Physics and Imaging in Radiation Oncology 21 (2022) 115–122

Contents lists available at ScienceDirect

Physics and Imaging in Radiation Oncology

journal homepage: www.sciencedirect.com/journal/physics-and-imaging-in-radiation-oncology

Review Article

Glial activation positron emission tomography imaging in radiation treatment of breast cancer brain metastases

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ARTICLE INFO

Keywords:
Breast cancer brain metastases (BCBM)
Glial activation imaging
Radiation therapy
Positron emission tomography (PET)

ABSTRACT

Brain metastases affect more breast cancer patients than ever before due to increased overall patient survival with improved molecularly targeted treatments. Approximately 25–34% of breast cancer patients develop brain metastases in their lifetime. Due to the blood–brain barrier (BBB), the standard treatment for breast cancer brain metastases (BCBM) is surgery, stereotactic radiosurgery (SRS) and/or whole brain radiation therapy (WBRT). At the cost of cognitive side effects, WBRT has proven efficacy in treating brain metastases when used with local therapies such as SRS and surgery. This review investigated the potential use of glial activation positron emission tomography (PET) imaging for radiation treatment of BCBM. In order to put these studies into context, we provided background on current radiation treatment approaches for BCBM, our current understanding of the brain microenvironment, its interaction with the peripheral immune system, and alterations in the brain microenvironment by BCBM and radiation. We summarized preclinical literature on the interactions between glial activation and cognition and clinical studies using translocator protein (TSPO) PET to image glial activation in the context of neurological diseases. TSPO-PET is not employed clinically in assessing and guiding cancer therapies. However, it has gained traction in preclinical studies where glial activation was investigated from primary brain cancer, metastases and radiation treatments. Novel glial activation PET imaging and its applications in preclinical studies using breast cancer models and glial immunohistochemistry are highlighted. Lastly, we discuss the potential clinical application of glial activation imaging to improve the therapeutic ratio of radiation treatments for BCBM.

1. Introduction

Early diagnosis and application of molecularly targeted therapies in breast cancer have improved extracranial disease control and overall survival but are associated with increased brain metastases incidence [1]. This prompted the reappraisal of brain metastases management. A recent review established that 25–34% of breast cancer patients will develop brain metastases in their lifetime [2]. Historically, the treatment of choice for breast cancer brain metastases was surgery, stereotactic radiosurgery (SRS), and/or whole brain radiation therapy (WBRT). WBRT is an effective treatment for micro-metastases that are not visible radiologically and reduces intracranial failure when combined with SRS and surgery [3]. Despite this, WBRT is commonly omitted following SRS or surgery due to late neurocognitive side effects [4]. Irradiating the brain, activates glial cells, initiates inflammation, and causes tissue damage. When inflammation persists and becomes chronic, it can

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https://doi.org/10.1016/j.phro.2022.02.016
Received 3 September 2021; Received in revised form 18 February 2022; Accepted 20 February 2022

contribute to cognitive decline [5].

The effect of radiation on tumors is widely known; however, the immune system's vital role in the efficacy of radiation therapy is complex and multifaceted. Besides the DNA damage induced by radiation, the immune system response to the damage and cancer plays a key role in tumor cell death. This interaction is further complicated in cancers within the central nervous system (CNS), such as cancers that have metastasized in the brain with its immune privilege status as reviewed recently [6,7]. To understand the immune system's response to radiotherapy and brain metastases, an intimate knowledge of brain microenvironment and neuroinflammation is required. Of particular interest are glial cells, specifically microglia, the resident CNS parenchymal macrophages forming the innate immune response in the brain. Microglia are one of the first responders to damage in the brain and are responsible for inducing inflammation. The connection between activated glial cells, neuroinflammation, and cognition is well studied in neurological disease but less common for radiation and cancer [8,9]. Positron emission tomography (PET) with novel translocator protein (TSPO) radiotracers have been used to assess neuroinflammation through glial activation. Imaging glial activation from radiation and cancer has the potential to improve brain metastases prevention and management. Herein, we will review the connection between glial activation and cognition with a focus on the neuroinflammatory response. We will first consider the effects of radiation and cancer on glial activation before discussing the current and potential use of TSPO-PET imaging.

2. Methods and materials

This review begins with a brief summary of the current radiotherapy treatment approaches for breast cancer brain metastases (BCBM) (3.1). This is followed by a review of the current understanding of the brain microenvironment including the role of microglia in neuroinflammation (3.2), and the interactions of the brain immune responses with the peripheral immune system (3.3). Alterations in the brain microenvironment from the presence of BCBM and radiation are then discussed (3.4, 3.5). We then review the connection between glial activation and cognitive decline with clinical and preclinical studies (3.6). In the preclinical studies, we highlighted studies of glial activation caused by radiation treatment with glial immunohistochemistry or glial activation PET imaging, as well as studies that specifically employed breast cancer animal models. Lastly, we discuss the potential clinical application of glial activation imaging to improve the therapeutic ratio of radiation treatments for BCBM.

