Diagnostic Clinical Trials in Breast Cancer Brain Metastases: Barriers and Innovations

Jawad Fares, Deepak Kanojia, Aida Rashidi, Atique U. Ahmed, Irina V. Balyasnikova, Maciej S. Lesniak

Abstract

Optimal treatment of breast cancer brain metastases (BCBM) is often hampered by limitations in diagnostic abilities. Developing innovative tools for BCBM diagnosis is vital for early detection and effective treatment. In this study we explored the advances in trial for the diagnosis of BCBM, with review of the literature. On May 8, 2019, we searched ClinicalTrials.gov for interventional and diagnostic clinical trials involving BCBM, without limiting for date or location. Information on trial characteristics, experimental interventions, results, and publications were collected and analyzed. In addition, a systematic review of the literature was conducted to explore published studies related to BCBM diagnosis. Only 9 diagnostic trials explored BCBM. Of these, 1 trial was withdrawn because of low accrual numbers. Three trials were completed; however, none had published results. Modalities in trial for BCBM diagnosis entailed magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), PET-CT, nanobodies, and circulating tumor cells (CTCs), along with a collection of novel tracers and imaging biomarkers. MRI continues to be the diagnostic modality of choice, whereas CT is best suited for acute settings. Advances in PET and PET-CT allow the collection of metabolic and functional information related to BCBM. CTC characterization can help reflect on the molecular foundations of BCBM, whereas cell-free DNA offers new genetic material for further exploration in trials. The integration of machine learning in BCBM diagnosis seems inevitable as we continue to aim for rapid and accurate detection and better patient outcomes.

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Introduction

Breast cancer is the most common cancer in women, regardless of race or ethnicity.[1] In 2018, an estimated 266,120 new cases of invasive breast cancer were diagnosed in women in the United States alone.[2] Autopsy studies reveal that close to 30% of these patients will eventually develop neurological symptoms due to brain metastases at the later stages of the disease.[3] Brain metastases are usually characterized by multiple lesions spread variably at the gray-white junction and/or smooth margins of the brain.[4] They can also present as small tumor foci with or without abundant vasogenic edema,[5] depending on tumor size. Brain metastases can lead to significant morbidity and mortality; however, early detection of breast cancer can have a significant effect on survival and quality of life.[6,7]

Treatment options for breast cancer brain metastases (BCBM) are limited to surgery, whole-brain radiotherapy, stereotactic radiosurgery, and systemic drug therapy,[8] with limited efficacy. Targeted therapies with the monoclonal antibody, trastuzumab, have shown some promise for oncologic management of patients with HER2-positive BCBM.[9] Furthermore, targeting estrogen receptor (ER)-positive BCBM with endocrine agents, cyclin-dependent kinase inhibitors, and mechanistic target of rapamycin kinase inhibitors have considerably affected the decision-making process in the treatment of patients with BCBM.[10] Although hardly curative, early diagnosis and treatment of patients with BCBM have prolonged remission.[11] Therefore, it is crucial to understand the current concepts of assessment in these patients because accurate and timely diagnosis is essential for effective treatment.

Diagnosis of BCBM relies heavily on clinical information and neuroimaging modalities, and can be confirmed with pathological

Department of Neurological Surgery, Feinberg School of Medicine, Northwestern University, Chicago, IL

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Address for correspondence: Maciej S. Lesniak, MD, MHCM, FAANS, Department of Neurological Surgery, Northwestern University, Feinberg School of Medicine, 676 N St Clair St, Chicago, IL 60611
Fax: 312-695-3294; E-mail contact: maciej.lesniak@northwestern.edu

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examination. MR imaging (MRI) is the neuroimaging modality of choice in BCBM settings.[12] Computed tomography (CT) scan can be a helpful diagnostic tool in acute settings to rule out hemorrhage and effusions; however, it lacks the resolution, coverage, and attention to detail that are offered with MRI. Still, CT is widely accessible and its diagnostic results can be obtained swiftly. Histology, in addition to clinical and radiological inputs, helps differentiate BCBM from primary brain tumors. Immunohistochemistry markers, like GATA binding protein 3, mammaglobin, gross cystic disease fluid protein 15, and ER can also be helpful in confirming the breast tissue of origin.[13] Nevertheless, pathological evaluations are often limited by poor differentiation and/or unavailability of BCBM tissue to reach accurate diagnoses.

