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# Application of Cerebral Glucose PET Imaging in Cancer-Related Cognitive Impairment before and after Treatment in Tumor Patients

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## Abstract

With the improvement of cancer survival rates, cancer-related cognitive impairment (CRCI) has become a key complication affecting the quality of life of more than 70% of tumor patients. Its pathogenesis is complex, involving the interaction of multiple factors such as chemotherapy-induced neurotoxicity, neuroinflammation, and metabolic disorders, but the specific imaging features and pathological mechanisms still need to be systematically clarified. By systematically reviewing relevant domestic and foreign literature, this review summarizes the cerebral glucose metabolic characteristics before and after chemotherapy, potential mechanisms, and clinical intervention methods. Understanding the dynamic changes in cerebral glucose metabolism provides an important basis for the early identification and intervention of CRCI. Future research should focus on integrating multimodal PET imaging and radiomics data to develop individualized neuroprotective strategies based on metabolic feature typing, and ultimately promote the transformation of CRCI management from neurotoxicity control to neurofunctional improvement.

## Keywords

$^{18}$F-Fluorodeoxyglucose, Cancer-Related Cognitive Impairment, Chemotherapy, Neurotoxicity, Blood-Brain Barrier

## 1. Research Background and Significance

With the advancement of cancer diagnosis and treatment, the scale of cancer sur-

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vivors has expanded significantly [1], and the potential impact of anti-tumor therapy on the central nervous system (CNS) has gradually become a research focus. In this context, cancer-related cognitive impairment (CRCI) has emerged as a highly prevalent complication, affecting up to 70% of patients [2] [3]. The core clinical manifestations of CRCI are memory decline and attention deficit, and numerous studies have confirmed a significant association between its occurrence and chemotherapy. Notably, CRCI has a persistent onset time domain: cognitive impairment may appear before the start of treatment, progress continuously during treatment, and even persist for several years after treatment ends [4]. This long-term cognitive dysfunction not only significantly impairs the quality of life of patients throughout the treatment cycle and survival period but also may reduce treatment compliance, thereby potentially affecting anti-tumor efficacy. Although the clinical importance of CRCI has been widely recognized, there are still significant knowledge gaps in its underlying neuroimaging characteristics (especially changes in brain functional metabolism), molecular mechanisms, and effective intervention strategies, which urgently require interdisciplinary in-depth exploration [5].

CRCI refers to observable or self-reported cognitive decline related to cancer itself or its treatment that occurs after cancer diagnosis, during treatment, or after treatment completion. Its clinical manifestations mainly include decreased attention and concentration, working and learning memory ability, and executive function. It is divided into primary and secondary CRCI: the former is caused by cancer itself (such as paraneoplastic syndrome, inflammatory factors produced by tumors affecting the brain) or diagnostic stress, occurring before treatment; the latter is caused by cancer treatment (chemotherapy, radiotherapy, targeted therapy, endocrine therapy, etc.) or treatment-related side effects (such as severe fatigue, anemia, sleep deprivation, or mood disorders).

Chemotherapy is an effective treatment for various malignant tumors, but it is often accompanied by significant neurological side effects that affect patients' quality of life, social function, and treatment compliance. Despite its great clinical significance, the exact neurobiological mechanism of chemotherapy-related cognitive impairment remains unclear. Traditional neuroimaging techniques (such as CT and conventional MRI) often fail to detect abnormalities before structural changes occur in the brain. A growing body of evidence points to the direct or indirect neurotoxic effects of chemotherapeutic drugs on the CNS, which may involve complex processes such as neuroinflammation, oxidative stress, DNA damage, inhibition of neurogenesis, and neurotransmitter system disorders. In this context, it is crucial to explore the impact of chemotherapy on brain functional activities, especially energy metabolism.