In the present review, the literature search was performed using the PubMed database with search terms specific to the sections. Articles were identified in the search using the terms: 1) "breast cancer brain metastases" AND "radiation/radiation therapy" AND "microenvironment", 2) "immune privilege" AND "neuroinflammation", 3) "glial activation" AND "cognition" AND "TSPO", 4) "TSPO-PET" AND "radiation therapy/radiation" AND "brain metastases". Relevant articles referenced in the identified articles were also included. The overall search identified a total of 139 articles, which were manually screened to include articles that reported or reviewed neuroinflammation in the brain, the connection between glial activation and cognition, or glial activation assessment in BCBM. Only neurological studies that reported on clinical assessment using TSPO-PET were included. This left a total of 104 articles for abstract review. After abstracts were reviewed, 53 studies met the inclusion criteria and were reviewed with full text. From the full-text review, an additional 35 studies were added that were referenced in the relevant articles, for a total of 88 articles discussed in the following sections.

3. Results

3.1 Breast cancer brain metastases radiotherapy management strategies

Metastatic treatment is often approached differently from primary treatment to prolong the patient's life, palliate symptoms, and delay disease progression. However, if breast cancer patients only have oligometastatic disease in the brain without active extracranial disease, this may prompt reconsiderations of treatment goals [10]. This is especially true in the era of effective targeted treatments for estrogen (ER), progesterone (PR) and/or human epidermal growth factor (HER2) positive cancers. Typically, local therapies, i.e., surgery and radiation, are used to treat BCBM since the blood–brain barrier (BBB) prevents penetration of antibodies into brain such as those targeting HER2. Unlike luminal A, B, and HER2 + breast cancers that are driven by ER, progesterone PR and HER2, respectively, triple negative breast cancers (TNBC) do not have these receptors. This limits treatment options for TNBC, making it the most aggressive type of breast cancer that often results in brain metastases [11]. SRS delivering a high dose in a small number of fractions (i.e., 18–24 Gy/1, 27 Gy/3, or 35 Gy/5) to visible growths is a standard treatment for BCBM [12]. It is recommended for patients with up to four brain metastases, with local tumor control rates between 90 and 95% [13–16]. WBRT may follow SRS to improve brain metastases' regional control but at the expense of neurocognitive side effects [3,17,18].

Brown et al. [18] investigated the effect of SRS with and without WBRT on patients' cognitive function with one to three brain metastases in a randomized clinical trial. The brain metastases were from different types of cancer, including lung, breast, and melanoma. At the three month assessment, SRS alone was found to have less cognition deterioration (40/63 patients [63.5%]) compared to SRS with WBRT (44/48 patients [91.7%]) [18]. However, SRS alone had a shorter time to intracranial failure and lower intracranial tumor control rates (79/105 patients [75.3%]) compared to SRS with WBRT (89/95 patients [93.7%]). While the addition of WBRT significantly improves intracranial tumor control, there is a significant increase in cognitive deterioration. In patients surviving longer than one year, cognitive deterioration incidence was lower for SRS alone at three months (5/11 patients [45.5%] vs. 16/17 patients [94.1%]) and 12 months (6/10 patients [60%] vs. 17/18 patients [94.41%]) compared to SRS with WBRT [18]. WBRT still has its place in BCBM treatment for patients not eligible for surgery or SRS. This patient group typically has a median survival of approximately three months and typically do not live longer than 16 months. The onset of long-term cognitive deterioration is not a significant concern, as patients receive palliative WBRT to alleviate symptoms, temporarily halt brain metastases growth and improve neurological deficits in the short term to improve their quality of life [19–21].

Hippocampal sparing (HS), an advanced radiation therapy technique, is used to reduce the cognition deficits associated with WBRT. The avoidance of hippocampal structures aims to delay or minimize onset and/or severity of cognitive decline while attaining intracranial control of cancer. The hippocampus is responsible for the learning, consolidation, and retrieval of information and is critical for forming new memories [22]. The hippocampus is centrally located in the brain and requires intensity modulated radiotherapy or volumetric modulated arc therapy techniques to avoid it. In a phase II randomized trial, Yang et al. [23] investigated whether HS-WBRT preserves neurocognition in brain metastases patients. Patients who received HS-WBRT of 30 Gy in 10 fractions were found to have better memory preservation six months post-irradiation than conventional WBRT. However, no differences were evident between HS and conformal groups for verbal fluency and executive function [23].

3.2. The brain microenvironment and neuroinflammation: Background

The brain microenvironment plays a vital role in maintaining and protecting brain function, including preventing cancer metastasis in the brain. Cancer cells have to adapt to the brain microenvironment to survive, develop and progress to metastases. The brain is primarily composed of neurons, glial cells, and endothelial cells. Glial cells are responsible for maintaining tissue homeostasis. There are three types of glial cells: oligodendrocytes, astrocytes, and microglia, accounting for approximately 75%, 20%, and 5% of the glial cells in the gray matter of the human cerebral cortex, respectively [24]. Despite being a minor component, microglia are the resident CNS parenchymal macrophages forming the innate immune response in the brain. In the CNS, activation of the microglia releases inflammatory mediators triggering immune responses and altering the brain's microenvironment.