A number of clinical trials are currently running with the aim of optimizing BCBM diagnoses. In this work we explored the advances in these trials to achieve a clearer understanding of the developments in diagnostic technology, and aim for better treatment and management of patients with BCBM.

Methods

Study Design

ClinicalTrials.gov is a large clinical trial database that registers a high number of trial entries, weekly. Its submission process compels providing thorough information on trial profile and history, and description of registered protocols. The ability to conduct analyses and extrapolate conclusions on clinical trials' data from the registry has been previously elaborated.[14-16]

On May 8, 2019, we searched ClinicalTrials.gov for all trials involving BCBM, without limiting for date or location. After an elimination schema similar to that used by Fares et al,[17] 13 trials were removed because they were noninterventional studies and/or clinical trials that did not list BCBM in the title or as a condition treated. Another 128 trials were excluded because they were nondiagnostic (Figure 1).

Data Collection

Information was acquired from the final data set on trial characteristics, including: phase, status, start and end dates, outcome measures, selection criteria, sample size, study design, experimental interventions, location, results, and publication. Trial history of changes was obtained using the ClinicalTrials.gov archives site. Trial publications were obtained using the ClinicalTrials.gov registry number (NCTID). We searched PubMed/Medline and Embase/Scopus records for NCTID identifiers to locate publications. If the trial was published, the NCTID identifier is included as part of the original report and the report will appear in the search results.

Literature Review

A review of PubMed/Medline and Embase/Scopus databases was conducted to identify published studies on current diagnostic modalities in BCBM. Combinations of search terms used included "breast cancer," "breast neoplasms," "brain metastases," "brain tumors," "brain malignancy," "diagnostic modalities," "magnetic resonance imaging," "MRI," "computed tomography," "CT," "positron emission tomography," "PET," "circulating tumor cells," "nanobodies," "clinical trials," "artificial intelligence," "AI" and "machine learning." Studies available in English were included. All identified abstracts from these searches were analyzed, and those that reviewed or examined diagnostic modalities associated with BCBM were included.

Results

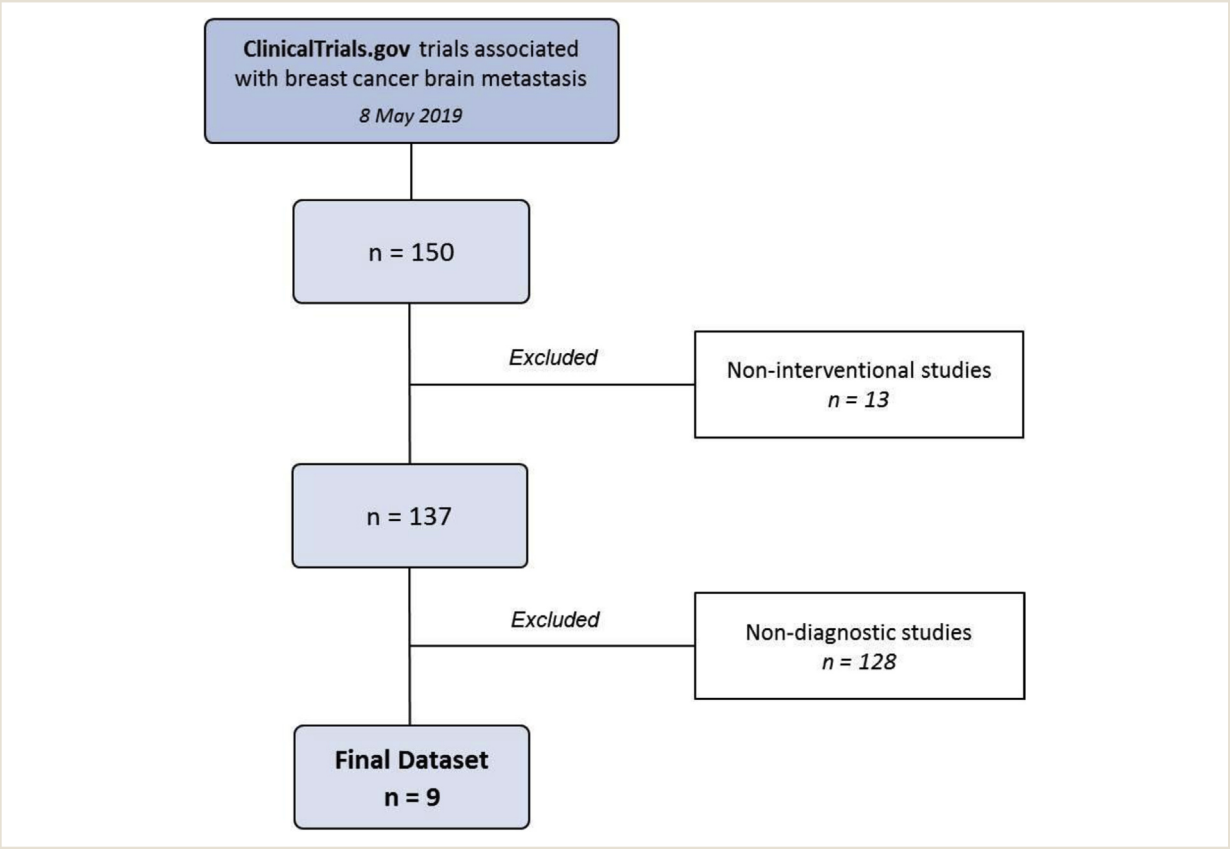
Only 9 diagnostic trials exclusively explored BCBM (Table 1). Of which, 1 trial was withdrawn because of low accrual numbers. The rest continue to progress. Three trials are yet to reach their primary completion dates. Four trials were located in the United States, 3 in Belgium, 1 in Canada, and 1 in Brazil. Of all trials, 3 were completed. None of the trials have provided results or led to publications.