Cerebral glucose metabolism, as a direct biomarker of neuronal functional activity, has unique value in evaluating CRCI. The fluorine-18-fluorodeoxyglucose positron emission tomography ($^{18}$F-FDG PET) imaging technology can dynamically visualize the distribution of whole-brain glucose metabolism, directly reflecting the characteristics of neuronal activity and providing key imaging evidence

for the objective identification and quantitative evaluation of CRCI [6]. Integrating brain function analysis tools such as Statistical Parametric Mapping (SPM) into the PET data processing workflow enables voxel-level accurate localization of brain regions with metabolic differences. This technical approach not only provides molecular imaging evidence for the neural mechanisms of cognitive changes in tumor patients but also may lay a translational research foundation for the development of early intervention strategies and the management of patients' mental health [7]. This article aims to summarize the characteristics of changes in cerebral glucose metabolism in cancer patients and their correlation with cognitive and emotional disorders, and to deeply explore the pathogenesis of chemotherapy-related cognitive impairment, so as to provide a new perspective for understanding and managing CRCI.

## 2. Discussion on the Mechanism of Brain Metabolic Changes

The pathological mechanism of CRCI is highly complex and heterogeneous. The mechanisms by which systemic malignant tumors cause brain metabolic damage may be related to multiple factors, such as pro-inflammatory cytokines (e.g., TNF-$\alpha$, IL-1$\beta$) secreted by tumor cells, the body's immune response to tumors, tumor neuroendocrine function, patients' psychological stress at the onset of disease, anti-tumor treatment damage, and the long-term painful course of disease. These mechanisms may ultimately lead to the reconstruction of brain metabolic networks and cognitive impairment through pathways such as neurovascular unit damage, inhibition of synaptic plasticity, and activation of glial cells [8]-[10].

The distribution of FDG ($^{18}$F-fluorodeoxyglucose) in the brain parenchyma in CRCI is mainly based on its tracer characteristics of glucose metabolism. PET imaging reveals the pattern of abnormal energy metabolism in the brains of CRCI patients and the correlation mechanism with neurocognitive function damage. FDG is a glucose analog that enters cells through membrane glucose transporters (such as Glut-1) and is phosphorylated to 6-phospho-FDG by hexokinase, then retained in the cells. Its uptake reflects the glucose metabolic activity of tissues. Brain neuronal activity is highly dependent on glucose for energy supply. When neuronal activity decreases, $^{18}$F-FDG uptake is reduced, showing hypometabolism on PET images; hypermetabolism on PET images indicates increased neuronal activity in that region. Therefore, FDG-PET can reflect the metabolic status of relevant brain regions and quantitatively detect their metabolic intensity.

### 2.1. Direct Toxicity Mechanism

Blood-brain barrier (BBB) damage and central neuroinflammation are important pathological bases of CRCI, and their inducing mechanisms mainly involve two aspects: the impact of tumors themselves and the effect of chemotherapy. On the one hand, tumor growth recruits immune cells and tumor cells, increasing the levels of pro-inflammatory cytokines such as IL-6, IL-1$\beta$, and TNF-$\alpha$ and triggering systemic inflammation. These cytokines can cross the BBB through receptor-

mediated endocytosis or passive diffusion, activating meningeal and choroid plexus immune cells as well as microglia in the brain, thereby inducing neuroinflammation, destroying neural plasticity and neuronal function, and ultimately leading to CRCI [11] [12]. On the other hand, previous studies have shown that in tumor-bearing rodent models, chemotherapy can directly trigger the activation of microglia in the brain, which further induces central neuroinflammatory responses and exacerbates nerve damage, also becoming an important inducement of CRCI [13].

Dysregulation of astrocyte-neuron metabolic coupling is one of the important manifestations of chemotherapy-induced neurotoxicity. The occurrence of chemotherapy-related encephalopathy stems from highly complex and heterogeneous molecular mechanisms. Chemotherapeutic drugs induce neurotoxicity through dual pathways: first, all common chemotherapeutic drugs (such as cisplatin, carboplatin, paclitaxel, cyclophosphamide, vincristine) have been confirmed to damage the integrity of the BBB [3] [14] [15], leading to increased permeability and exposing brain tissue to peripheral harmful factors. This damage directly triggers neuronal injury: drugs represented by oxaliplatin and cisplatin cross the damaged BBB into the brain, form mitochondrial DNA adducts [16], inhibit neuronal mitochondrial energy metabolism and synaptic plasticity; at the same time, they trigger secondary inflammatory cascade reactions: BBB dysfunction allows circulating pro-inflammatory factors to invade the center, activate microglia and astrocytes, and amplify cytokine storms [3] [17]. In addition, chemotherapy continuously damages neural structures, manifested as abnormal dendritic spine morphology and disordered neurotransmitter release/reuptake [3] [18], and further weakens BBB function, forming a vicious circle. Approximately half of the anticancer drugs approved by the FDA are reactive oxygen species (ROS) inducers, and ROS can also directly damage the BBB through various pathways such as oxidative stress [19]. The above pathological changes together form the basis of chemotherapy-related cognitive impairment, clinically presenting as learning and memory decline, mood swings, and decreased executive function.