Inflammation is an important biological response governed by the immune system. Maintaining homeostasis and identifying harmful stimuli, including pathogens, damaged cells, or irritants by the body, will induce an inflammatory response. Inflammation in the brain differs from peripheral inflammation since fewer antibodies and leukocytes are present. The BBB is mainly responsible for reduced leukocytes presence, although inflammation can increase immune cell traffic across the BBB and leukocyte recruitment [25]. Neuroinflammation and subsequent immune reactions are cultivated and regulated by simultaneous communication and response between the immune system and the CNS [26].

3.2.1. The role of microglia in neuroinflammation

Homeostasis disturbances activate microglia as part of the innate immune response. Microglia and astrocytes are not considered professional antigen presenting cells (APCs) because they do not acquire APC ability in the absence of co-stimulatory cytokine molecules. Professional APCs such as dendritic cells, circulating macrophages, and B cells phagocyte extracellular proteins, and the resulting peptide fragments from proteins are presented by the major histocompatibility complex (MHC) class II molecules on the cell surface. On the other hand, all nucleated cells express MHC class I molecules, and they present on the cell surface both normal self-antigens and foreign antigens (e.g., from viruses) found in the cytosol. Activated microglia can express MHC class I and II molecules together with co-stimulatory molecules similar to professional APCs. Antigens presented by MHC class I molecules are recognized by cytotoxic $CD8^+$ T-cells, while CD4 + helper T-cells recognize MHC II. Antigen presentation by APCs triggers an adaptive T-cell-based immune response.

Activated macrophages in simple sense can go from M1 (pro-inflammatory, tissue repair) to M2 (inflammation resolution, phagocytotic) polarization, in actuality, there is a spectrum of behaviour that spans from M1-like to M2-like [27]. The microglia's phenotype, i.e., M1 or M2, is linked to the brain microenvironment, determined by the presence and quantity of cytokines and chemokines. Microglia express an M1 phenotype in a pro-inflammatory environment when cytokines and chemokines are in abundance. The resultant microglia activation comes from various stimulating factors including IFN-γ and lipopolysaccharides that polarise toward the production of pro-inflammatory cytokines, such as tumor necrosis factor (TNF), interleukin-1β (IL-1β), IL-6, IL-12, IL-18, and IL-23 [28]. Pro-inflammatory chemokines secreted by activated microglia include CXCL-8, CCL2, CCL3, CCL4, CCL5, CCL11, and CXCL10, with an extensive list shown in Fig. 1 [29]. Activated M1 microglia can be identified by increased surface marker expression of CD40 and CD86 (also known as B7-2 or T-lymphocyte activation antigen) that are responsible for IL-2 secretion and immune cell proliferation [30]. Other surface markers promoting inflammation include CD16, CD32, and inducible nitric oxide synthase (iNOS). The majority of pro-inflammatory cytokines are produced by activated microglia, playing an integral role in the subsequent activation of downstream pathways.

Alternatively, microglia can create an anti-inflammatory microenvironment when they changed polarization to an M2 phenotype. Microglia in the M2 polarization induce an immunosuppressive response, helping to stop inflammation and restore homeostasis to the surrounding microenvironment. Identification of activated M2 microglia is through CD206 and CD163 surface markers, cytokines (IL-1

