Gadophrin	-
Mn-DPDP	Mangafodipir trisodium	Cliavist
Gd-EOB-DTPA	Gadoxetate	Sinerem
Gd-BOPT	Gadobenate dimeglumine	-
AMI-25	Ferumoxides (SPIO)	Combidex
SH U 555 A	Ferucarbotran (SPIO)	-
AMI-227	Ferumoxtran-10 (USPIO)	-

Manganese, in the form of manganese chelates or manganese-based nanoparticles, is used as a contrast agent. Manganese chelates such as manganese dipyridoxyl diphosphate (Mn-DPDP) have been used to detect liver lesions [59]. Manganese ion (Mn2+) as contrast agents have applications in animal studies, usually referred to as Manganese Enhanced MRI (MEMRI) [59]. Manganese is taken up by the liver cells and excreted into the bile, whereas the DPDP component is excreted by the kidneys [60]. Unfortunately research on Mn-based nanoparticles is at an early stage in comparison with other well-studied nanoparticles based on iron oxide [61]. Iron oxide: Superparamagnetic contrast agents are categorized into superparamagnetic iron oxide (SPIO) and ultrasmall superparamagnetic iron oxide (USPIO). Using SPIO and USPIO successfully resulted in diagnosis of hepatic tumors in some cases [52]. In spite of enormous improvement in nanotechnology which makes disease-specific biomarkers visible at microscopic and molecular levels leading to greater attention as potential MRI contrast agents in other nanoparticles, iron oxide nanoparticles are still used in clinical practice [62]. Iron Platinum: Superparamagnetic particles specifically targeted human prostate cancer cells in vitro, and these results suggest that SIPPs may have a role as tumor-specific contrast agents. These contrast agents are still under investigation and have not yet been studied in humans [53]. In the United States, A list of Gd chelated contrast agents approved by the U.S. Food and Drug Administration (FDA) is presented in table 5.

Table 5. Gd chelated agents approved by the United States FDA. ECF, extracellular fluid; Gd-DTPA, gadolinium (III) diethylene triamine pentaacetate; Gd-DOTA, gadoterate dotarem; Gd-DTPA-BMA, gadolinium 3-diethylenetriamine pentaacetate-bis (methylamide), Gd-EOB-DTPA, gadolinium ethoxybenzyl diethylenetriamine pentaacet.

Short Name	Generic Name	Trade Name
Gd-DTPA	Gadopentate dimeglumine	Magnevist
Gd-DOTA	Gadoterate meglumine	Dotarem, Artirem
Gd-DTPA-BMA	Gadodiamide injection	Omniscan
Gd-HP-DO3A	Gadoteridol injection	ProHance
Gd-DTPA-BMEA	Gadoversetamide	OptiMARK
Gd-DO3A-butrol	Gadobutrol	Gadovist
Gd-BOPTA	Gadobenate dimeglumine	MultiHance
Gd-EOB-DTPA	Gadoxetate	Primovist, Eovist
MS-325	Gadofosveset	AngioMARK, Vasovist, Ablavar

MRI oral contrast agents (OCAs) are basically on the heavy metal ions comprising gadolinium, manganese (III), manganese (II), copper (II) and iron (III). Air and clay are applied for lower T2 signal [63]. The oral use of MRI contrast agents including manga¬nese is a noninvasive approach of imaging. Conversely, the intravascular route of use of MRI contrast agents is more practical and is the more generally handled route for MRI scans [64]. A list of OCAS is presented in table 6.

Table 6. Agents administered orally. MPIO, micron size iron oxide particles.

Short Name	Generic Name	Trade Name
Gd-DTPA	Gadopentate dimeglumine	Magnevist Enteral
-	Ferric amonium citrate	Ferriseltz
-	Manganese chloride	LumenHance
-	Gadolinium-loaded zeolite	Gadolite
OMP	Ferristene (MPIO)	Abdoscan
AMI-121	Ferumoxsil (MPIO)	GastroMARK
PFOB	Perfluoro-octylbromide	Imagent GI

Imaging details of TME in breast cancer through 3 modalities

Angiogenesis and blood flow

Angiogenesis is regularly observed as a regulating event in the multi-step metastatic cascade and might organise a rate-limiting step in solid tumor growing. The angiogenic response and blood flow remodeling in solid tumors might lead clinical indicators and update on response and development on treatment [40]. PET using radiolabeled water (H215O-PET) is sensitive method that intends to noninvasively measurement and measure the physiology of tumor microcirculation. PET applies positron-emitting tracers, of which H215O can be exploited to study tumor blood flow. This method is now being applied in several phase I, II, and III clinical trials assessing tumor vascular response to antiangiogenic drugs. H215O-PET findings need the accessibility of an onsite cyclotron also the predictive value of H215O-PET has to be verified in phase III trials with predefined cutoff values for response explanation before validations on clinical usage can be made [65]. Due to its outstanding sensitivity of label detection, optical imaging is a compelling approach to assess tissue angiogenesis down to the molecular or even genetic level. A wide variability of contrast means for key molecules in angiogenesis have been explained [66,67]. Nonetheless, clinical translation of OI for imaging angiogenesis is incomplete by the moderately low tissue penetration of photons, limiting its application to primarily superficial structures, and by the incomplete accessibility of tracers. More clinical purposes to come of contrast-enhanced OI for imaging tissue angiogenesis include intraoperative, endoscopic, e.g. cystoscopic [68] or laparoscopic techniques [69-71], as well as catheter-based instrumentation.

Lymph nodes

Since the prominence of sentinel lymph nodes (SLNs) in tumor staging and patient management, sensitive and precise imaging methods of SLNs have been reconnoitered. PET possesses advanced sensitivity and temporal resolution also PET lymphography has been examined with intradermal use of 18F-FDG for joint diagnostic and intraoperative visualization of LNs 79. Within 30 min after tracer injection, lymphatic vessels and LNs can be genuinely published by means of PET in an animal modal. However, the clinical application of 18F-FDG PET lymphography might be struggled by the fast migration of the small molecules into blood flow [72].