Neuroinflammation and blood-brain barrier (BBB) damage collectively induce the "extensive hypometabolism plus local targeted hypermetabolism" pattern in 18F-FDG PET imaging by disrupting cerebral glucose transport, metabolic enzyme activity, and neural cell function. Neuroinflammation bidirectionally regulates metabolism: tumor-associated signals activate microglia/astrocytes, increasing their metabolic demand and causing hypermetabolism in regions like the amygdala and putamen; sustained inflammation releases TNF-$\alpha$, IL-6, etc., inhibiting neuronal GLUT1/GLUT3 expression, impairing mitochondrial function, and leading to hypometabolism in cognition-related areas (e.g., prefrontal cortex, temporal lobe). BBB damage exacerbates abnormalities: integrity disruption causes leakage of inflammatory cells/toxins, amplifying neuroinflammation and impairing nutrient transport; increased vascular permeability induces local microenvironmental disorders, with some regions showing compensatory FDG uptake fluc-

tuations. Neuroinflammation is the core driver, and BBB damage plays a synergistic role.

In addition to chemotherapy itself, the combined application of chemotherapy and adjuvant hormone therapy has also been reported to aggravate CRCI [20]. In the field of breast cancer, regimens using chemotherapy combined with hormone therapy such as tamoxifen, exemestane, or anastrozole have been observed to be associated with an increased risk of cognitive impairment. Although the mechanism has not been fully elucidated, the age-dependent effect of tamoxifen on cognition and the endocrine imbalance of the hypothalamic-pituitary-adrenal axis caused by decreased estrogen are considered contributing factors. The former impairs neural plasticity by inhibiting estrogen receptor $\beta$ (ER$\beta$) in the hippocampus, and the latter leads to abnormal activation of glucocorticoid receptor (GR) signaling.

Notably, new treatment methods such as targeted therapy and immunotherapy may also cause CRCI through their specific side effects. Immune checkpoint inhibitors (such as PD-1/CTLA-4 antibodies) directly attack neurons through T cell infiltration, inducing autoimmune encephalitis; anti-HER2 targeted drugs (such as trastuzumab) affect neuronal synaptic remodeling by inhibiting the nerve growth factor (NGF) pathway. The combination of targeted drugs and chemotherapy can also change the permeability of the BBB and accelerate the central accumulation of neurotoxic substances [5].

### 2.2. Indirect Regulatory Mechanism

Exosomes, as disease regulators, have important application prospects in the fields of neurodegenerative diseases and cancer treatment [21]. Exosomes released by the choroid plexus can be taken up by microglia and astrocytes. During systemic inflammation, choroid plexus-derived exosomes are internalized by microglia and astrocytes, which can trigger miRNA target inhibition and induce the upregulation of inflammatory genes [22]. Koh *et al.* [23] pointed out that differences in the content (such as miRNAs and proteins) and release of exosomes may have protective or destructive effects, thereby changing the functions of the brain and CNS and leading to cognitive decline in cancer survivors.

Central nervous system (CNS) insulin resistance plays a key role in brain metabolic disorders. Under physiological conditions, insulin stimulates the uptake of glucose by neurons by promoting the translocation of glucose transporter 4 (GLUT4, an insulin-sensitive glucose transporter) to the neuronal cell membrane, thereby maintaining the optimal energy supply in cognitive-related brain regions. However, a systematic review and meta-analysis by Jensen *et al.* [24] pointed out that evidence based on fasting FDG PET scans shows that individuals with type 2 diabetes/prediabetes and other insulin resistance-related diseases (excluding obesity) have significantly lower cerebral glucose metabolism rates compared with metabolically healthy, normoglycemic, and/or non-obese individuals. Central insulin resistance impairs cognitive function through multiple mechanisms: it can

directly weaken the efficiency of neuronal glucose uptake and utilization, leading to insufficient energy supply; induce and amplify neuroinflammatory responses; weaken endogenous antioxidant defense capabilities and exacerbate oxidative stress damage; and impair synaptic function, plasticity, and neurotransmission efficiency, ultimately resulting in cognitive and behavioral disorders.