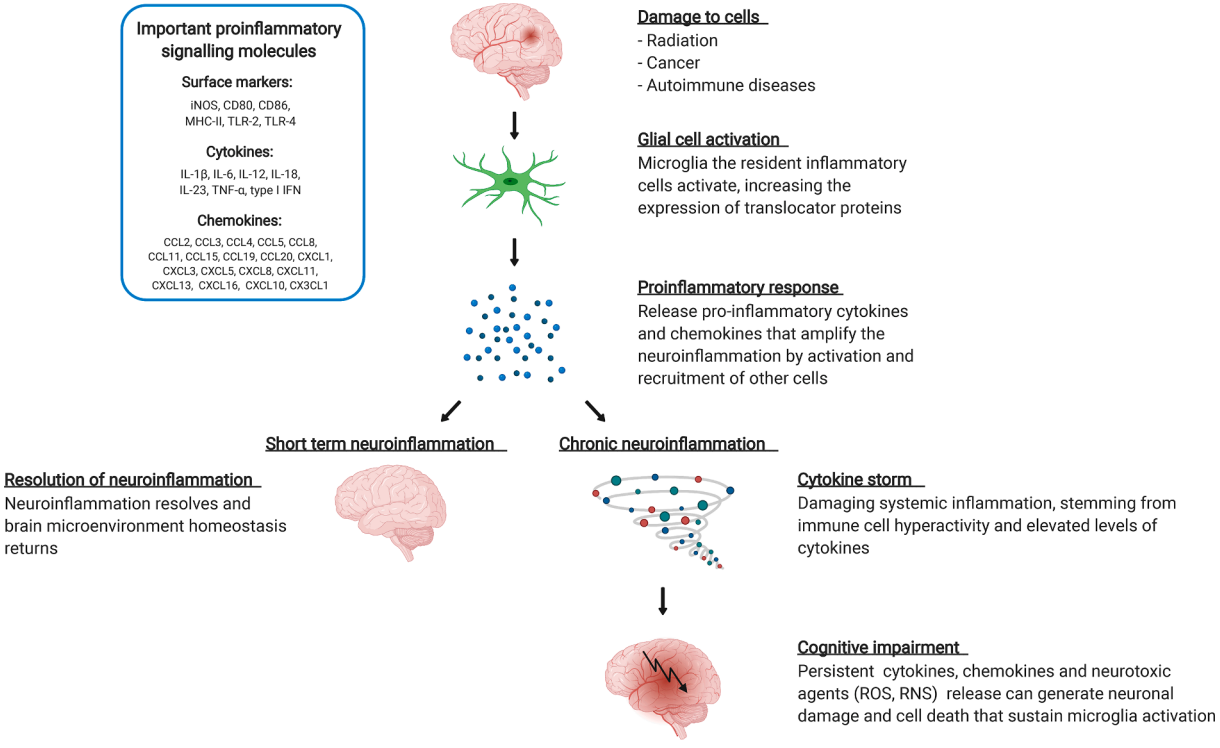

Fig. 1. Diagram of the cascading relationship of radiation induced glial activation to cognitive impairment. Created with biorender.com.

receptor antagonist (IL-1Ra), IL-4, IL-10, IL-13, and transforming growth factor (TGF-β)) and chemokines (CCL2, CCL22, CCL17, and CCL24) [30]. This is accompanied by increased secretion of antibodies and the release of several protective and trophic factors, enhancing phagocytosis of pathogens and supporting neuronal growth, inflammation regulation, and repair. The ratio of markers present can be used in tissue or culture to determine which phenotype is predominant.

3.3. The central nervous system and immune privilege

The BBB is a physical and biological barrier with specialized proteins accountable for transport across the membrane. For instance, a multidrug-resistant protein actively pumps out drugs that crossed into the brain, e.g., chemotherapy drugs. Studies reported that CNS tissues lacked lymphatic vessels [31–33]. These led to the belief that the CNS is isolated by the BBB and does not interact with the peripheral immune cells, giving it the status of being one of the immune-privileged sites in the human body [33]. However, it was demonstrated recently that the CNS has immune competency and active interaction with peripheral immune cells (reviewed in [34]).

The lymphatic system is an essential component of the immune system consisting of a network of lymph nodes connected by lymphatic vessels facilitating the defense response. Until recently, the link between the CNS and the lymphatic pathway was unknown. In 2015, Louveau et al. [6] and Aspelund et al. [7] reported that lymphatic vessels line the dural sinuses and connect to cervical lymph nodes, with the capability of transporting immune cells from the cerebrospinal fluid [6,7]. The sinus-associated lymphatic vessels were discovered to be strongly associated with T-lymphocytes and suggested responsibility for providing the means for peripheral immune cells to leave the cranium [6]. The lymphatic pathway enables soluble antigens present in the brain parenchyma to drain into the cervical lymph nodes. Thus, the BBB maintains the brain parenchyma's immune privilege status, while the lymphatic pathway enables it to be an active participant in the immune surveillance of the CNS. Dendritic cells in the lymphatics will also take up antigens from the CNS and bring them into the lymph nodes. The dendritic cells are present in the brain's meninges lining and choroid plexus of the ventricles but are not found throughout the brain parenchymal. Thus, the CNS has a restricted capacity to transport antigens to lymph nodes and induce T-cell activation [35]. When the innate immune response in the CNS is insufficient, antigen introduction in the lymph nodes is necessary for the lymphatic system to initiate adaptive immunity.

T-cells activated by pathogens outside of the CNS can detect antigenic targets within the CNS. Medawar demonstrated this phenomenon experimentally in the late 1940s [36,37]. The slow rejection rate of foreign tissue grafts transplanted within the CNS compared to rapid rejection seen in skin grafts showed immune privilege. Interestingly, the CNS rejection response mimicked the skin grafts response when transplantation of skin grafts was before the CNS grafts. Furthermore, skin graft transplanted after the CNS graft accelerated its rejection response. Thus, these studies showed the ability of peripheral identified foreign antigens to initiate an additional immune response within the CNS despite its privileged immune status.

Communication between immunity in the brain and body in a general sense is a two-way process and has the potential to allow peripheral cells to join in the response. The origin and recruitment of immune cells from stimulus within the CNS can be extended to peripheral cells, as signals can be sent to peripheral cells to initiate a reaction. CNS inflammation can be initiated in two ways: 1) by antigens derived from the CNS that result from direct damage to the brain parenchyma or 2) from a source originating outside of the CNS. In both cases, myelin-specific T-cells are primed and then entered the brain (reviewed in [38]). Inducing a T-cell response in the CNS requires antigens to drain into the cervical lymph nodes and T-cells to enter the CNS.