Mesenchymal Stem Cell

MSCs are fibroblast-like cells with heterogeneous population which are observed surrounding blood vessels, comparable to pericytes, and are focused in the bone marrow and adipose tissue where they are regularly segregated. They can likewise be separated from cord blood and placental tissues [73-75]. Novel dual-modality (PET/MRI) nanoparticle contrast agents are presently being advanced to tag cells without transfection reagents; these might show to be paramount in animal replicas and in the clinic based on their high cell-labeling efficacy and low cytotoxicity [76]. PET and PET/CT (computed tomography) scans are commonly used clinically to detect human malignancies and have been used to detect cytolytic T cells or therapeutic cells. Other data, tagged with the HSV1-tk reporter gene or the HSV1-sr39tk mutant. Reporter gene expression, detected by injection of 18F-FHBG, can be used to image cell migration to glioblastoma or other tumors [77,78]. The clinical utility of PET scans makes them easy to translate into short- or long-term MSC monitoring applications in patients, depending on the contrast reagent used. Studies have shown that with MRI [79] and bioluminescence [80] imaging in vivo, we can monitor the tumor effects and localization of MSCs, pre-labeled with an imaging probe and co-injected with tumor cells. Accumulation of the MSCs in tumors and developing combined treatment/imaging MSC moieties, made them as desirable target for [81,82] cell tracking and treatment monitoring [83,84].

MMPs

The matrix metalloproteinase family shares specific structural and functional components: the pre, pro, and catalytic domains required for extracellular secretion, enzyme activation, and enzyme activity, respectively [85]. MMP family members are further categorized based on supplementary protein domains that influence to their individual characteristics [86,87]. Recently, several types of PET/SPECT tracers have been developed for cancer imaging. For example, [18F]-2-deoxy-2-fluoro-D-glucose (FDG) and 1-[methyl-11C]-methionine are the most commonly and successfully used clinical diagnostics of cancer [88]. FDG monitors glucose metabolism and is used for cancer staging and diagnosis, radiotherapy planning, treatment response and prognosis assessment. Methionine measures amino acid uptake and helps plan radiation therapy. Tumor uptake of both tracers is thought to correlate with tumor growth, a key feature of tumor malignancies [88]. For imaging MMPs in vivo, several modalities and targeted probes such as MRI have been devised [89]. Assessing MMP activity, molecular MRI by using protease-modulated contrast agents is emerging that is potentially quantitative and it is possible to acquire anatomical (morphological) data in the same setting [90].

PH and hypoxia

The pH of TME is typically more acidic than that of normal tissues. This is mainly due to the formation of lactate under aerobic conditions along with protons from hydrolysis during ATP synthesis [91]. The extracellular pH of normal tissues is maintained at pH 7.4, whereas the pH of TME ranges from 6.2 to 6.9 [92]. The Warburg effect seen in cancer cells was readily extrapolated to tumor imaging, primarily due to the glucose uptake measurements demonstrated using his 18F-FDG-PET. 18F-FDG PET/CT imaging provides valuable clinical insight for cancer staging and recurrence detection [40]. Optical imaging has several advantages due to its high sensitivity and fast acquisition speed. NIR fluorescence has low autofluorescence and absorption of endogenous molecules, resulting in increased sensitivity and spatial resolution in deep tissue. A recently reported probe, DiIR783-S, is activated by hydrazine bond cleavage at low pH, reducing self-quenching effects and activating NIR fluorescence [66]. Several non-invasive imaging modalities have been developed to measure extracellular (PHe) and intracellular (PHi) pH in tumors [93,94]. umor pHe and pHi distribution can be assessed by 31P MRS/MRSI using pH markers such as 3-aminopropylphosphonate [95,96]. However, the lack of sensitivity and limited spatial resolution of 31P-MRSI has led to the use of 1H-MRSI pHE labeling to further improve detection sensitivity [96,97]. Chemical exchange saturation transfer (CEST) MRI was developed to detect pH-dependent chemical exchange between amide protons and surrounding water molecules [97,98]. A dual-tracer MRI-based therapy was developed to track drug release from nanocarriers using SPION and gadolinium diethylenetriaminepentaacetic acid bismethylamide (GdDTPA-BMA) [99]. With GdDTPA-BMA, SPIONs lead to a preponderance of negative rather than positive reinforcement, resulting in pH-based therapeutic probes reaching deep tissue [100]. Oxygen deprivation may affect the diagnosis and prognosis of breast tumors.

Hypoxia plays an important role in carcinogenesis, causing metabolic dysregulation and leading to more aggressive tumors indicated by an increased risk of invasion and metastasis [101,102]. Noninvasive approaches to detect and monitor changes in blood oxygen levels, such as magnetic resonance imaging, have been proposed to visualize tissue hypoxia in human tumors. Dynamic contrast-enhanced (DCE) MRI has been proposed as a suitable technique to assess tumor hypoxia [103,104]. Tumor hypoxia is directly and noninvasively imaged and visualized by hypoxic markers that accumulate in hypoxic cells using electron paramagnetic resonance (EPR) or 19F-MRS (magnetic resonance spectroscopy) [105-108]. Magnetic resonance spectroscopy (MRS) was developed with a probe that utilizes the relaxation of hexamethyldisoroxane (HMDSO(1H MRS)) [109]. To measure the extent of deoxygenation. Aggressive contrast enhancement is achieved using gadolinium-tetraazacyclododecane-tetraacetic acid to improve the imaging modality. 2-Nitro-imidazole monoacid conjugate (GdDO3NI) [110]. Due to the relationship between hypoxia and vascular tissue oxygenation, a number of MRI modalities based on vascular features associated with tumor hypoxia, such as BOLD, TOLD, and DCE-MRI, are capable of detecting changes in tumor hypoxia. Known [111-113]. Tissue oxygen tension has also been demonstrated by 19F MRI oximetry using perfluorocarbons [113].