Studies have also shown that chemotherapy-related anemia may be a risk factor for fatigue and cognitive impairment in cancer patients [25]. At the same time, a low education level and advanced age are also considered potential confounding factors [19].

In addition, previous international studies have revealed that depressed patients and malignant tumor patients have similar brain metabolic patterns: both show a significant reduction in glucose metabolism in key brain regions of the limbic system, such as the prefrontal cortex, hippocampus, and amygdala. This metabolic overlap suggests that depressive mood may be an important synergistic factor in the occurrence of CRCI by regulating the metabolic activity of the frontal-limbic system [26].

## 3. Correlation between Metabolic Changes and Cognitive Dysfunction

Previous FDG PET studies have consistently found that in solid tumor patients without brain metastasis, abnormal glucose metabolism occurs in multiple brain regions, especially in the frontoparietal cortex [10] [27]. As a key node for selective memory, abstract thinking, and concept integration, metabolic disorders in the frontal lobe can directly interfere with the function of cognitive networks, thereby providing an imaging basis for emotional and cognitive disorders.

Li Pei *et al.* pointed out in the study on the correlation between resting cerebral glucose metabolism changes and emotional disorders that the standardized uptake values (SUV) of the left frontal lobe, right frontal lobe, and left temporal lobe in the experimental group were negatively correlated with the total scores of the Hamilton Depression Rating Scale (HAMD) and the Memory Assessment Scale (MAS), respectively, and the SUV of the left frontal lobe and left temporal lobe were negatively correlated with the total scores of MAS, verifying that the occurrence of emotional disorders in lung cancer patients is associated with metabolic function damage in the frontotemporal lobes, and further revealing the pathological significance of abnormal cerebral metabolism in lung cancer patients, that is, brain metabolic damage mainly in the frontotemporal lobes may be the neuropathological basis for the onset of emotional disorders in lung cancer patients [28]. Yang *et al.* [29] pointed out in the study exploring the correlation between the incidence of depression and anxiety in cancer patients and cerebral PET glucose metabolism that the incidence of depression and anxiety in lung cancer patients is higher than that in patients with other tumors, and the SUV and metabolic volume of the bilateral frontotemporal lobes, bilateral caudate nucleus and hippocampus, and left cingulate gyrus are lower than those in patients with other tu-

mors. It was also found that poor pathological differentiation and advanced TNM stage are independently associated with the risk of depression and anxiety. The SUV of the bilateral frontotemporal lobes, bilateral caudate nucleus and hippocampus, and left cingulate gyrus are negatively correlated with HAMD and MAS scores.

Scholars found in the correlation analysis between cerebral glucose metabolism and cognitive function in patients with Diffuse Large B-Cell Lymphoma (DLBCL) that when the metabolic activity of abnormal brain regions in the frontal lobe was correlated with the scores of delayed memory, attention, and abstraction subitems in the Montreal Cognitive Assessment (MoCA), the lower the metabolic activity of abnormal brain regions, the lower the scores of attention and delayed recall [30]. In addition, post-chemotherapy lymphoma patients with CRCI showed decreased $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) uptake in cognitive-related regions such as the prefrontal cortex, cerebellum, medial cortex, and limbic system during the resting state or task performance [5].

## 4. Characteristics of Cerebral Metabolism in Tumor Patients before Treatment

Domestic and foreign researchers have used PET to study changes in cerebral glucose metabolism in patients with different types of malignant tumors, and all have shown decreased metabolism in multiple brain regions involved in mental and emotional functions such as the insula, prefrontal lobe, temporal lobe, and cingulate gyrus [31] [32]. Subsequently, researchers also found extensive hypometabolic regions in the brains of malignant tumor patients before treatment, especially in the frontal and temporal cortices; at the same time, local hypermetabolism was found in regions such as the hippocampal-parahippocampal complex and cerebellum [33].