Although the CNS has many barriers that protect the brain from cellular infiltration, activated and memory T-cells can cross these barriers by expressing integrins, adhesion molecules, and chemokine receptors [39]. Activated T-cells can use various routes to reach distinct areas of the CNS. For example, certain T-cells can cross the BBB into perivascular space and fluid-filled spaces in the brain surrounding perforating vessels, and activated T-cells can cross the BBB and cerebral spinal fluid barrier to enter the brain subarachnoid space [39]. Once T-cells enter the brain, they can interact with microglia in the brain parenchyma.

3.4 Changes in the brain microenvironment from brain metastases

The interaction between the brain microenvironment and metastatic cells impacts tumor progression and survival [40,41]. Doron et al. [42] reviewed the role of various immune cells in the brain tumor microenvironment (TME) and their contribution to inflammation in influencing disease progression. Pathogen invasion or tissue damage trigger damage signals that initiate inflammation. Surrounding microglia and astrocytes are rapidly activated, acting as first responders. Peripheral T-cells become involved if microglia and astrocytes have not managed to control the invasion or damage, inducing widespread neuroinflammation. Changes in the brain microenvironment from tissue damage and dysregulation are similar to changes introduced by metastatic growth in the brain, including the induction of neuroinflammation [42,43]. The positive feedback loop generated with activated microglia and reactive astrocytes in response to damage signals can initiate colonization of cancer cells [44]. The changes and reactions occurring in the brain microenvironment suggest that metastatic cells take over the tissue damage response. Understanding the role of neuroinflammation could further uncover the inner workings of brain metastases development [43,45].

Microglia polarization plays an essential role in the progression of tumors. Typically, M1 cells are produced in non-malignant tumors to induce tumor death, as the hindrance of cancer stem cells' sphere-forming capacity will inhibit tumor growth [46]. Komohara et al. [47] investigated the role of M1 and M2 cells in tumor proliferation and found that M2 cells' expression of STAT3 is key to tumor progression. Furthermore, the TME of brain metastases is different among primary cancers (reviewed in[48]).

Primary breast cancer cells that have spread to the brain are met by various immune cells on arrival, including microglia. Cytokines, chemokines, and neurotoxic agents secreted by microglia directly or indirectly play a role in immunosuppression, angiogenesis, tumor proliferation, invasion, and neuroinflammation [49,50]. Prolonged neuroinflammation can exacerbate these effects through the continuous cycle of molecule secretion and activation of microglia. Commonly, activated microglia will surround lesions in the brain, and their inhibition has demonstrated reduced tumor proliferation [51]. Reactive astrocytes have also been found in the vicinity of brain lesions and promote cancer growth through the secretion of cytokine, growth factors, and enzymes. Lorger et al. [52] examined the brain microenvironment during the first stages of hematogenous BCBM in an animal model with the involvement of different resident brain cells. *In vivo* experiments using mouse models with MDA-MB-435, MDA-MB-231, MDA-MB-231/brain, 4 T1, and MCF-7 cells investigated breast cancer cell arrest and extravasation into the brain parenchyma. MDA-MB-435, MDA-MB-231/brain, and 4 T1 cells were found to provide better models for examining the earliest events involved with breast cancer cells infiltration into the brain and were the only cell types to develop lesions consistently. Regardless of the host's immune state and tumor cell model, breast cancer cells were found arrested in the microvasculature of the mouse brain and were in the process of extravasation from day three onward. Cancer cell arrest, extravasation, and invasion of the brain parenchyma often result in concentrated activated microglia and reactive astrocytes [52]. However, the authors mentioned that the functional contributions of the different glial populations remain unknown.

Brain tumors, primary or metastatic, alter the brain microenvironment. For instance, the BBB integrity can degrade from tumor angiogenesis [53]. Increased angiogenic growth factors such as vascular endothelial growth factor (VEGF) that disrupt endothelial permeability by promoting endocytosis of endothelial cell adhesion molecule VE-cadherin, leading to increased immune cell infiltration from the peripheral circulation [54].

Tumors take advantage of macrophage polarization, creating a microenvironment conducive to growth. Tumor-associated macrophages (TAMs) are among the main immune cells that induce an immunosuppressive TME and significantly contribute to tumor cell invasion, development, and growth (reviewed in [55]). The TME is responsible for M2 polarization of TAMs and its release of factors, including IL-4, IL-10, IL-13, and TGF-β [56]. M2 macrophage polarization changes antigen presentation, receptor expression, and cytokine production, aligning with immunoinhibitory, pro-tumor, and angiogenic effects when the tumor establishes itself [57]. This holds for most tumors, including breast cancer. Furthermore, TAM rich microenvironments suggest aggressive tumor progression with increased metastatic potential.