Proteoglycan (Hyaluronan) Imaging

Proteoglycan hyaluronan (hyaluronic acid) is a nonsulfated glycosaminoglycan in ECM that often used as a tumor marker for breast and prostate cancer, monitoring the progression of the disease [114-116]. Of note that, depends on its molecular weight may be as a tumor suppressor or developer. Hyaluroni-dase-1, 2 (Hyal1, Hyal2) that have studied mainly in cancer, result in degradation of hyaluronan [116]. It is reported that Hyal1 over-expression has been related with more aggressive tumors in an enormous kinds of epithelial cancers such as breast, bladder, colorectal and ovary [116]. In recent years, the advancement of various HA probes to image HA turnover and clearance [117,118] has expanded extremely. HA probes often use the high specificity of HA for the CD44, are a receptor for hyaluronic acid and overexpressed in different type of tumor cells [119]. Single moiety, HA-based CAs have been applied to image Hyals activity by MRI [120]. In order to assess the Hyal activity, HA probes often consist of more than one CA moiety to control the strength of multimodal imaging such as MRI/optical imaging [121,122], MRI/computer tomography (CT) [123], resulting in much better diagnostic capability and improve therapy efficiency [124].

Cancer-associated fibroblasts (CAFs) and imaging

Cancer-related fibroblasts are rich cell types in a tumor stroma that show a strategic function in advancing cancer, progression and metastasis [125]. CAFs are determined by numerous markers including α-smooth muscle actin (α-SMA), vimentin and fibroblast-activation protein α (FAP) [126]. FAP expresses in tumor cells and also increasingly elevates in CAFs that makes it as an ideal target for diagnostic and therapeutic imaging [127-129]. Due to peptide substrates share with other postprolyl peptidases by FAP in FAP-targeted in vivo imaging probes, resulting non-specific binding in vivo [128], To do so, Granot et al. CAF was used in vitro with the contrast agents biotin-bovine serum albumin-gadolinium diethylenetriaminepentaacetic acid, Feridex, or 1,10-dioctadecyl-3,3,3-tetramethylindotricarbocyanine iodine [128,130]. Many investigations revealed that on the basis of depletion of FAP-expressing stromal cells with multimodal imaging probes can seriously improve treatment responses in cancer [131].

Tumor vasculature and Lymphatics-endothelial Cells

Endothelial cells (ECs) constitute the foremost available elements of blood vessels and are responsible for tumor enhanced angiogenic potential, which prominently affect tumor progression [132,133]. Recent attention has focused on the importance of vascular endothelial cells, as endothelial cell dysfunction contributes to tumor cell adhesion, migration and metastasis through reduced synthesis of vasoprotective mediators. Suppression of breast cancer metastasis [134,135]. Therefore, tumor vascularity has been assessed in vivo noninvasively by MRI imaging [17]. Lymphatic endothelial cells express specific antigens such as podoplanin to promote their migration, adhesion and lymphogenesis. Podoplanin is the most commonly used marker for lymphatic endothelial cells, and a probe targeting lymphoid cells has been developed for his MRI imaging [95]. Yang et al. developed polyethylene glycol (PEG)-GoldMag NPs which were conjugated with anti-podoplanin antibody (PodAb), resulting in assessment of the tumor lymph angiogenesis in vivo using MRI in breast cancer [136].

Interstitial Fluid Pressure (IFP)

An imbalance in angiogenic factors such as vascular endothelial growth factor (VEGF), matrix metalloproteinases (MMPs) and angiopoietins leads to abnormal blood vessel formation. In some cases, high permeability allows the exchange of molecules within the tumor vasculature without maintaining gradients. This leads to abnormalities in his IFP [137,138].

CONCLUSION

Breast cancer (BC) is the most common malignant tumor and the second cause of death, after heart diseases, among women

worldwide. External factors in mutual cooperation with internal factors initiates and progresses breast malignancies which one of them is TME. There are 3 indispensable methods which have important role in detecting role of TME in progression of breast cancer. PET, MRI and Optical Imaging methods have been discussed through diverse detection of TME components using their numerous capabilities.

COMPETING INTERESTS

Mr. Ramin Ghasemi Shayan declares that he has no conflict of interest. Dr. Fakhrosadat Sajjadian declares that she has no conflict of interest.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

N/A

CONSENT FOR PUBLICATION

N/A

AVAILABILITY OF DATA AND MATERIAL

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

FUNDING

This article did not have any funding resources.

AUTHORS' CONTRIBUTIONS

The main idea of the article was from Mr Ramin Ghasemi Shayan and literature search and data analyses were performed by all the authors. Dr Fakhrosadat Sajjadian drafted and critically revised the work.

ACKNOWLEDGEMENTS

N/A.

SOURCE(S) OF SUPPORT

There was no funding source endorsing this articles preparation process.

