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The glymphatic system in oncology: from the perspective of a radiation oncologist

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ABSTRACT

The brain and spinal cord, which constitute the central nervous system, were historically considered immune-privileged sites, as it was believed they lacked an equivalent to the systemic lymphatic system. However, in 2013, a pathway facilitating the clearance of waste products through the brain parenchyma via the perivascular space was proposed, garnering attention as the ‘glymphatic system’. Similar to the systemic lymphatic system, the glymphatic system plays a critical role in immune responses and has been implicated not only in Alzheimer’s disease and inflammatory brain disorders but also in conditions such as hydrocephalus and glaucoma, which are associated with cerebrospinal fluid circulation impairments. Recent studies have suggested that dysfunction of the glymphatic system may promote the progression of brain tumors and reduce the efficacy of immune responses and pharmacological therapies targeting tumors. Radiotherapy is a major treatment option for brain tumors; however, while it can enhance immune responses against tumors, it may also suppress these responses at the same time. Additionally, cranial irradiation has been suggested to impair the function of the glymphatic system. This review provides an overview of the structure and functional evaluation methods of the glymphatic system, summarizes the effects of its dysfunction on brain tumor treatment, and explores recent findings on the impact of radiation therapy on glymphatic system functioning. Lastly, it also explores the potential for radiation therapy strategies that account for their effects on the glymphatic system.

Keywords: glymphatic system; tumor immunology; brain tumor; radiotherapy

INTRODUCTION

In the systemic circulation outside the central nervous system (CNS), plasma constantly moves from the capillaries into the interstitial space. Most of this plasma is either absorbed by tissue cells or reabsorbed into the vascular branches and a portion enters the lymphatic system along with metabolic waste products, including proteins derived from inflammation and metabolism. The lymphatic system facilitates the transport of fluids throughout the body and ultimately drains into the venous system, thereby playing a crucial role in the removal of waste products from the body.

For a long time, the CNS was thought to lack an analogous lymphatic structure, and cerebrospinal fluid (CSF) was considered to act as a 'sink' to collect metabolic waste. However, in 2013, a hypothesis was proposed that CSF flows through the perivascular space (PVS) surrounding arteries (also known as the Virchow-Robin space), enters the brain parenchyma via aquaporin-4 (AQP4) channels expressed on astrocytes, and exits along the PVS on the venous side, carrying waste products from the brain [1]. This system, likened to a lymphatic network within the brain, was termed the 'glymphatic system', a portmanteau word of 'glia' and 'lymphatic'. Since its discovery, extensive research has been conducted on its functions and the methods for evaluating it.

Since the initial proposal, the glymphatic system has garnered significant attention for its potential role in diseases associated with the accumulation of harmful metabolic byproducts in the brain, such as in Alzheimer's disease. Recent animal studies have reported that enhancing glymphatic system functioning improves cognitive performance in Alzheimer's disease mouse models, underscoring its potential as a novel therapeutic target [2]. Emerging evidence suggests that impaired glymphatic functioning is observed in certain brain tumors and may contribute to tumor progression and treatment resistance.

This review provides an overview of the glymphatic system, discusses its relationship with brain tumors, and examines the effects of radiation therapy on glymphatic functioning and future directions of research.

CLASSICAL CSF CIRCULATION AND THE GLYMPHATIC SYSTEM

The brain is an organ responsible for extensive information processing. Although it accounts for only approximately 2% of total body weight, it consumes about 20% of the total daily energy intake of the body in the form of glucose [3]. Consequently, the proper removal of metabolic waste products is essential for maintaining its functions. In organs other than the brain, the lymphatic system plays a role in waste clearance. Since the brain parenchyma was historically believed to lack anatomical structures equivalent to lymphatic vessels, it was hypothesized that CSF, circulating through the ventricles and cisterns, functions as a sink to collect waste products. CSF was believed to be produced in the choroid plexus within the cerebral ventricles, to flow through the cerebral aqueduct into the fourth ventricle, and to then pass through the foramina of Magendie and Luschka into the subarachnoid space, ultimately being absorbed via the arachnoid granulations into the