Although cancer patients have certain common characteristics of abnormal brain metabolism, differences in tumor type and stage will significantly affect mental state, and their brain metabolic patterns also show heterogeneity. Fu Chang *et al.* [34] [35] conducted preliminary studies on changes in brain metabolism in lung cancer patients with different histological types and stages. The study found that changes in cerebral glucose metabolism in lung cancer patients are significantly related to their histological types and clinical stages. The range of decreased brain metabolism in small cell lung cancer patients is wider than that in the adenocarcinoma and squamous cell carcinoma groups, and the degree of metabolic decrease in affected brain regions is also significantly greater than that in adenocarcinoma and squamous cell carcinoma. With the increase in tumor stage, the number and range of affected brain regions gradually increase, further confirming that tumor stage is positively correlated with the degree of brain metabolic decrease. These metabolic change patterns (the higher the stage and the higher the malignancy, the more extensive and severe the metabolic abnormalities) are consistent with previous clinical observations, that is, advanced tumor patients are often ac-

companied by more severe brain function damage. Zhang *et al.* [36] found in a retrospective PET/CT study on changes in cerebral glucose metabolism in patients with non-small cell lung cancer before treatment that regions related to visceral signal processing (such as the bilateral insula, putamen, globus pallidus, thalamus, hippocampus, amygdala, right orbital part of the inferior frontal gyrus, right cerebellum, and vermis) had increased metabolism; while regions involved in the dorsal attention network and visuospatial function (such as the left superior parietal lobule, bilateral inferior parietal lobule, and left fusiform gyrus) showed decreased metabolism. A recent study [37] further confirmed this metabolic disorder through quantitative ratio analysis and supplemented more specific findings: the metabolic ratios in the frontal lobe, inferior temporal gyrus, right cingulate gyrus, and paralingual gyrus were significantly decreased, while the metabolic ratios in the right caudate nucleus and right globus pallidus were relatively increased.

You Yang *et al.* [38] found in the study on resting cerebral glucose metabolism changes in lymphoma patients that multiple brain regions of lymphoma patients had decreased glucose metabolism, mainly including bilateral superior, middle, and inferior temporal gyri, bilateral superior frontal gyri, right middle frontal gyrus, and right cerebellum, with no significant hypermetabolic brain regions. Another study showed that even patients with extranodal natural killer/T-cell lymphoma (ENKTL) at an early clinical stage (stage I/II) and with low lesion load (manifested as low total lesion glycolysis, TLG) had regional cerebral glucose metabolism abnormalities before treatment, specifically manifested as decreased metabolism in the bilateral prefrontal cortex, orbitofrontal cortex, part of the parietal and occipital cortices, cingulate gyrus, and cerebellum, accompanied by increased metabolism in the bilateral putamen, amygdala, and parahippocampal gyrus [39]. This finding suggests that ENKTL-related brain metabolic changes may occur in the early stages of the disease and do not completely depend on obvious systemic tumor load. Similarly, DLBCL patients showed a characteristic regional metabolic decrease in cerebral glucose metabolism before treatment, mainly involving the bilateral frontal lobes (right superior frontal gyrus, left middle frontal gyrus, right precentral gyrus), bilateral parietal lobes (bilateral postcentral gyrus, right inferior parietal gyrus), left inferior temporal gyrus, and left cuneus, with no hypermetabolic regions in the whole brain [30].

Inagaki *et al.* [40] specifically focused on patients with depression after pancreatic cancer diagnosis, before treatment initiation, and without antidepressant use. Using $^{18}$F-FDG PET technology to evaluate regional cerebral glucose metabolism, it was found that these patients had significantly increased glucose metabolism in the subgenual anterior cingulate cortex (sgACC) of the brain.