Magnetic Resonance Imaging

Since the 1980s, contrast-enhanced MRI has become the preferred imaging modality for the diagnosis of BCBM. It is more sensitive than either nonenhanced MRI or CT scanning in detecting lesions in patients suspected of having brain metastases.[18] It is also superior in differentiating metastases from other central nervous system (CNS) lesions. Often, when neurological symptoms are present, the metastases are too large and/or numerous to be treated with a curative intent; therefore, diagnosis of small and isolated BCBM will allow neurosurgical resection or locally ablative radiation therapy. Early detection of CNS metastases in women with invasive breast cancer using gadolinium-enhanced MRI is in trial (NCT00398437, NCT02706964, and NCT03881605). This will allow the documentation of patterns of early metastatic spread of breast cancer, and provide a basis to determine how to optimize future surveillance imaging protocols with respect to the time to progression, rate of tumor growth, and affected organs.

There are multiple ways through which MRI can enhance the visibility of BCBM. Increasing the MRI field strength and the levels of gadolinium-based contrast agents can increase sensitivity and lead to detection of small BCBM (< 5 mm).[19] Nevertheless, the nephrotoxicity resulting from increasing contrast remains a concern often counseled against by the Food and Drug Administration (FDA).[20] Yet, the availability of contrast agents that exhibit different biophysical properties allows for selecting the most suitable contrast agent while taking into account the dosing, field strength, and safety profile. Furthermore, increasing the time between contrast injection and acquisition of images can enhance the detection of BCBM. Kushnirsky et al[21] instated a time delay of 15 minutes after contrast injection and found that at least 1 additional brain lesion was detected in 43% of patients. Nonetheless, time delay might be problematic for patients because it increases costs and time spent in a potentially uncomfortable setting.[12] In addition, practitioners and researchers might find it inconvenient because it increases time of image acquisition and data collection. Moreover, the MRI sequence chosen and the relative slice thickness can also affect the detection of BCBM. Volumetric contrast-enhanced acquisition with a slice thickness of 1 to 2 mm (without a gap) yields detailed and finer images that can be reconstructed in a plane.[22] This enhances the detection of smaller BCBM. Besides, the incorporation of artificial intelligence (AI), particularly deep learning, has shown remarkable progress in image-recognition tasks.[23] Algorithms, in addition to the interpretation of radiologists and practitioners, lead to greater sensitivity and better accuracy of BCBM diagnoses.

Figure 1 Clinical Trial Selection Process



Using a variety of techniques, MRI can provide a breadth of physiological data on BCBM, beyond just brain metastasis anatomy. MR perfusion imaging can generate data like cerebral blood volume (blood within a defined volume of tissue), cerebral blood flow (blood that passes through the tissue per unit of time), and a transfer contrast coefficient that is related to the leakiness of blood vessels (K-trans).[24] MR diffusion techniques can show the metastatic tumor's vasogenic edema, which appears bright on diffusion-weighted images. It can also display the capacious growth pattern of BCBM that can displace surrounding tissue as can be revealed by diffusion-tensor images (DTI). Proton spectroscopy can provide clues on tumor histology and grade. It can also help in locating the best site for biopsy. Altogether, these techniques enhance the accuracy of BCBM diagnosis and subsequently lead to a better estimation of the therapeutic response.