REFERENCES

1. Sun YS, Zhao Z, Yang ZN, Xu F, Lu HJ, Zhu ZY, et al. (2017). Risk Factors and Preventions of Breast Cancer. Int J Biol Sci. 13(11):1387-1397.
2. McGuire S. (2016). World Cancer Report 2014. Geneva, Switzerland: World Health Organization, International Agency for Research on Cancer, WHO Press, 2015. Adv Nutr. 7(2):418-419.
3. Tudoran OM, Balacescu O, Berindan-Neagoe I. (2016). Breast cancer stem-like cells: clinical implications and therapeutic strategies. Clujul medical (1957). 89(2):193-198.
4. Parkin DM, Bray F, Ferlay J, Pisani P. (2005). Global cancer statistics, 2002. CA Cancer J Clin. 55(2):74-108.
5. DeSantis CE, Fedewa SA, Goding Sauer A, Kramer JL, Smith RA, Jemal A. (2016). Breast cancer statistics, 2015: Convergence of incidence rates between black and white women. CA Cancer J Clin. 66(1):31-42.
6. Voduc KD, Cheang MC, Tyldesley S, Gelmon K, Nielsen TO, Kennecke H. (2010). Breast cancer subtypes and the risk of local and regional relapse. J Clin Oncol. 28(10):1684-1691.
7. Buchsbaum RJ, Oh SY. (2016). Breast Cancer-Associated Fibroblasts: Where We Are and Where We Need to Go. Cancers (Basel). 8(2):19.
8. Quail DF, Joyce JA. (2013). Microenvironmental regulation of tumor progression and metastasis. Nat Med. 19(11):1423-1437.
9. Matthews SB, Sartorius CA. (2017). Steroid Hormone Receptor Positive Breast Cancer Patient-Derived Xenografts. Horm Cancer. 8(1):4-15.
10. Prat A, Perou CM. (2011). Deconstructing the molecular portraits of breast cancer. Mol Oncol. 5(1):5-23.
11. Hiatt RA, Brody JG. (2018). Environmental Determinants of Breast Cancer. Annu Rev Public Health. 39(1):113-133.
12. Hiatt RA, Porco TC, Liu F, Balke K, Balmain A, Barlow J, et al. (2014). A multilevel model of postmenopausal breast cancer incidence. Cancer Epidemiol Biomarkers Prev. 23(10):2078-2092.
13. Wu S, Zhu W. (2018). Evaluating intrinsic and non-intrinsic cancer risk factors. 9(1):3490.
14. Tomasetti C, Li L, Vogelstein B. (2017). Stem cell divisions, somatic mutations, cancer etiology, and cancer prevention. Science. 355(6331):1330-1334.
15. Wu S, Powers S, Zhu W, Hannun YA. (2016). Substantial contribution of extrinsic risk factors to cancer development. Nature. 529(7584):43-47.
16. Maller O, Martinson H, Schedin P. (2010). Extracellular matrix composition reveals complex and dynamic stromal-epithelial interactions in the mammary gland. J Mammary Gland Biol Neoplasia. 15(3):301-318.
17. Narunsky L, Oren R, Bochner F, Neeman M. (2014). Imaging aspects of the tumor stroma with therapeutic implications. Pharmacol Ther. 141(2):192-208.
18. Place AE, Jin Huh S, Polyak K. (2011). The microenvironment in breast cancer progression: biology and implications for treatment. Breast Cancer Res. 13(6):227.
19. Tam WL, Weinberg RA. (2013). The epigenetics of

epithelial-mesenchymal plasticity in cancer. Nat Med. 19(11):1438-1449.

20. Hernot S, Unnikrishnan S, Du Z, Shevchenko T, Cosyns B, Broisat A, et al. (2012). Nanobody-coupled microbubbles as novel molecular tracer. J Control Release. 158(2):346-353.
21. Poon RT, Fan ST, Wong J. (2001). Clinical implications of circulating angiogenic factors in cancer patients. J Clin Oncol. 19(4):1207-1225.
22. Zhou Z, Lu ZR. (2017). Molecular imaging of the tumor microenvironment. Adv Drug Deliv Rev. 113:24-48.
23. Weissleder R. (2006). Molecular Imaging in Cancer. Science. 312(5777):1168-1171.
24. Mao Y, Keller ET, Garfield DH, Shen K, Wang J. (2013). Stromal cells in tumor microenvironment and breast cancer. Cancer Metastasis Rev. 32(1-2):303-315.
25. Panieri E. (2012). Breast cancer screening in developing countries. Best Pract Res Clin Obstet Gynaecol. 26(2):283-290.
26. Godavarty A, Rodriguez S, Jung Y-J, Gonzalez S. (2015). Optical imaging for breast cancer prescreening. Breast cancer (Dove Medical Press). 7:193-209.
27. Frangioni JV. (2008). New technologies for human cancer imaging. J Clin Oncol. 26(24):4012-4021.
28. Zhou Z, Lu ZR. (2013). Gadolinium-based contrast agents for magnetic resonance cancer imaging. Wiley Interdiscip Rev Nanomed Nanobiotechnol. 5(1):1-18.
29. James ML, Gambhir SS. (2012). A molecular imaging primer: modalities, imaging agents, and applications. Physiol Rev. 92(2):897-965.
30. Malanchi I, Santamaria-Martinez A, Susanto E, Peng H, Lehr HA, Delaloye JF, et al. (2011). Interactions between cancer stem cells and their niche govern metastatic colonization. Nature. 481(7379):85-89.
31. Kong HJ, Mooney DJ. (2007). Microenvironmental regulation of biomacromolecular therapies. Nat Rev Drug Discov. 6(6):455-463.
32. Jain RK. (2013). Normalizing tumor microenvironment to treat cancer: bench to bedside to biomarkers. J Clin Oncol. 31(17):2205-2218.
33. Kaplan RN, Rafii S, Lyden D. (2006). Preparing the "soil": the premetastatic niche. Cancer Res. 66(23):11089-11093.
34. Stasinopoulos I, Penet M-F, Chen Z, Kakkad S, Glunde K, Bhujwalla ZM. (2011). Exploiting the tumor microenvironment for theranostic imaging. NMR in biomedicine. 24(6):636-647.
35. Pouyssegur J, Dayan F, Mazure NM. (2006). Hypoxia signalling in cancer and approaches to enforce tumour regression. Nature. 441(7092):437-443.
36. Hanahan D, Coussens LM. (2012). Accessories to the crime: functions of cells recruited to the tumor microenvironment. Cancer Cell. 21(3):309-322.
37. Pickup MW, Mouw JK, Weaver VM. (2014). The extracellular matrix modulates the hallmarks of cancer. EMBO Rep. 15(12):1243-1253.
38. Romero-Garcia S, Moreno-Altamirano MM, Prado-Garcia H, Sanchez-Garcia FJ. (2016). Lactate Contribution to the Tumor Microenvironment: Mechanisms, Effects on Immune Cells and Therapeutic Relevance. Front Immunol. 7:52.
39. Correia AL, Bissell MJ. (2012). The tumor microenvironment is a dominant force in multidrug resistance. Drug Resist Updat. 15(1-2):39-49.
40. LeBleu VS. (2015). Imaging the Tumor Microenvironment. Cancer journal (Sudbury, Mass). 21(3):174-178.
41. Choi SR, Ploessl K, Zhu L, Kung HF. (2017). PET Imaging Agents for Alzheimer's Disease. In: Wolfe MS, editor. Alzheimer's Disease II. Cham: Springer International Publishing. p. 181-197.
42. Cherry S, Sorenson J, Phelps M. (2012). Physics in Nuclear Medicine.
43. Alcantara D, Leal MP, García-Bocanegra I, García-Martín ML. (2014). Molecular imaging of breast cancer: present and future directions. Front Chem. 2:112.
44. Pierce MC, Javier DJ, Richards-Kortum R. (2008). Optical contrast agents and imaging systems for detection and diagnosis of cancer. Int J Cancer. 123(9):1979-1990.
45. Bremer C, Ntziachristos V, Weissleder R. (2003). Optical-based molecular imaging: contrast agents and potential medical applications. European Radiology. 13(2):231-243.
46. Liu D, Huxford RC, Lin W. (2011). Phosphorescent nanoscale coordination polymers as contrast agents for optical imaging. Angewandte Chemie (International ed in English). 50(16):3696-3700.
47. Sun G, Berezin MY, Fan J, Lee H, Ma J, Zhang K, et al. (2010). Bright fluorescent nanoparticles for developing potential optical imaging contrast agents. Nanoscale. 2(4):548-558.