Jeong et al. [58] evaluated the relationship between marker expression in breast cancer and the presence of TAMs. Examination of 367 patients with invasive breast cancer revealed a high degree of TAM infiltration with high histological grade, greater tumor size, ER negativity, PR negativity, and Ki-67 proliferation index. TNBC is hormone receptor negative and associated with a poor prognosis resulting from aggressive behavior and lack of targets for treatment. In the context of immunotherapy, the TAM phenotype can play a role in the outcome [59].

3.5. Radiation induced changes in the brain microenvironment

Many radiation-induced alterations in the brain contribute to pro-inflammatory immune responses. These include DNA damage, cell death, senescence, hypoxia, cellular stress, tumor antigens, damage-associated molecular patterns (DAMPs), and neoantigens (reviewed in [60]). Low-grade inflammation is needed to clear toxins and damaged cells, protect and heal tissue [61]. However, chronic inflammation and the resultant cytokine storm (i.e., persistently elevated proinflammatory cytokines, chemokines, and neurotoxic agents) promote and sustain M1 activation and pro-inflammatory molecule production [62]. Cytokine storms are associated with immune cell hyperactivity, which produces reactive oxygen species (ROS) and reactive nitrogen species (RNS) that are toxic to cells, create a destructive environment, and induce pathological consequences, including neuronal damage and cell death [63–66]. The resultant neuronal damage and cell death initiate more microglial activation, sustaining a proinflammatory environment [44]. Studies have looked into suppressing this immune response by inhibiting $CD4^+$ T-cell activation, which is necessary for cells to enter the brain as a result of the inflammatory response (reviewed in [67]). Furthermore, chronic inflammation is found to be a major contributor to cognitive decline [68,69]. The assessment of glial activation duration and severity associated with neuroinflammation will help understand the relationship to cognitive side effects. The cascading relationship of the neuroinflammatory response and detrimental impact on cognition is illustrated in Fig. 1. The damage/injury to the brain from radiation includes acute, early delayed, and late injuries. Acute injuries resolve within hours to days, with symptoms such as headaches and drowsiness. Early delayed injuries resolve within a few weeks and do not have a lasting effect on cognition, including short-term memory loss and decreased attentiveness associated with WBRT stemming from transient demyelination [70]. Late brain injuries are more concerning and can significantly affect the quality and quantity of a patient's life. Late injuries from cranial irradiation are typically irreversible, occur more than six months later. Several publications have reviewed the immune reactions and subsequent inflammation in the brain induced from irradiation leading to cognitive impairments and morphological changes, including vascular abnormalities, demyelination, white matter necrosis [60,61,68,69]. However, cognition impairments can also occur with no detectable morphological changes [70]. Cognitive impairments manifest with varying severity in memory, learning, critical thinking, and IQ performance [70].

3.6 The connection between glial activation & cognition: Clinical TSPO-PET and preclinical studies

In the brain's microenvironment, the initial pro-inflammatory response to damage must be countered with an anti-inflammatory response to restore equilibrium and maintain homeostasis. TSPO-18 kDa, previously known as the peripheral benzodiazepine receptor, is a protein located on the outer mitochondrial membrane within glial cells. Under normal physiological conditions TSPO expression in the brain is low, but in response to glial activation, it is upregulated on activated microglia and reactive astrocytes. Several TSPO-PET radiotracers have been developed to visualize TSPO biodistribution and expression, with development efforts focused on improving pharmacokinetics and image quality. TSPO radiotracers are designed with a TSPO ligand with high binding affinity and selectivity. Zhang et al. [71] provided a comprehensive review of recent TSPO-PET radiotracers developments and neuroimaging. The precise mechanism regarding the elevated expression of TSPO in glial cells is not fully understood. However, the transition of microglia from resting to active state and glial proliferation resulting from tissue damage has demonstrated a significant increase in TSPO expression [72,73]. Below, we will begin by reviewing the connection between glial activation using TSPO-PET imaging and cognition in the clinical setting. This is followed by preclinical studies linking cognition with glial activation using TSPO-PET imaging or immunohistochemistry.

3.6.1. TSPO-PET imaging assessment in clinical studies

Neuroinflammation assessment with TSPO-PET has been used in clinical studies for neurodegenerative diseases, including MS, Alzheimer's disease, and Parkinson's disease [74–77]. Additionally, several TSPO-PET radiotracers are approved for human imaging, including [^{11}C]PK11195 , [^{11}C]PBR28, [^{11}C]DAA1106, [^{18}F]DPA-714, [^{18}F]PBR06, [^{18}F]FEPPA and [^{18}F]PBR111 (reviewed in [78]). Sucksdorff et al. [76] recently investigated MS progression using TSPO-PET with [^{11}C]PK11195. The data collected demonstrated that increased uptake of TSPO predicts greater clinical disability. Similar to cancer and radiation damage, MS progression correlates with adopting a proinflammatory phenotype within the CNS [79]. Neurodegenerative diseases are associated with neuroinflammation and are characterized by microglia changes, increased cytokine abundance, oxidative stress, and neuronal loss, resulting from the chronic nature of the disease [80]. Studies of neurodegenerative neuroinflammation imaging assessments are more abundant than those regarding cancer and have been approved for human use. The next logical step is to examine neuroinflammation in response to cancer and treatment.