In 2018, the FDA approved ferumoxytol, an intravenously injected ultra-small superparamagnetic iron oxide, as a supplemental new treatment for individuals with iron-deficiency anemia who cannot tolerate or are unresponsive to oral iron.[25] Due to its MRI contrast characteristics,[26] ferumoxytol has also been investigated as an imaging agent in metastatic brain tumors, including BCBM. After injection, ferumoxytol is taken by tumor-associated macrophages to showcase tumor volume and size. Hamilton et al[27] found no difference between T1-weighted MRI when they compared a gadolinium-based contrast agent with ferumoxytol in untreated brain tumors. Because ferumoxytol does not contain gadolinium, nephrotoxicity can be avoided. Moreover, ferumoxytol was tested as a predictive biomarker of tumor deposition for MM-398 (nanoliposomal irinotecan; nal-IRI). Nal-IRI is a nanoliposomal agent that is believed to have an antitumor activity in metastatic breast cancer. It is designed to exploit areas of blood–brain barrier breakdown for enhanced drug delivery to tumors. Tumor deposition of nal-IRI and subsequent conversion to SN-38, a hyperactive antineoplastic nal-IRI metabolite, in neoplastic cells and tumor-associated macrophages might instigate clinical benefit and antitumor response.[28] The pattern of distribution of ferumoxytol in tumor-associated macrophages is similar to that of nal-IRI.[29] As such, BCBM permeability to ferumoxytol might be a predictive biomarker for nal-IRI deposition and tumor response. A phase I study is being conducted in patients with BCBM treated with nal-IRI to determine and evaluate the feasibility of ferumoxytol-MRI in measuring tumor-associated macrophages and predicting patient response to treatment (NCT01770353).

Computed Tomography Imaging

The rise of MRI ousted CT as the preferred imaging of choice for the diagnosis and follow-up of patients with BCBM. As such, CT imaging is not currently in trial for BCBM. Nevertheless, CT scans, despite lower sensitivity, continue to be prioritized for screening patients with acute neurological symptoms and/or in emergency

Table 1 Diagnostic Clinical Trials in Breast Cancer Brain Metastases as Found in ClinicalTrials.gov as of May 8, 2019 (n = 9)

NCTID	Trial	Status	Condition	Interventions	Phase	Outcome Measures	Study Design	Preplanned Population	Study Start	Primary Completion	Location
NCT00398437	Magnetic Resonance Imaging for the Early Detection of CNS Metastases in Women With Stage IV Breast Cancer	Withdrawn	Breast cancer brain metastases	Trastuzumab; chemotherapy; MRI	NA	Survival without neurological symptoms	Randomized	96	September 2006	—	Belgium
NCT01985971	F18 EF5 PET/CT Imaging in Patients With Brain Metastases From Breast Cancer	Completed	Breast cancer brain metastases	PET/CT imaging	NA	Number of adverse events	—	10	March 2011	August 2016	United States
NCT01770353	MM-398 (Nanoliposomal Irinotecan, Nal-IRI) to Determine Tumor Drug Levels and to Evaluate the Feasibility of Ferumoxytol Magnetic Resonance Imaging to Measure Tumor Associated Macrophages and to Predict Patient Response to Treatment	Completed	Breast cancer brain metastases	Ferumoxytol MRI and MM-398	I	Tumor levels of irinotecan and SN-38	Nonrandomized; single group assignment; open-label	45	November 2012	October 2018	United States
NCT01621906	18F-FLT-PET Imaging of the Brain in Patients With Metastatic Breast Cancer to the Brain Treated With Whole Brain Radiation Therapy With or Without Sorafenib: Comparison With MR Imaging of the Brain	Recruiting	Breast cancer brain metastases	18F-FLT-PET imaging	NA	Radiographic response	Nonrandomized; parallel assignment; Open-label	20	June 2012	June 2019	United States
NCT02706964	Imaging the Patterns of Breast Cancer Early Metastases (BCMetPats)	Active, not recruiting	Metastatic breast cancer	PET, MRI, and CT scans	NA	Number, size, and location of metastases	Single group assignment; open-label	13	April 2016	January 2018	United States
NCT02941536	Correlation Between Circulating Tumor Cells and Brain Disease Control After Focal Radiotherapy for Metastases of Breast Cancer	Completed	Breast cancer brain metastases	Circulating tumor cells evaluation	NA	Brain progression-free survival; overall survival	Single group assignment; open-label	40	November 2016	October 2018	Brazil
NCT02966574	Magnetic Resonance Imaging of the Whole Body, Including Diffusion, in the Medical Evaluation of Breast Cancers at High Risk for Metastasis and the Follow-up of Metastatic Cancers	Recruiting	Hormone-sensitive metastatic breast cancer	Whole-body MRI	NA	Apparent diffusion coefficient; number and location of cancer lesions	Single group assignment; open-label	50	December 2016	September 2018	Belgium
NCT03331601	Evaluation of 68-GaNOTA-Anti-HER2 VHH1 Uptake in Brain Metastasis of Breast Carcinoma Patients	Recruiting	HER2-positive and HER2-negative breast cancer	68GaNOTA-Anti-HER2 VHH1	II	Tumor targeting potential in brain metastasis	Single group assignment	30	February 2017	September 2021	Belgium