superior sagittal sinus. This pattern of circulation has traditionally been referred to as the bulk flow theory. According to this hypothesis, metabolic waste from the brain parenchyma would diffuse into the CSF and subsequently be eliminated through the systemic circulation. However, the diffusion of waste products from the brain parenchyma into the CSF was found to be an exceedingly slow process, raising concerns about the efficiency of this mechanism [4]. In addition, the observation that CSF production is maintained even after choroid plexus removal has led to the hypothesis that CSF may also be produced by capillaries outside the choroid plexus within the brain parenchyma [5]. Studies using magnetic resonance imaging (MRI) and tracer injection into the cerebrospinal system have revealed that CSF does not travel as far as previously suggested by the bulk flow theory [6, 7]. Although the traditional bulk flow theory is no longer considered entirely accurate in light of recent findings, it remains a widely used educational model. As of 2022, it was still being taught to more than half of medical students to facilitate understanding of the pathophysiology of non-communicating hydrocephalus [8].

From the late 20th century, attempts were made to investigate the waste clearance pathways of the brain parenchyma by injecting substances such as India ink or albumin labeled with radioactive isotopes into the brain parenchyma or the subarachnoid space [9–11]. The results have suggested that substances injected into the CSF diffused into the brain parenchyma, whereas those injected into the brain parenchyma were eliminated via the PVS. This clearance route was later confirmed through laser-guided bolus dye injections and multiphoton imaging [12]. It was suggested that tracers entering the PVS might either drain into the bloodstream via arachnoid granulations or exit through the extracellular compartments surrounding olfactory nerves, ultimately reaching the deep cervical lymph nodes via the nasal mucosa [9, 10].

In 2013, Nedergaard *et al.* introduced the concept of the glymphatic pathway, bringing significant attention to this clearance system [1]. This mechanism involves the circulation of CSF through the PVS located between the blood vessel walls of intracerebral arteries and veins and the end-feet of astrocytes. Driven by arterial pulsations, CSF enters the brain parenchyma from the PVS surrounding arteries, facilitating the clearance of metabolic waste. The waste-laden CSF is then drained through the PVS surrounding veins, effectively flushing out waste products from the brain parenchyma (Fig. 1). AQP4, expressed on the vascular side of astrocytic end-feet, plays a critical role in the movement of water in the glymphatic pathway. Animal studies demonstrated that the absence of AQP4 led to a ~70% reduction in CSF influx mediated by astrocytes and significantly impaired the clearance of soluble proteins from the brain parenchyma, further supporting the existence of this system [13].

In 2015, lymphatic vessels, which were previously believed to be absent from the CNS, were discovered in the meninges [14, 15]. This meningeal lymphatic network appears to start from both eyes and track above the olfactory bulb before aligning adjacent to the sinuses. It was reported that lymphatic drainage via the cribriform plate enters lymphatic vessels within the nasal mucosa and connects to the deep

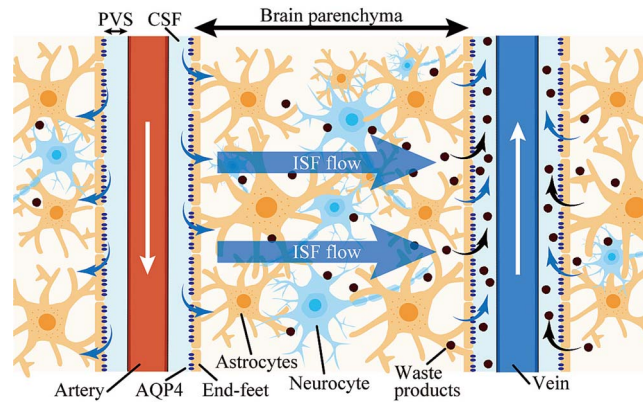


Fig. 1. Diagram illustrating the transport of CSF and ISF, as well as the concept of the glymphatic system. The blue arrows indicate the movement of CSF and ISF, while the black arrows represent the movement of waste products. The CSF entering from the PVS surrounding the arteries flows toward the venous side as ISF, facilitating the clearance of waste products from the brain parenchyma into the PVS on the venous side for excretion. AQP4, expressed in the end-feet of astrocytes, plays a crucial role in the fluid dynamics of the glymphatic system.

cervical lymph nodes [14]. Additionally, glymphatic pathways associated with the optic nerve [16, 17] and the inner ear have also been reported [18] (Fig. 2). The meningeal lymphatic system is thought to be positioned downstream of the glymphatic system and facilitates the clearance of waste products from the brain as well as it also plays a role in antigen presentation from antigen-presenting cells (APCs) to T-cells [19]. Specifically, the dural meninges surrounding the dural venous sinuses serves as a critical interface in the immune–blood–brain interaction. It has been suggested that immune responses to antigens derived from the CNS are regulated through the capture of these antigens by APCs in the dura mater, which then present them to T-cells [19] (Fig. 3). Antigens that enter the meningeal lymphatic vessels may also trigger immune responses by subsequently draining into the cervical lymph nodes [20].