Research in neuroinflammation imaging has typically focused on PET imaging with TSPO radiotracers, however, it remains challenging to quantify and has limitations that include low-affinity binding in at least 5% of the population due to a polymorphism in the TSPO gene as well as expression in non-glial cells (e.g. platelets, endothial cells and cancer cells) [8,9]. Narayamaswami et al. [81] identified several alternative neuroinflammation targets for neurodegenerative diseases, including glycogen synthase kinase, monoamine oxidase-B, reactive oxygen species, imidazoline-2 binding sites, and cyclooxygenase. Recent promising PET tracers also target the macrophage colony-stimulating factor 1 receptor (CSF1R) [82] and triggering receptor expressed on myeloid cells 1 (TREM1) [83]. Although promising, most alternatives to TSPO-PET have only been demonstrated in preclinical studies and have yet to be translated to patients studies.

3.6.2. Preclinical evaluations of glial activation and cognition

Typically, neuroinflammation assessment involves the evaluation of glial activation using immunohistochemistry and medical imaging. PET imaging with TSPO-targeted radiotracers has shown to be sensitive at the onset of disease in clinical and preclinical studies in neurological disease [84]. The reviewed studies include glial activation and, in turn, inflammation arising from multiple sclerosis (MS), stroke, traumatic brain injury, human immunodeficiency virus infection, and psychiatric diseases, but not from radiation.

Cosenza et al. [85] performed a comprehensive immunohistochemical analysis of TSPO expression in the abnormal human brain. TSPO expression was confirmed to be predominated by microglia and macrophages; however, activated astrocytes can also express TSPO. Recently, Zhang et al. [86] investigated the role of microglia with cognitive deficits in a rotenone-induced Parkinson's disease model. Rotenone was used to induce cognitive deficits, as demonstrated by reduced performance in novel object recognition, passive avoidance, and Morris water maze compared to controls. Microglia were depleted or inactivated by a colony-stimulating factor-1 (CSF-1) receptor, PLX3397, or minocycline. Depleted microglia reduced neuronal damage and exhibited an ameliorated cognitive performance deficit in rotenone-injected mice [86]. This study showed that glial activation plays a critical role in cognitive decline in mice and adds experimental evidence for the link between glial activation and cognitive decline.

Similarly, Acharya et al. [87] examined how the elimination of microglia affected cognitive function following cranial irradiation in a murine model. Microglia eliminated by CSF-1 receptor inhibition had improved cognitive deficits in irradiated mice compared to controls, assessed with novel object recognition and object in place exploration tasks.

Wlodarek et al. [88] investigated radiation induced cognitive impairment rectification in a murine model. WBRT is associated with cognitive impairments stemming from regional neuroinflammation, resulting in neuronal damage and microglial activation in the surrounding area, causing increased neuronal death and cognitive decline from a cytokine storm [4,5,88]. However, the amount of radiation and delivery schedule required to cause these effects is unknown. Wlodarek et al. [88] implanted hematopoietic stem cells from young and old mice irradiated for ten minutes at a rate of 1 Gy/min (10 Gy total, Cs-137 irradiator). Novel object recognition and open-field tests assessed the mice's learning and memory. Interestingly, in areas of the brain associated with learning and memory, microglia-like cells in young mice were polarized to a reparative phenotype in irradiated mice. The self-renewing young hematopoietic stem cells were able to enter the brain and differentiate into anti-inflammatory microglia. The increase in anti-inflammatory microglia present in the brain worked toward maintaining homeostasis and positively affected cognition [88]. This demonstrated the strong connection between the presence of activated microglia activation and its subsequent neuroinflammation with cognition.

Recently, ultra-rapid "FLASH" radiation has demonstrated normal tissue sparing compared to conventional radiation therapy at the same dose level [89,90]. Simmons et al. [91] evaluated FLASH radiation for its capability to mitigate neurodegeneration, neuroinflammation, and associated cognitive impairments found with conventional delivery. Three-month-old male C57BL6/J mice were evaluated ten weeks post 30 Gy WBRT using spatial and non-spatial object recognition and neuroinflammation immunohistochemistry. The cohort that received FLASH radiation had significantly less expression of microglia marker CD68 and exhibited reduced memory impairment in object location and novel object recognition tests than conventional radiotherapy and showed no significant differences from the control. Reduction in cognitive impairments could be the result of ameliorated neuroinflammation [91].

Parente et al. [92] investigated the effect of WBRT on glial activation and behavior in rats using TSPO-PET. Male Wistar-Unilever rats received WBRT of 10 Gy or 25 Gy (N = 8 per group), followed by PET imaging with [^{11}C]PK11195 on days three and 31. Radiotracer uptake for the whole brain was similar in all groups at day three and significantly decreased for the control and 10 Gy group at day 31, while the 25 Gy group had a similar uptake on day three and day 31, suggesting that higher than 10 Gy dose is required to elicit a sustained activation of microglia [92]. This supports a dose-dependent relationship with glial activation, in line with differences in severity of tissue damage with dose. The longitudinal study allowed for monitoring of glial activation and provided insight into acute and late effects of radiation but lacked immunohistochemistry confirmation.