Table 1 Continued

NCTID	Trial	Status	Condition	Interventions	Phase	Outcome Measures	Study Design	Preplanned Population	Study Start	Primary Completion	Location
NCT03881605	MRI Screening Versus SYMptom-directed Surveillance for Brain Metastases Among Patients With Triple Negative or $HER2^{+}$ MBC	Recruiting	Breast cancer brain metastases	MRI	NA	Screening for brain metastases	Randomized	50	November 2018	June 2021	Canada

Abbreviations: CT = computed tomography; FLT = 3′-deoxy-3′ [18F]-fluorothymidine; MM-398 = nanoliposomal irinotecan; MRI = magnetic resonance imaging; NCTID = ClinicalTrials.gov registry number; PET = positron emission tomography.

settings.[12] Furthermore, presenting patients with implanted devices that are contraindicated to undergo MRI might have to settle for a CT scan instead.

Positron Emission Tomography

Positron emission tomography (PET) provides metabolic information on BCBM to complement the anatomical and physiological data collected by MRI or CT. PET measures glucose consumption in tumor cells through a positron emitter 18-fluorine (^{18}F) incorporated in a common tracer, fluorodeoxyglucose (FDG).[30] This tracer is a glucose analogue that has a long half-life and is taken by the active BCBM cell. Therefore, PET imaging will reveal the extent of glucose metabolism in BCBM cells. Nevertheless, the brain consumes up to 20% of the energy produced by the body, with glucose being the basic source of energy. FDG tracers can be challenged by background signaling coming from high metabolic activity and glucose consumption in the brain.[31] In addition, FDG has low specificity in the presence of treatment-induced inflammation around the tumor site,[32] because inflammatory cells have the ability to uptake FDG. This results in overestimating tumor cell quantity, which confines the ability of FDG-PET to detect smaller lesions of BCBM.

Noninvasive molecular imaging biomarkers of cellular proliferation have the potential to characterize brain tumors and predict their responses to personalized therapeutic regimens in BCBM. A new clinical approach to assess tumor proliferation uses the PET marker 3′-deoxy-3′[^{18}F]-fluorothymidine (FLT). One trial (NCT01621906) is currently recruiting patients to prove that FLT-PET is better than MRI and will be more informative about the brain metastases after whole-brain radiotherapy. Unlike FDG, FLT's ability of evaluating whole tumor heterogeneity instead of glucose metabolism allows for fewer false positive results.[33]