Historically, the brain was considered an immune-privileged site due to the observation that graft rejection following transplantation into the brain was weaker than in other body sites. This immune privilege was attributed to the absence of a lymphatic system in the brain, which would otherwise transport antigens to lymph nodes to initiate immune responses, and also to the presence of the blood–brain barrier (BBB), which restricts the entry of immune effector cells and immune-related molecules into the brain [21]. However, as described above, the glymphatic system and its downstream meningeal lymphatic system facilitate the transport of brain-derived antigens to the deep cervical lymph nodes, and these lymphatic networks also play a role in immune cell trafficking. These findings indicate that the brain is not completely isolated from the immune system [1, 14].

Much of the current knowledge about the glymphatic system and meningeal lymphatic vessels has been derived from animal studies. Given potential interspecies differences, caution is warranted when directly extrapolating these findings to humans. The glymphatic system, which facilitates the clearance of waste products from the brain parenchyma, and the meningeal lymphatic vessels, which mediate CSF drainage from the intracranial to the extracranial space and contribute

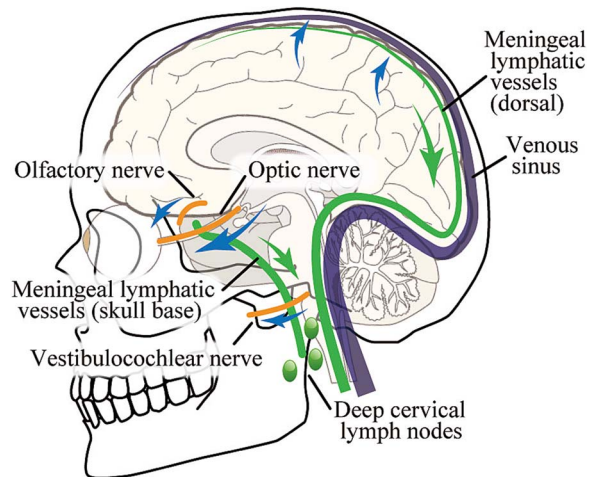


Fig. 2. Diagram of the meningeal lymphatic system. The blue arrows indicate the movement of CSF, while the green arrows represent lymphatic flow. This system comprises the dorsal lymphatic network observed along the venous sinuses and the basal lymphatic pathways, which are thought to drain through structures such as olfactory nerve, optic nerve, and vestibulocochlear nerve. Both pathways are believed to ultimately drain into the cervical lymph nodes, including the deep cervical lymph nodes.

to immune regulation, are two distinct systems. The structural and functional interactions between these systems in the human body remain largely unexplored [22]. Nevertheless, due to the current difficulty in clearly distinguishing their respective structures and functions, this review collectively refers to both as the glymphatic system in the broader sense.

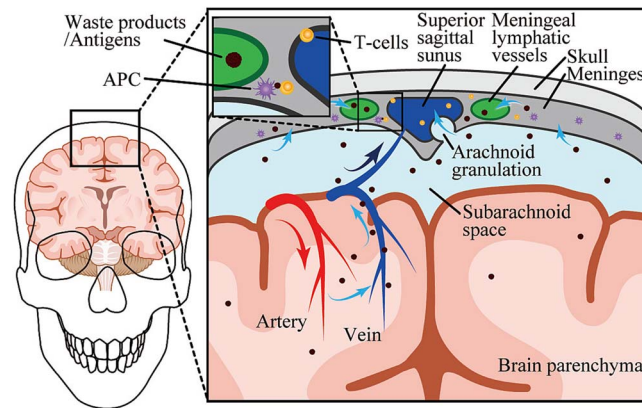


Fig. 3. Diagram of the superior sagittal sinus structure and CNS-derived antigen presentation to immune cells. The light blue arrows indicate the movement of CSF, the dark blue arrows represent the movement of venous blood, and the red arrows denote the movement of arterial blood. While the precise mechanism by which CSF in the subarachnoid space reaches the meningeal lymphatic vessels remains unclear, it has been suggested that CSF first moves into the meninges before subsequently entering the meningeal lymphatic vessels. Additionally, CNS-derived waste products and antigens are also thought to migrate into the meninges, where some are taken up by the meningeal lymphatic vessels, while others are captured by APCs and subsequently presented to T-cells within the meninges [15].