48. Giepmans BN, Adams SR, Ellisman MH, Tsien RY. (2006). The fluorescent toolbox for assessing protein location and function. Science (New York, NY). 312(5771):217-224.

49. Contag CH. (2007). In vivo pathology: seeing with molecular specificity and cellular resolution in the living body. Annu Rev Pathol. 2:277-305.

50. Smith TE, Steven A, Bagert BA. (2019). Gadolinium Deposition in Neurology Clinical Practice. Ochsner J. 19(1):17-25.

51. Mitchell DG. (1996). Liver I: Currently available gadolinium chelates. Magn Reson Imaging Clin N Am. 4(1):37-51.

52. Nakamura H, Ito N, Kotake F, Mizokami Y, Matsuoka T. (2000). Tumor-detecting capacity and clinical usefulness of SPIO-MRI in patients with hepatocellular carcinoma. J Gastroenterol. 35(11):849-855.

53. Taylor RM, Huber DL, Monson TC, Ali AM, Bisoffi M, Sillerud LO. (2011). Multifunctional iron platinum stealth immunomicelles: targeted detection of human prostate cancer cells using both fluorescence and magnetic resonance imaging. J Nanopart Res. 13(10):4717-4729.

54. Clough TJ, Jiang L, Wong KL, Long NJ. (2019). Ligand design strategies to increase stability of gadolinium-based magnetic resonance imaging contrast agents. Nat Commun. 10(1):1420.

55. Blumfield E, Swenson DW, Iyer RS, Stanescu AL. (2019). Gadolinium-based contrast agents-review of recent literature on magnetic resonance imaging signal intensity changes and tissue deposits, with emphasis on pediatric patients. Pediatr Radiol. 49(4):448-457.

56. Lentschig MG, Reimer P, Rausch-Lentschig UL, Allkemper T, Oelerich M, Laub G. (1998). Breath-hold gadolinium-enhanced MR angiography of the major vessels at 1.0 T: dose-response findings and angiographic correlation. Radiology. 208(2):353-357.

57. Jost G, Frenzel T, Boyken J, Schoeckel L, Pietsch H. (2019). Gadolinium Presence in the Brain After Administration of the Liver-Specific Gadolinium-Based Contrast Agent Gadoxetate: A Systematic Comparison to Multipurpose Agents in Rats. Invest Radiol. 54(8):468-474.

58. Alabousi M, Salameh JP, Gusenbauer K, Samoilov L, Jafri A, Yu H, et al. (2019). Biparametric vs multiparametric prostate magnetic resonance imaging for the detection of prostate cancer in treatment-naive patients: a diagnostic test accuracy systematic review and meta-analysis. BJU Int. 124(2):209-220.

59. Silva AC, Lee JH, Aoki I, Koretsky AP. (2004). Manganese-enhanced magnetic resonance imaging (MEMRI): methodological and practical considerations. NMR Biomed. 17(8):532-543.

60. Algarni AA, Alshuhri AH, Alonazi MM, Mourad MM, Bramhall SR. (2016). Focal liver lesions found incidentally. World J Hepatol. 8(9):446-451.

61. Zhen Z, Xie J. (2012). Development of manganese-based nanoparticles as contrast probes for magnetic resonance imaging. Theranostics. 2(1):45-54.

62. Na HB, Song IC, Hyeon T. (2009). Inorganic Nanoparticles for MRI Contrast Agents. Advanced Materials. 21(21):2133-2148.

63. Cordova T, Sosa M, Hernandez-Gonzalez M, Reyes-Aguilera J, Solorio S, Ramirez C, et al. (2012). Medlar (Achras Sapota L.) as Oral Contrast Agent for MRI of the Gastrointestinal Tract. Applied Magnetic Resonance. 42:161-167.

64. Cloyd RA, Koren SA, Abisambra JF. (2018). Manganese-Enhanced Magnetic Resonance Imaging: Overview and Central Nervous System Applications With a Focus on Neurodegeneration. Front Aging Neurosci. 10:403.

65. de Langen AJ, van den Boogaart VE, Marcus JT, Lubberink M. (2008). Use of H2 (15)O-PET and DCE-MRI to measure tumor blood flow. Oncologist. 13(6):631-644.