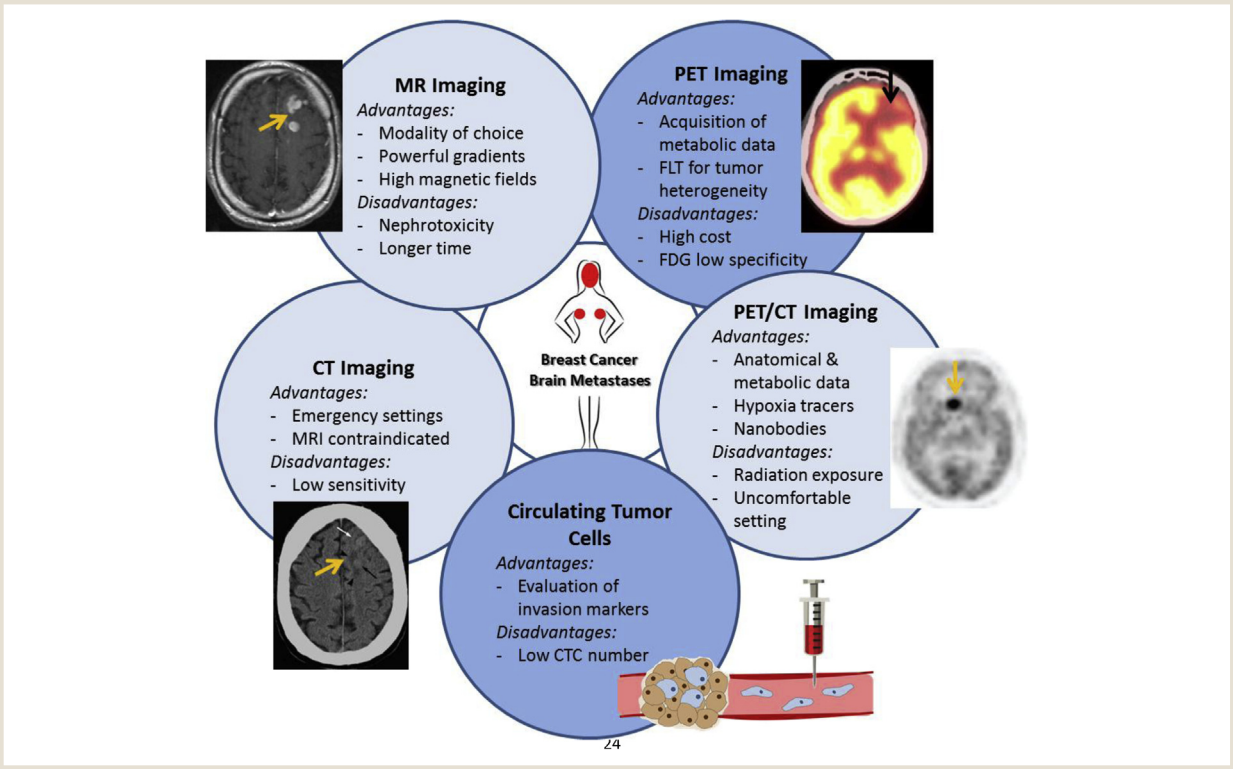
Positron Emission Tomography/CT

Image fusion with PET/CT views correlates the information from the 2 different modalities and interprets them on 1 image. Functional measures captured by PET, like blood flow, oxygen use, and glucose metabolism, are added to the anatomical information provided by CT. The combined PET/CT scans provide images that pinpoint the anatomic location of abnormal metabolic activity within the body. The combined scans have been shown to provide more accurate diagnoses than the 2 scans performed separately.[34]

Angiogenesis, formation of new blood vessels, is vital for the growth of BCBM. Nevertheless, angiogenesis is often unable to keep up with the rapidly-growing metastases, which hampers blood supply to the tumor. The lack of oxygen and nutrient delivery to the tumor leads to a state of tumor hypoxia. Imaging of hypoxia has been the subject of intense research in neuro-oncology because hypoxic brain tumors tend to confer resistance to radiotherapy.[35] Furthermore, the remaining hypoxic tissue might contribute to the failure of treatment after radiotherapy.[36] Counter-resistance can be achieved by increasing the doses of radiotherapy through stereotactic radiosurgery. This has been shown to improve survival in patients after receiving whole-brain radiotherapy.[37]

Determining the amount of hypoxic tissue remaining after radiotherapy is vital to identify patients who can benefit from dose escalation. A clinical trial was designed to detect residual tumor

Figure 2 Diagnostic Modalities of Breast Cancer Brain Metastases That Are in Trial, as of May 8, 2019



Abbreviations: CT = computed tomography; CTC = circulating tumor cell; FDG = fluorodeoxyglucose; FLT = 3′-deoxy-3 ′ [18F]-fluorothymidine; MR = magnetic resonance; PET = positron emission tomography.