METHODS FOR ASSESSING THE GLYMPHATIC SYSTEM

MRI is primarily used to assess the functions of the glymphatic system, with imaging techniques categorized into some that utilize exogenous contrast agents (Gadolinium-based contrast agent [23, 24] and ^{17}O -labeled water [25–27]) and those that do not (diffusion-weighted imaging (DWI) and chemical exchange saturation transfer (CEST) MRI [28]). There have been reports utilizing ^{15}O -labeled water as a positron emission tomography (PET) tracer [29–31], as well as studies evaluating the correlation between morphological features—such as arachnoid cuff exit site (ACES) cysts in the parasagittal sinus region—and the function of the glymphatic system and cognitive performance [32, 33]. Since recent reviews [18, 24] provide a comprehensive discussion on this topic, this paper focuses on the most widely used DWI-based evaluation method, along with recent advancements involving the application of artificial intelligence (AI).

FUNCTIONAL EVALUATION OF THE GLYMPHATIC SYSTEM USING DWI

The DWI enables the visualization of the diffusional motion of water molecules in biological tissues, and is widely utilized for the diagnosis of acute ischemic stroke. DWI also facilitates the reconstruction of neural fiber pathways through diffusion tensor imaging (DTI), which captures the anisotropic movement of water molecules along nerve fibers [34, 35]. This methodology also permits the evaluation of water diffusion along PVS, but assessing glymphatic flow within the brain parenchyma is challenging due to the dominant influence of white matter fiber diffusion in most brain regions.

Diffusion tensor image analysis along the PVS (DTI-ALPS) method [36] overcomes this limitation by leveraging the anatomical arrangement of PVS, projection fibers, and association fibers, which intersect perpendicularly at the level of the lateral ventricle body. This technique extracts the diffusion components along PVS from

3D diffusion tensor data to compute a quantitative metric known as the ALPS index (Fig. 4).

The ALPS index is calculated as follows [23]:

$$\text{ALPS index} = \text{mean} (D_{x\text{proj}}, D_{x\text{assoc}}) / \text{mean} (D_{y\text{proj}}, D_{z\text{assoc}})$$

where $D_{x\text{proj}}$ and $D_{x\text{assoc}}$ represent diffusivity along the X-axis in projection and association fiber regions, respectively, while $D_{y\text{proj}}$ and $D_{z\text{assoc}}$ correspond to the diffusivity along the Y-axis in projection fiber regions and the Z-axis in association fiber regions, respectively.

The DTI-ALPS method offers the advantage of enabling a simple and non-invasive evaluation of glymphatic system functions without requiring the administration of exogenous contrast agents. This method has been applied to the evaluation of various pathological conditions, including Alzheimer's disease [36], Parkinson's disease [37], sleep disorders [38], corticobasal syndrome [39], and pediatric acute lymphoblastic leukemia [40]. Notably, these studies have reported significant correlations between the ALPS index and clinical symptoms or recurrence risk categories. A recent genome-wide association study identified a shared genetic basis between the ALPS index, ventricular volumes, and CSF tau protein levels [41], further supporting the reliability of the ALPS index and the robustness of studies utilizing the DTI-ALPS method.

It is important to note that the ALPS index does not directly quantify the functions of the glymphatic system. Taoka *et al.*, who originally proposed the DTI-ALPS method, have stated that this technique evaluates only limited aspects of interstitial fluid (ISF) dynamics in the brain. They emphasize that a comprehensive evaluation of ISF dynamics requires a multimodal approach incorporating multiple assessment methods [42]. The ALPS index may also be influenced by factors such as axonal degeneration [43], the imaging plane, the number of motion-probing gradient axes, and echo time (TE) in the imaging sequence [44]. Another limitation of DTI-ALPS is its reliance on the manual