66. Eisenblätter M, Höltke C, Persigehl T, Bremer C. (2010). Optical techniques for the molecular imaging of angiogenesis. Eur J Nucl Med Mol Imaging. 37(Suppl 1):S127-S137.

67. Fischer T, Ebert B, Voigt J, Macdonald R, Schneider U, Thomas A, et al. (2010). Detection of rheumatoid arthritis using non-specific contrast enhanced fluorescence imaging. Acad Radiol. 17(3):375-381.

68. Mostafid H, Bunce C. (2009). Improved detection and reduced early recurrence of non-muscle-invasive bladder cancer using hexaminolaevulinate fluorescence cystoscopy: results of a multicentre prospective randomized study (PC B305). BJU Int. 104(7):889-890.

69. Gahlen J, Prosst RL, Pietschmann M, Haase T, Rheinwald M, Skopp G, et al. (2002). Laparoscopic fluorescence diagnosis for intraabdominal fluorescence targeting of peritoneal carcinosis experimental studies. Ann Surg. 235(2):252-260.

70. Gahlen J, Pietschmann M, Prosst RL, Herfarth C. (2001). Systemic vs local administration of delta-aminolevulinic acid for laparoscopic fluorescence diagnosis of malignant intra-abdominal tumors. Experimental study. Surg Endosc. 15(2):196-199.

71. Hariri LP, Bonnema GT, Schmidt K, Winkler AM, Korde V, Hatch KD, et al. (2009). Laparoscopic optical coherence tomography imaging of human ovarian cancer. Gynecol Oncol. 114(2):188-194.

72. Niu G, Chen X. (2015). Lymphatic imaging: focus on imaging probes. Theranostics. 5(7):686-697.

73. Reagan MR, Kaplan DL. (2011). Concise review: Mesenchymal stem cell tumor-homing: detection methods in disease model systems. Stem cells (Dayton, Ohio). 29(6):920-927.

74. Zhang X, Hirai M, Cantero S, Ciubotariu R, Dobrila L, Hirsh A, et al. (2011). Isolation and characterization of mesenchymal stem cells from human umbilical cord blood: reevaluation of critical factors for successful isolation and high ability to proliferate and differentiate to chondrocytes as compared to mesenchymal stem cells from bone marrow and adipose tissue. J Cell Biochem. 112(4):1206-1218.

75. Liang L, Dong C, Chen X, Fang Z, Xu J, Liu M, et al. (2011). Human umbilical cord mesenchymal stem cells ameliorate mice trinitrobenzene sulfonic acid (TNBS)-induced colitis. Cell Transplant. 20(9):1395-1408.

76. Patel D, Kell A, Simard B, Xiang B, Lin HY, Tian G. (2011). The cell labeling efficacy, cytotoxicity and relaxivity of copper-activated MRI/PET imaging contrast agents. Biomaterials. 32(4):1167-1176.

77. Yaghoubi SS, Gambhir SS. (2006). PET imaging of herpes simplex virus type 1 thymidine kinase (HSV1-tk) or mutant HSV1-sr39tk reporter gene expression in mice and humans using [18F]FHBG. Nat Protoc. 1(6):3069-3075.

78. Yaghoubi SS, Jensen MC, Satyamurthy N, Budhiraja S, Paik D, Czernin J, et al. (2009). Noninvasive detection of therapeutic cytolytic T cells with 18F-FHBG PET in a patient with glioma. Nat Clin Pract Oncol. 6(1):53-58.

79. Loebinger MR, Kyrtatos PG, Turmaine M, Price AN, Pankhurst Q, Lythgoe MF, et al. (2009). Magnetic resonance imaging of mesenchymal stem cells homing to pulmonary metastases using biocompatible magnetic nanoparticles. Cancer Res. 69(23):8862-8867.

80. Meleshina AV, Cherkasova EI, Shirmanova MV, Klementieva NV, Kiseleva EV, Snopova LB, et al. (2015). Influence of mesenchymal stem cells on metastasis development in mice in vivo. Stem Cell Res Ther. 6(1):15.

81. Droujinine IA, Eckert MA, Zhao W. (2013). To grab the stroma by the horns: from biology to cancer therapy with mesenchymal stem cells. Oncotarget. 4(5):651-664.

82. Caimi PF, Reese J, Lee Z, Lazarus HM. (2010). Emerging therapeutic approaches for multipotent mesenchymal stromal cells. Curr Opin Hematol. 17(6):505-513.

83. Shah K. (2012). Mesenchymal stem cells engineered for cancer therapy. Adv Drug Deliv Rev. 64(8):739-748.

84. Sasportas LS, Kasmieh R, Wakimoto H, Hingtgen S, van de Water JA, Mohapatra G, et al. (2009). Assessment of therapeutic efficacy and fate of engineered human mesenchymal stem cells for cancer therapy. Proc Natl Acad Sci U S A. 106(12):4822-4827.

85. Scherer RL, McIntyre JO, Matrisian LM. (2008). Imaging matrix metalloproteinases in cancer. Cancer Metastasis Rev. 27(4):679-690.

86. Nagase H, Woessner JF, Jr. (1999). Matrix metalloproteinases. J Biol Chem. 274(31):21491-21494. Massova I, Kotra LP, Fridman R, Mobashery S. (1998). Matrix metalloproteinases: structures, evolution, and diversification. Faseb J. 12(12):1075-1095.

87. Kubota K. (2001). From tumor biology to clinical Pet: a review of positron emission tomography (PET) in oncology. Ann Nucl Med. 15(6):471-486.

88. Lebel R, Lepage M. (2014). A comprehensive review on controls in molecular imaging: lessons from MMP-2 imaging. Contrast Media Mol Imaging. 9(3):187-210.

89. Yang Y, Hong H, Zhang Y, Cai W. (2009). Molecular Imaging of Proteases in Cancer. Cancer growth and metastasis. 2:13-27.