hypoxia in patients with BCBM who were receiving whole-brain radiation therapy by using a noninvasive imaging biomarker ^{18}F-EF5 (EF5) and PET/CT imaging (NCT01985971). Several hypoxia tracers have been tested; however, the most promising has been EF5.[38] Preclinical and clinical studies have shown that EF5 is associated with aggressive tumors like malignant glioma, head and neck squamous cell carcinoma, and sarcomas.[39,40]

The overexpression of the HER2 protein is associated with increased BCBM.[41] Hence, determining HER2 status is essential for identifying patients who would benefit from anti-HER2 treatment. Common diagnostic modalities that reveal HER2 status include a biopsy of tumor sample followed by tests such as immunohistochemistry and fluorescence in situ hybridization staining.[41] Unfortunately, these tests are operator-dependent, prone to sampling error in biopsy, and not easily repeatable. PET/CT molecular imaging provides a platform whereby these inadequacies can be addressed, and a more accurate and quantitative assessment of HER2 expression in patients with breast cancer is possible.

Nanobodies are the smallest (12-15 kDa) fully functional and intact antigen-binding antibody fragments.[42] In addition to their adequately small size, they show high stability, rapid targeting, and fast blood clearance, which make them ideal candidates for molecular imaging probing.[42] In preclinical settings, HER2 imaging, using nanobodies with PET-labeled analogues, was performed 1 hour after injection.[43] Results showed significant differences in HER2 expression between tumor and muscle, and tumor and blood. Validation studies revealed high specific contrast imaging of HER2-positive tumors with no observed toxicity.[44] Subsequently, a phase II clinical trial was designed to investigate the uptake of the radiopharmaceutical anti-HER2 nanobody, 68-GaNOTA-anti-HER2 VHH1, in BCBM using PET/CT imaging (NCT03331601). Ultimately, uptake in patients with HER2-positive BCBM will be compared with that in patients with HER2-negative BCBM.

Circulating Tumor Cells

Circulating tumor cells (CTCs) in patients with breast cancer originate from the primary breast tumor. They can continuously flow in the blood or can cluster together to colonize distant sites, like the brain parenchyma.[45] No matter the destination, CTCs continue to preserve the information of their primary origin. This information is vital for cancer diagnosis and/or treatment. For this reason, a clinical trial was designed to assess the number of CTCs before and after radiotherapy (NCT02941536). Potential invasion markers in these CTCs will be evaluated and correlated with incidence of BCBM. A positive association will offer the ability to target BCBM in real-time.

Circulating tumor cells were first described in 1869.[46] In the past decade, studies have emerged to show that CTCs can act as markers of disease progression and metastasis in patients with cancer.[47,48] Elevated levels of CTCs correlate with aggressive disease and increase in metastases. Although it is still not clearly established that

CTCs are indeed metastatic cells, CTCs were capable of initiating metastases in xenograft models.[49] Therefore, CTCs can be important indicators and contributors in tumor staging and patient stratification in BCBM.

Circulating tumor cells can be obtained through minimally invasive blood collection. It is estimated that patients with cancer might have only 5 to 50 CTCs per teaspoon of blood.[50] Fortunately, technological advancements in the past decades have allowed the isolation of CTCs from the white blood cell fraction.[51] Assessing numbers of CTCs accompanied with molecular characterization possesses the potential to guide therapy and predict disease progression and survival.

Discussion

The poor survival associated with BCBM warrants the development of new and innovative diagnostic tools that can detect metastatic potential of breast cancer cells as early as possible (Figure 2). This is further emphasized by the fact that the outcome of surgical, radiation, and/or targeted therapy is largely dependent on early diagnosis of BCBM. Therefore, multicenter collaborations and extensive participation in clinical trials is essential so that BCBM diagnostic trials succeed in their mission to remove the "end-stage disease" label associated with BCBM.

Magnetic resonance imaging has evolved into the premier diagnostic modality for BCBM. Higher-field magnets offer the ability to achieve spatial resolutions that can visualize in detail the exquisite brain anatomy.[52] In addition, the availability of intraoperative MRI has influenced neurosurgical therapy of BCBM. Intraoperative image updates can be obtained in short-time and the resection progress can be readily monitored.[52] Furthermore, new functional MRI sequences have been widely useful in determining the Grade, heterogeneity, and extent of BCBM. Some have even suggested that DTI might be used to aid in neurosurgical planning, radiotherapy preparation, and monitoring of tumor recurrence and response to therapy.[53] Although DTI has not been widely studied in clinical trials, many neurosurgeons actively use it to achieve an ideal resection without harming vital brain functions. Mapping functional centers in the brain and delineating their relationship to BCBM might improve neurosurgical outcomes.