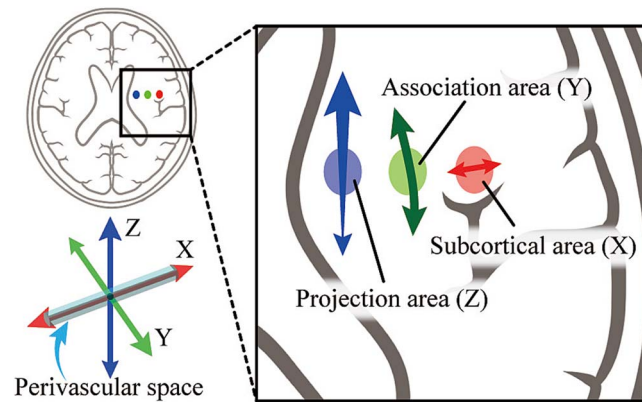


Fig. 4. Conceptual sketch for the diffusion tensor image analysis along the PVS (DTI-ALPS) method. In the white matter outside of the lateral ventricular body, the medullary vessels run in the left–right direction (*X*-axis), the projection fibers run in the vertical direction (*Z*-axis), and the association fibers run in the anteroposterior direction (*Y*-axis). Thus, in this region, diffusion in the direction of the PVS of the medullary arterioles can be assessed separately from the diffusion effects of the large white matter fibers.

region of interest (ROI) placement, which introduces variability and reduces reproducibility. Differences in MRI equipment and imaging protocols across institutions also contribute to inter-site variability in the results [45].

RECENT ADVANCES IN ALPS INDEX STANDARDIZATION

To address these challenges, Tatekawa *et al.* proposed a technique to correct for head positioning, significantly reducing the ALPS index variability using publicly available neuroimaging data from The Open Access Series of Imaging Studies (OASIS)-3 [46]. Similarly, Saito *et al.* developed an automated ALPS index calculation method, which improved reproducibility [47, 48]. Statistical methods have been also introduced to harmonize neuroimaging data acquired across different institutions. Among these, the COMBined Association Test (COMBAT) has demonstrated the best performance in mitigating inter-site variability [49–51], contributing to the gradually improving standardization of the ALPS index.

FUTURE PROSPECTS: AI IN MRI-BASED GLYMPHATIC IMAGING

In recent years, the application of AI and machine learning in imaging diagnostics, including the evaluation for glymphatic functions, has been actively explored [52, 53]. Japan, which has one of the highest MRI scanner densities per capita globally [54], presents a highly favorable environment for AI-driven research and development in neuroimaging [55, 56]. Although current standard methods for evaluating glymphatic functions do not incorporate AI-based approaches, future advancements in AI integration can be expected to enhance both the accuracy and efficiency of glymphatic function assessments.

GLYMPHATIC SYSTEM DYSFUNCTION AND ITS RELATIONSHIP WITH CNS TUMORS: INSIGHTS FROM GLIOMA STUDIES

Dysfunction of the glymphatic system has been implicated in the pathogenesis of various neurological disorders, making it an active area

of research. Specifically, impaired CSF circulation has been associated with the development of idiopathic normal pressure hydrocephalus [17], glaucoma [16], and Ménière's disease [18], while defective waste clearance from the brain parenchyma has been linked to Alzheimer's disease [13] and cerebral small vessel disease [57]. An association between glymphatic dysfunction and inflammatory neurological disorders such as multiple sclerosis has also been suggested [58]. The glymphatic system is also associated with sleep. It has been reported that during sleep or anesthesia, the circulation of CSF and ISF increases, facilitating the clearance of metabolic waste from the brain [59]. A positive correlation has been observed between the quality of sleep and the efficiency of the glymphatic system functions [60].

Recent research has highlighted the role of the glymphatic system in CNS tumors, particularly gliomas. Dysfunction of this system has been linked to tumor progression, impaired immune response, and reduced drug penetration, making it a critical factor in glioma pathophysiology and treatment outcomes. Tumor growth itself also affects glymphatic functions.

Siri *et al.* reported that mechanical stress induced by tumor expansion may directly impair glymphatic fluid transport. Their study demonstrated that while a 20% mechanical strain on the basement membrane of capillaries reduced the venous outflow rate by only 2%, the same level of strain applied to astrocytic networks and interstitial spaces reduced outflow rates by 7% and 22%, respectively [61]. Gliomas also downregulate the expression of AQP4 in perivascular astrocytes, leading to glymphatic dysfunction [62].