90. Tannock IF, Rotin D. (1989). Acid pH in tumors and its potential for therapeutic exploitation. Cancer Res. 49(16):4373-4384.

91. Anemone A, Consolino L, Arena F, Capozza M, Longo DL. (2019). Imaging tumor acidosis: a survey of the available techniques for mapping in vivo tumor pH. Cancer metastasis Rev. 38(1-2):25-49.

92. Bokacheva L, Ackerstaff E, LeKaye HC, Zakian K, Koutcher JA. (2014). High-field small animal magnetic resonance oncology studies. Phys Med Biol. 59(2):R65-R127.

93. Del Vecchio S, Zannetti A, Iommelli F, Lettieri A, Brunetti A, Salvatore M. (2010). Molecular imaging of tumor microenvironment: challenges and perspectives. Q J Nucl Med Mol Imaging. 54(3):249-258.

94. Sikkandhar MG, Nedumaran AM, Ravichandar R, Singh S, Santhakumar I, Goh ZC, et al. (2017). Theranostic Probes for Targeting Tumor Microenvironment: An Overview. Int J Mol Sci. 18(5):1036.

95. Raghunand N. (2006). Tissue pH measurement by magnetic resonance spectroscopy and imaging. Methods Mol Med. 124:347-364.

96. Pérez-Mayoral E, Negri V, Soler-Padrós J, Cerdán S, Ballesteros P. (2008). Chemistry of paramagnetic and diamagnetic contrast agents for Magnetic Resonance Imaging and Spectroscopy pH responsive contrast agents. Eur J Radiol. 67(3):453-458.

97. Moon BF, Jones KM, Chen LQ, Liu P, Randtke EA, Howison CM, et al. (2015). A comparison of iopromide and iopamidol, two acidoCEST MRI contrast media that measure tumor extracellular pH. Contrast Media Mol Imaging. 10(6):446-455.

98. Sternlicht MD, Wirkner U, Bickelhaupt S, Lopez Perez R, Tietz A, Lipson KE, et al. (2018). Radiation-induced pulmonary gene expression changes are attenuated by the CTGF antibody Pamrevlumab. Respir Res. 19(1):14.

99. Moon SH, Yang BY, Kim YJ, Hong MK, Lee YS, Lee DS, et al. (2016). Development of a complementary PET/MR dual-modal imaging probe for targeting prostate-specific membrane antigen (PSMA). Nanomedicine. 12(4):871-879.

100. Vaupel P. (2009). Prognostic potential of the pre-therapeutic tumor oxygenation status. Adv Exp Med Biol. 645:241-246.

101. Gilkes DM. (2016). Implications of Hypoxia in Breast Cancer Metastasis to Bone. Int J Mol Sci. 17(10):1669.

102. Jensen RL, Mumert ML, Gillespie DL, Kinney AY, Schabel MC, Salzman KL. (2014). Preoperative dynamic contrast-enhanced MRI correlates with molecular markers of hypoxia and vascularity in specific areas of intratumoral microenvironment and is predictive of patient outcome. Neuro Oncol. 16(2):280-291.

103. Halle C, Andersen E, Lando M, Aarnes EK, Hasvold G, Holden M, et al. (2012). Hypoxia-induced gene expression in chemoradioresistant cervical cancer revealed by dynamic contrast-enhanced MRI. Cancer Res. 72(20):5285-5295.

104. Vikram DS, Zweier JL, Kuppusamy P. (2007). Methods for noninvasive imaging of tissue hypoxia. Antioxid Redox Signal. 9(10):1745-1756.

105. Koyasu S, Tsuji Y, Harada H, Nakamoto Y, Nobashi T, Kimura H, et al. (2016). Evaluation of Tumor-associated Stroma and Its Relationship with Tumor Hypoxia Using Dynamic Contrast-enhanced CT and (18)F Misonidazole PET in Murine Tumor Models. Radiology. 278(3):734-741.

106. Ljungkvist AS, Bussink J, Kaanders JH, van der Kogel AJ. (2007). Dynamics of tumor hypoxia measured with bioreductive hypoxic cell markers. Radiat Res. 167(2):127-145.

107. Penet MF, Krishnamachary B, Chen Z, Jin J, Bhujwalla ZM. (2014). Molecular imaging of the tumor microenvironment for precision medicine and theranostics. Adv Cancer Res. 124:235-256.

108. Kodibagkar VD, Cui W, Merritt ME, Mason RP. (2006). Novel 1H NMR approach to quantitative tissue oximetry using hexamethyldisiloxane. Magn Reson Med. 55(4):743-748.

109. Gulaka PK, Rojas-Quijano F, Kovacs Z, Mason RP, Sherry AD, Kodibagkar VD. (2014). GdDO3NI, a nitroimidazole-based T1 MRI contrast agent for imaging tumor hypoxia in vivo. J Biol Inorg Chem. 19(2):271-279.

110. Stoyanova R, Huang K, Sandler K, Cho H, Carlin S, Zanzonico PB, et al. (2012). Mapping Tumor Hypoxia In Vivo Using Pattern Recognition of Dynamic Contrast-enhanced MRI Data. Transl Oncol. 5(6):437-447.

111. White DA, Zhang Z, Li L, Gerberich J, Stojadinovic S, Peschke P, Mason RP. (2016). Developing oxygen-enhanced magnetic resonance imaging as a prognostic biomarker of radiation response. Cancer Lett. 380(1):69-77.

112. Mason RP, Zhao D, Pacheco-Torres J, Cui W, Kodibagkar VD, Gulaka PK, et al. (2010). Multimodality imaging of hypoxia in preclinical settings. Q J Nucl Med Mol Imaging. 54(3):259-280.

113. Gritsenko PG, Ilina O, Friedl P. (2012). Interstitial guidance of cancer invasion. J Pathol. 226(2):185-199.

114. Josefsson A, Adamo H, Hammarsten P, Granfors T, Stattin P, Egevad L, et al. (2011). Prostate cancer increases hyaluronan in surrounding nonmalignant stroma, and this response is associated with tumor growth and an unfavorable outcome. Am J Pathol. 179(4):1961-1968.