3.6.3. Preclinical assessment of glial activation in breast cancer brain metastases

In recent years, preclinical studies have begun exploring glial activation associated with brain irradiation and cancer but not yet clinically in patients. With strong evidence for the connection between glial activation and cognitive deficits, preclinical studies have begun to examine the contributions to glial activation and neuroinflammation, including primary cancer [93,94], brain metastasis [95–98] and cancer treatments [87,88,91,92].

In a mouse model of TNBC (MDA-MB-231), Smart et al. [95] found that neuroinflammation was metastasis-drive in Female athymic nu/nu NRC mice. Comparable levels of neuroinflammation were observed in metastatic mice brains without and with WBRT, including fractionation of 30 Gy in 10 fractions and a single fraction of 15 Gy, but significantly lower to almost no neuroinflammation present in metastases free mice brains with the same WBRT. However, the group evaluated neuroinflammation with immunohistochemistry on day 28, had the evaluation timepoint been earlier, they might have seen a different relationship since microglia is the first step in the neuroinflammatory response.

O'Brien et al. [96] used TSPO-targeted radiotracers to examine glial activation in the early stages of brain metastasis with single-photon emission computed tomography (SPECT). The brain metastases mouse models used in the study involved direct injection or intracardiac injection of 4 T1 mammary mouse carcinoma into female BALB/c mice. SPECT imaging of brain metastasis in both models showed TSPO upregulation, indicating glial activation and providing a greater imaging target than the visible metastasis alone [96]. Interestingly, the glial activation was different between tumor models (diffuse versus local). The direct injection (intracerebral) model on day 14 showed reactive astrocytes had a more robust TSPO upregulation than microglia upon immunohistochemistry stains. In contrast, the intracardiac model imaged on day 21 showed reactive astrocytes mainly at the tumor periphery.

Similarly, Andreou et al. [97] examined glial activation using immunohistochemistry and immunofluorescence in BCBM. The group injected 4 T1-green fluorescent protein (GFP) mammary carcinoma cells directly into the brain of female BALB/c mice and completed a 28-day time-course study. Over the length of the study, the infiltration of microglia/macrophages was maintained and positively correlated with tumor burden. Both pro- and anti-inflammatory phenotypes were evident, although the metastatic burden was ameliorated by depleting the anti-inflammatory population with mannosylated clodronate liposomes. This provided evidence of the importance of glial cells' M2 polarization in supporting cancer growth.

In a metastatic breast cancer model, Simon et al. [98] explored the interaction between tumors and microglia. Using intravital imaging with an optical window implanted in Cx3cr1$^{GFP/+}$ mice, they found that MDA-MB-231 metastatic breast cancer cells impacted microglial morphology. Multiphoton microscopy performed through the optical window allowed for the visualization of activated microglia labeled with GFP and breast cancer cells transduced with recombined lentivirus for discosoma red (DSRed). Activated microglia surrounded the lesion, and intravital brain imaging showed tumor cell infiltration and microglia recruitment to the lesion [97]. The studies reviewed indicate microglia have an active role in developing and progressing brain metastases and

suggesting anti-inflammatory phenotypes may be a promising target for therapeutic intervention.

4. Discussion

Cranial irradiation is an effective treatment for brain cancer; however, the cognitive impairments can be severe, leading to the investigation of approaches to reduce radiation induced cognition impairments. The connection between persistent microglial activation and effects on deficits in cognition in neurodegenerative diseases has been well studied (reviewed in [80]). The imaging methods used in these studies can be applied to radiation and cancer-induced glial activation to better manage patients with brain metastases and reduce radiation-induced cognitive impairments. However, no TSPO-PET studies look at radiation induced glial activation and its impact on cognitive functions with glial immunohistochemistry. More preclinical studies investigating glial activation from cancer and radiation are needed. As TSPO-PET has shown significant promise in measuring glial activation in the brain for neurological disease, it has the potential to impact radiation treatments for breast cancer patients. TSPO-PET could be used to evaluate post-irradiation glial activation (neuroinflammation) and modify WBRT for BCBM in an effort to reduce cognitive side effects. TSPO-PET may have very broad applications to include other forms of cancer treatments that alter the neuroinflammatory environment of the brain, including adjuvant or combination immunotherapy and anti-inflammatory steroids such as Dexamethasone.

The present review focuses on BCBM, because systemic treatments have increased breast cancer patients' overall survival, along with incidence of brain metastases. However, the results from the studies discussed could be applied to brain metastases originating from other primary cancers, especially in the brain metastasis patient population with controlled extracranial diseases and surviving long enough to experience radiation induced neuro-toxicities. Future investigation of the connection between radiation and cancer-induced glial activation is an essential step toward the refinement of radiation treatment of BCBM with the potential to minimize neurotoxicity.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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