Clinical studies have shown that grade 4 gliomas and IDH1-wild gliomas exhibit lower ALPS indices than IDH-mutant gliomas, suggesting greater glymphatic impairment in more aggressive tumors [63, 64]. Indeed, in glioblastoma (GBM), lymphatic outflow has been reported to be impaired, resulting in delayed clearance of waste products from the brain [65, 66]. Notably, patients with a low ALPS index in the contralateral hemisphere exhibit significantly shorter survival times compared to patients with a high ALPS index [67].

It remains a challenge to determine whether tumors of poor prognostic histological subtypes are more likely to impair the glymphatic

system function or whether dysfunction of the glymphatic system itself contributes to tumor progression, making disease control more difficult and ultimately leading to poorer treatment outcomes. However, it is possible that the interplay between poor-prognosis tumor histology and glymphatic system dysfunction exacerbates treatment outcomes. The following section provides an overview of the impact of glymphatic system dysfunction on brain tumors.

Glymphatic dysfunction and tumor progression

The glymphatic system plays a crucial role in maintaining interstitial homeostasis and removing inflammatory mediators. Tumor cells secrete various inflammatory signaling molecules, including vascular endothelial growth factors (VEGF)-A, VEGF-C, Neuropilin-2, fibroblast growth factor (FGF), hepatocyte growth factor (HGF), insulin-like growth factor (IGF), and platelet-derived growth factor (PDGF) [68]. In malignant gliomas, impaired glymphatic system functions may delay the clearance of these inflammatory signaling molecules from the brain parenchyma, potentially promoting tumor progression [65]. Additionally, in a tumor-induced vasogenic brain edema model, AQP-4 knockout mice exhibited significantly delayed clearance of excess water from the brain compared to wild-type mice [69]. These findings suggest that gliomas may exacerbate brain edema by downregulating AQP-4 expression in astrocytes.

Glymphatic dysfunction and impaired anti-tumor immune response

Since around 2013, increasing attention has been given to immune responses against tumors, leading to the proposal of the cancer-immunity cycle [70]. According to this model, when a tumor is destroyed and tumor antigens are released, APCs capture these antigens and migrate to the lymph nodes, where they activate T-cells. The activated T-cells then enter the bloodstream, infiltrate the tumor, and attack the target tumor cells. As tumor cells undergo cell death, additional tumor antigens are released, further amplifying the immune response.

Rustenhoven *et al.* demonstrated that antigens derived from the CNS, which drain into the CSF and meningeal lymphatic vessels, accumulate around the dural venous sinuses, where they are presented by APCs to T-cells [19]. Further, Hu *et al.* reported that in mice injected with GBM or melanoma cells into the subdural space or striatum, structural remodeling was observed predominantly in the dorsal meningeal lymphatic vessels near the transverse and superior sagittal sinuses, while lymphatic remodeling at the skull base was minimal. They also found that the dorsal meningeal lymphatic vessels were essential for tumor antigen presentation and APC transport to deep cervical lymph nodes. They also demonstrated that the immune response against tumors and the therapeutic efficacy of anti-PD-1/CTLA-4 therapy were suppressed upon removal of the dorsal meningeal lymphatic vessels, whereas VEGF-C, a key factor in lymphangiogenesis, enhanced the efficacy of anti-PD-1/CTLA-4 therapy [71].

Anti-PD-1/PD-L1 therapy exerts antitumor effects by activating T-cells in the lymph nodes, where tumor antigens are processed [72]. Song *et al.* reported that in tumors confined to the intracranial space, ligation of the deep cervical lymph nodes reduced the efficacy of immune checkpoint inhibitors (ICIs). However, when tumors

extended beyond the cranium, ligation of the deep cervical lymph nodes did not diminish the therapeutic effect of ICIs. Moreover, even in cases where tumors were confined to the intracranial space, exogenous upregulation of VEGF-C enhanced the efficacy of ICIs to a level comparable to that observed in tumors with extracranial extensions [73].