The introduction of FLT as an imaging tracer for PET can be promising because it provides higher specificity than FDG in the presence of inflammation and high metabolic brain activity. Moreover, FLT can provide more input on BCBM biology before, during, and after treatment. Nevertheless, other imaging modalities like MRI continue to have a cost-effective advantage. In the future, wider use of newer modalities like single photon emission CT/CT (SPECT/CT) and PET/MRI can provide greater imaging resolution and diagnostic advantage.

Lately, "liquid biopsy" has emerged as a novel minimally invasive method for the molecular assessment of metastasis. Detection of CTCs and cell-free DNA (cfDNA), which is out of tumor cells, can be promising biosources that contain clinically valuable data.[54]

Circulating tumor cell quantification is already an established prognostic factor that is in trial for BCBM. The next frontier in CTC research is to elucidate their biology and characterization with advanced genomic techniques.[55] This will help standardize detection and isolation of BCBM cells, and reveal the true clinical value of CTCs as diagnostic biomarkers and therapeutic targets.

In individuals with metastatic breast cancer, cfDNA that holds the mutations and methylation changes of its original tumor cell has been shown to be elevated.[56-58] cfDNA, as a liquid-based diagnostic tool, possessed equal sensitivity and specificity of 87% for breast cancer.[59] A meta-analysis further indicated that the plasma might be a good source of cfDNA for detection of breast cancer.[59] In a patient with HER2-positive BCBM, Siravegna et al[60] reported that cfDNA was more informative and sensitive than radiologic imaging. Nevertheless, detailed information on the volume measurements of brain metastases were missing. Bettegowda et al[61] showed that in cases of brain metastases, cfDNA, extracted from the cerebrospinal fluid (CSF), fluctuated as the variation in brain tumor burden changed over time. As such, CSF, which is more often in contact with the tumor, can be an effective source for genetic material.

Today, liquid biopsies might not be solely reliable either for the diagnosis of BCBM or for the stratification of patients for specific targeted therapies. Nonetheless, a combinatory diagnostic approach that involves the analyses of CSF, plasma, and/or neuroimaging might offer a more comprehensive description of the clinical case. Furthermore, liquid biopsy can potentially highlight specific genetic alterations that can ease the development of more personalized targeted therapies for patients with BCBM.

In the future, machine learning—a branch within AI—will have an important role in the diagnosis of BCBM and other brain tumors. Convolutional neural networks is a type of deep learning that can be used to swiftly analyze and process MRI results with efficiency and accuracy that can surpass that of human diagnosticians.[62] This would save time and allow the physician to focus on optimizing patient treatment and bettering clinical outcomes.[63,64] In addition, recent studies have shown that the use of AI can help reduce the amount of contrast agents used in imaging, like gadolinium, while significantly improving the quality of MRI.[65] This would prevent contrast-related toxicity and accumulation in brain tissue. Hopefully, ongoing research will pave the way for the use of intelligent machines in the diagnosis of metastatic brain tumors in a cost-effective manner.

Limitations

This study exclusively focused on diagnostic trials in BCBM. We took ample precautions to avoid any bias or improper analyses by having 2 authors, independently review all trials identified and the trial selection steps. Some data might be registered incorrectly and/or missing in ClinicalTrials.gov; nevertheless, this analysis is distinctive and imperative because it paints a realistic image of the current status of BCBM diagnostic trials and offers researchers and clinicians the opportunity to reflect upon future BCBM diagnostic tools.

Conclusion

We present herein an overview of current modalities in trial for the use in the diagnosis of BCBM. Current diagnostic clinical trials suffer from low accrual numbers and lack of published results. The development of new and innovative diagnostic tools for metastatic brain tumors is vital for early detection and treatment of BCBM. Neuroimaging continues to be at the forefront of the current array of diagnostic tools for BCBM. Advances in CTC and cfDNA

detection and characterization hold promise in inferring the genetic and molecular groundworks of BCBM. The integration of AI and machine learning seems inevitable as we continue to aim for rapid and accurate detection of brain metastases and better patient outcomes.

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Disclosure

The authors have stated that they have no conflicts of interest.

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