115. McAtee CO, Barycki JJ, Simpson MA. (2014). Emerging roles for hyaluronidase in cancer metastasis and therapy. Adv Cancer Res. 123:1-34.

116. Tripodo G, Trapani A, Torre ML, Giammona G, Trapani G, Mandracchia D. (2015). Hyaluronic acid and its derivatives in drug delivery and imaging: Recent advances and challenges. Eur J Pharm Biopharm. 97(Pt B):400-416.

117. Veiseh M, Turley EA. (2011). Hyaluronan metabolism in remodeling extracellular matrix: probes for imaging and therapy of breast cancer. Integr Biol (Camb). 3(4):304-315.

118. Song S, Qi H, Xu J, Guo P, Chen F, Li F, et al. (2014). Hyaluronan-based nanocarriers with CD44-overexpressed cancer cell targeting. Pharm Res. 31(11):2988-3005.

119. Shiftan L, Israely T, Cohen M, Frydman V, Dafni H, Stern R, et al. (2005). Magnetic resonance imaging visualization of hyaluronidase in ovarian carcinoma. Cancer Res. 65(22):10316-10323.

120. Cho HJ, Yoon HY, Koo H, Ko SH, Shim JS, Cho JH, et al. (2012). Hyaluronic acid-ceramide-based optical/MR dual imaging nanoprobe for cancer diagnosis. J Control Release. 162(1):111-118.

121. Hou L, Yang X, Ren J, Wang Y, Zhang H, Feng Q, et al. (2016). A novel redox-sensitive system based on single-walled carbon nanotubes for chemo-photothermal therapy and magnetic resonance imaging. Int J Nanomedicine. 11:607-624.

122. Li J, Hu Y, Yang J, Wei P, Sun W, Shen M, et al. (2015). Hyaluronic acid-modified Fe3O4@Au core/shell nanostars for multimodal imaging and photothermal therapy of tumors. Biomaterials. 38:10-21.

123. Swierczewska M, Han HS, Kim K, Park JH, Lee S. (2016). Polysaccharide-based nanoparticles for theranostic nanomedicine. Adv Drug Deliv Rev. 99(Pt A):70-84.

124. Shiga K, Hara M, Nagasaki T, Sato T, Takahashi H, Takeyama H. (2015). Cancer-Associated Fibroblasts: Their Characteristics and Their Roles in Tumor Growth. Cancers (Basel). 7(4):2443-2458.

125. Orimo A, Weinberg RA. (2007). Heterogeneity of stromal fibroblasts in tumors. Cancer Biol Ther. 6(4):618-619.

126. Koczorowska MM, Tholen S, Bucher F, Lutz L, Kizhakkedathu JN, De Wever O, et al. (2016). Fibroblast activation protein-α, a stromal cell surface protease, shapes key features of cancer associated fibroblasts through proteome and degradome alterations. Mol Oncol. 10(1):40-58.

127. Brennen WN, Isaacs JT, Denmeade SR. (2012). Rationale behind targeting fibroblast activation protein-expressing carcinoma-associated fibroblasts as a novel chemotherapeutic strategy. Mol Cancer Ther. 11(2):257-266.

128. Rüger R, Tansi FL, Rabenhold M, Steiniger F, Kontermann RE, Fahr A, et al. (2014). In vivo near-infrared fluorescence imaging of FAP-expressing tumors with activatable FAP-targeted, single-chain Fv-immunoliposomes. J Control Release. 186:1-10.

129. Granot D, Addadi Y, Kalchenko V, Harmelin A, Kunz-Schughart LA, Neeman M. (2007). In vivo imaging of the systemic recruitment of fibroblasts to the angiogenic rim of ovarian carcinoma tumors. Cancer Res. 67(19):9180-9189.

130. Lo A, Wang LS, Scholler J, Monslow J, Avery D, Newick K, et al. (2015). Tumor-Promoting Desmoplasia Is Disrupted by Depleting FAP-Expressing Stromal Cells. Cancer Res. 75(14):2800-2810.

131. Ghiabi P, Jiang J, Pasquier J, Maleki M, Abu-Kaoud N, Rafii S, et al. (2014). Endothelial cells provide a notch-dependent pro-tumoral niche for enhancing breast cancer survival, stemness and pro-metastatic properties. PLoS One. 9(11):e112424.

132. Kohlhapp FJ, Mitra AK, Lengyel E, Peter ME. (2015). MicroRNAs as mediators and communicators between cancer cells and the tumor microenvironment. Oncogene. 34(48):5857-5868.

133. Blazejczyk A, Papiernik D, Porshneva K, Sadowska J, Wietrzyk J. (2015). Endothelium and cancer metastasis: Perspectives for antimetastatic therapy. Pharmacol Rep. 67(4):711-718.

134. Suraj J, Kurpińska A, Zakrzewska A, Sternak M, Stojak M, Jasztal A, et al. Early and late endothelial response in breast cancer metastasis in mice: simultaneous quantification of endothelial biomarkers using a mass spectrometry-based method. Dis Model Mech. 2019;12(3):dmm036269.

135. Yang H, Zou LG, Zhang S, Gong MF, Zhang D, Qi YY, et al. (2013). Feasibility of MR imaging in evaluating breast cancer lymphangiogenesis using Polyethylene glycol-GoldMag nanoparticles. Clin Radiol. 68(12):1233-1240.

136. Binnemars-Postma K, Storm G, Prakash J. (2017). Nanomedicine Strategies to Target Tumor-Associated Macrophages. Int J Mol Sci. 18(5):979.

137. Hompland T, Ellingsen C, Ovrebo KM, Rofstad EK. (2012). Interstitial fluid pressure and associated lymph node metastasis revealed in tumors by dynamic contrast-enhanced MRI. Cancer Res. 72(19):4899-4908.