These findings suggest that for immune responses against intracranial tumors to be effectively activated and for immunotherapy to be efficacious, tumor antigens must be cleared from the brain parenchyma via the glymphatic system, presented by APCs to T-cells, and transported to the cervical lymph nodes, where T-cells are subsequently activated by ICIs. VEGF-C-mediated lymphangiogenesis is expected to potentiate this immune cascade, thereby enhancing the therapeutic effects of ICIs. Given that the glymphatic system plays a fundamental role in initiating antitumor immunity, its dysfunction may impair immune responses against tumors, potentially leading to tumor progression and resistance to therapeutic intervention.

Glymphatic dysfunction and reduced drug penetration

For a drug to transition from systemic circulation into the CNS, it must traverse the BBB, which consists of endothelial cells, pericytes, and astrocytic end-feet. However, due to the selective permeability of the BBB, it serves as a major obstacle to drug delivery into the CNS. Various approaches have been explored to enhance drug permeability, including receptor-mediated transcytosis, neurotropic viruses, nanoparticles, and exosomes; however, none of these methods have yet been definitively established as effective [74].

As previously mentioned, dysfunction of the glymphatic system may exacerbate brain edema associated with brain tumors. Increased intracranial pressure due to brain edema may reduce cerebral blood flow, further hindering the entry of systemically administered antitumor drugs into the intracranial space [62].

Direct intrathecal administration of antitumor agents or implantation of drug-releasing wafers into the tumor resection cavity are among the strategies used to circumvent BBB-associated drug delivery limitations. Since the glymphatic system facilitates the transport of CSF-borne drugs into the brain parenchyma, enhancing glymphatic system functioning may improve drug penetration into deep-seated intracranial lesions following intrathecal administration [75, 76]. Consequently, glymphatic system activation holds promise both for brain tumor therapy as well as for the treatment of neurodegenerative diseases, including dementia [77]. Conversely, impaired glymphatic functioning may hinder the distribution of intrathecally administered antitumor agents to tumor sites, thereby significantly reducing therapeutic efficacy [78, 79]. One potential explanation for the limited effectiveness of BCNU (carmustine) wafers is the insufficient drug concentration reaching the deeper regions of the brain parenchyma [80, 81].

THE IMPACT OF RADIATION THERAPY ON THE GLYMPHATIC SYSTEM

There is limited knowledge regarding the impact of radiation therapy on the glymphatic system. However, in patients who have undergone radiation therapy for brain tumors, cystic changes—presumably due to expansion of the Virchow-Robin space—have been observed within the irradiated area [82, 83]. In addition to radiation exposure,

Virchow-Robin space enlargement has also been reported in association with neuropsychiatric disorders, multiple sclerosis, traumatic brain injuries, and small vessel diseases. The exact mechanism underlying the expansion of the Virchow-Robin space remains unclear, but potential causes include increased arterial wall permeability and impaired CSF clearance [84]. This would suggest that the expansion of the PVS in these regions is not indicative of an enhancement in glymphatic system functions; rather, it is likely a consequence of glymphatic dysfunction. In other words, irradiation may contribute to a decline in glymphatic system functioning.

Recent reports have evaluated the effects of radiotherapy on the glymphatic system functions in patients who have undergone whole-brain irradiation or radiation therapy for nasopharyngeal carcinomas. Taoka *et al.* assessed the glymphatic system functions in 22 patients who received whole-brain irradiation for brain tumors using diffusion-weighted image analysis (DWI-ALPS method), a simplified version of the diffusion tensor imaging analysis (DTI-ALPS). Their findings demonstrated a significantly lower ALPS index in the radiotherapy group compared to a healthy control group, with a particularly pronounced decreased ALPS index in patients aged 40 years or older [85]. However, no statistically significant difference was observed between the irradiated and control groups in younger patients (aged 20–39 years). A weak negative correlation was found between the ALPS index and the biologically equivalent dose (BED), with higher BED values corresponding to lower ALPS indices.

Similarly, Zheng *et al.* evaluated glymphatic system functioning using the DTI-ALPS method in patients with nasopharyngeal carcinomas before and after radiation therapy. Their results showed a significantly lower DTI-ALPS index in post-treatment patients compared to pre-treatment patients. A significant negative correlation was also observed between the maximum radiation dose to the temporal lobe and the DTI-ALPS index. Based on these findings, the authors concluded that a reduced DTI-ALPS index could serve as a biomarker for early radiation-induced brain necrosis [86].

Although the DTI-ALPS index does not necessarily reflect the overall glymphatic system function of the brain and could be influenced by confounding factors such as chemotherapy and differences in radiation fields, it is an intriguing finding that the ALPS index reduction occurs even when the lateral body of the lateral ventricle is not directly irradiated, as seen in cases where radiation is administered to the nasopharynx and neck. The mechanism by which radiation exposure impairs the glymphatic system remains unclear, necessitating further research.

POTENTIAL OF RADIOTHERAPY CONSIDERING THE GLYMPHATIC SYSTEM

GBM, the most common malignant tumor of the CNS, remains a disease with extremely poor prognosis despite the combination of surgery, radiotherapy, and chemotherapy. Therefore, improving treatment outcomes is an urgent clinical challenge. Applying ICIs has failed to demonstrate significant efficacy as a monotherapy for newly diagnosed or recurrent GBM [87–89]. However, GBM cells are suggested to strongly suppress the immune response to the tumor [90], prompting various attempts to enhance anti-tumor immune responses as a means to improve treatment outcomes [91].

Not only in the peripheral systems but also in the CNS, radiotherapy exhibits a dual role in modulating immune responses—it can both enhance and suppress anti-tumor immunity, making it a double-edged sword [92–96]. Radiation exposure promotes the release of tumor antigens from tumor cells, increases the infiltration of lymphocytes into the tumor, and enhances antigen presentation by dendritic cells. Recent studies have demonstrated that radiotherapy enhances the immune response and improves the efficacy of ICIs by modulating the expression of molecules such as the FAS ligand and PD-L1 on the surface of tumor cells, as well as it promotes T-cell recruitment [92, 97]. Positron emission tomography/computed tomography (PET/CT) has emerged as a valuable tool for noninvasively monitoring these changes by detecting PD-1/PD-L1 expression patterns [98]. However, radiotherapy may also increase the proportion of regulatory T-cells, which suppress immune responses, and affect myeloid-derived suppressor cells, thereby potentially attenuating anti-tumor immunity [94]. As the irradiated volume increases, more lymphocytes within the cerebral blood circulation are exposed to radiation. Naïve T-cells circulating in the bloodstream exhibit extreme sensitivity to radiation [99]; consequently, such exposure results in lymphocyte depletion and impaired anti-tumor immune responses, which may ultimately result in poorer tumor control [100]. A small prospective Phase II trial comparing two treatment groups with different irradiation fields for GBM reported superior outcomes in a group receiving more limited-field irradiation [101].

The concept of the glymphatic system offers a new perspective on the impact of radiotherapy for brain tumors. The studies discussed in this review suggest that, like the peripheral lymphatic system, the glymphatic system plays a crucial role in fluid circulation, waste clearance, and immune responses to foreign substances. Radiotherapy is hypothesized to impair glymphatic system function; however, the extent of its impact may vary depending on the specific irradiated regions. For instance, irradiation of the dorsal meningeal lymphatic vessels, which are thought to facilitate antigen presentation to T-cells near the dural venous sinuses, may directly disrupt anti-tumor immune responses. Additionally, irradiation of the meningeal lymphatic network at the skull base may reduce CSF outflow, leading to impaired waste clearance, which could weaken anti-tumor immune responses and also contribute to cognitive decline. While this review proposes a hypothesis without definitive evidence, further data accumulation may help identify specific irradiation fields and doses that are associated with adverse effects on the glymphatic system. This knowledge could help minimize radiation exposure to critical areas or identify regions where radiation exposure is less likely to affect the glymphatic functions. Advances in highly precise radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT) and particle therapy, allow for the selective reduction of radiation doses to specific regions while maintaining high doses to the tumor, potentially enabling glymphatic system-preserving radiotherapy.

CONCLUSIONS

Although the structure, function, and evaluation methods of the glymphatic system in humans have not yet been fully established, impaired glymphatic functioning has been suggested to contribute to the onset and progression of various diseases and tumors. Research on the

relationship between the glymphatic system and radiotherapy remains in the early stages. Nevertheless, glymphatic system-preserving radiotherapy holds promise for eventually improving treatment outcomes, including patient survival and tumor control, in GBM and other refractory brain tumors while mitigating adverse effects such as cognitive decline.

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CONFLICT OF INTEREST

The authors have no conflict of interest to declare related to this study.

PRESENTATION AT A CONFERENCE

None.

CLINICAL TRIAL REGISTRATION NUMBER

None.

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