Chen Rongjun *et al.* pointed out in a retrospective study on changes in glucose metabolism in brain PET imaging of nasopharyngeal carcinoma patients based on brain function software SPM analysis that the regions with decreased glucose metabolism in nasopharyngeal carcinoma patients before treatment included the bi-

lateral insular white matter, right superior frontal gyrus white matter, right inferior parietal angular gyrus white matter, left cingulate gyrus, and right parahippocampal gyrus, indicating that nasopharyngeal carcinoma patients have local abnormal cerebral glucose metabolism [41].

## 5. Changes in Cerebral Metabolism in Tumor Patients after Chemotherapy

Shamchi *et al.* [42] found in the study on cerebral glucose metabolism in newly diagnosed multiple myeloma patients that patients with multiple myeloma who received high-dose chemotherapy followed by autologous stem cell transplantation (HDC/ASCT) showed a significant decrease in FDG uptake in the supratentorial brain and cerebellum, while patients who received conventional dose chemotherapy (CDC) did not show significant changes in cerebral FDG uptake.

Yu *et al.* [13] revealed the dynamic changes in cerebral glucose metabolism in advanced non-small cell lung cancer (NSCLC) patients after chemotherapy: all advanced lung cancer patients in the experimental group showed decreases in cerebral glucose metabolism in different regions or to varying degrees, mainly involving the bilateral frontoparietal-temporal lobes and limbic lobes. Moreover, after chemotherapy, the longer the interval between the PET scan and the last chemotherapy, the smaller the area of decreased cerebral glucose metabolism; the greater the number of chemotherapy cycles, the larger the area of cerebral glucose hypometabolism, and there is a trend of transfer from the front to the back.

Baudino *et al.* [43] explored the long-term effects of chemotherapy on brain metabolism and cognitive function in patients with lymphoma. The study found that, compared with patients who did not receive chemotherapy, patients in the chemotherapy group showed a significant bilateral decrease in glucose metabolism rate in key brain regions such as the prefrontal cortex, cerebellum, medial cortex, and limbic system. The degree of metabolic decrease in these brain regions was negatively correlated with the number of chemotherapy cycles (*i.e.*, the more cycles, the lower the metabolism), but positively correlated with the time after chemotherapy (*i.e.*, the longer the time after chemotherapy, the better the metabolic recovery trend).

Shrot *et al.* [44] tracked the longitudinal changes of cerebral glucose metabolism (evaluated by FDG uptake) in pediatric non-Hodgkin lymphoma (NHL) patients after chemotherapy. The study found that with the passage of time after chemotherapy, the metabolism of specific brain regions showed significant bidirectional changes: FDG uptake in the bilateral parietal cortex and cingulate cortex increased with time, while FDG uptake in the basal ganglia and brainstem regions decreased annually.

Chen Rongjun *et al.* [41] used Statistical Parametric Mapping (SPM) software to retrospectively analyze changes in cerebral glucose metabolism in nasopharyngeal carcinoma (NPC) patients before and after chemoradiotherapy. After treatment, the metabolism of gray matter in the right middle frontal gyrus increased,

while the metabolism of gray matter in the right superior thalamic nucleus decreased.

Therefore, there are many factors affecting the abnormal changes in cerebral glucose metabolism in tumor patients after treatment, mainly depending on treatment methods, types and intensity of drugs, FDG PET scanning time, and tumor pathological type and stage.

Tumor itself and tumor treatment-driven cerebral FDG metabolic characteristics exhibit significant differences. Metabolic abnormalities driven by the tumor itself are based on extensive hypometabolism supplemented by locally targeted hypermetabolism, with heterogeneity closely related to tumor pathological type, stage, and malignancy. Hypermetabolic regions are concentrated in brain areas associated with emotion regulation and visceral signal processing, while the scope and degree of hypometabolism increase with tumor stage, showing distinct manifestations across different tumor types. Metabolic changes driven by tumor treatment are dominated by hypometabolism overall, accompanied by compensatory or reparative hypermetabolism in some brain regions, presenting obvious dynamic characteristics. These changes are influenced by treatment modality, number of chemotherapy cycles, and follow-up time: high-dose chemotherapy has a more significant impact on metabolism, the degree of hypometabolism is positively correlated with the number of chemotherapy cycles, some brain regions show a recovery trend with the extension of time after treatment, while regions such as the basal ganglia may experience continuous decline. The newly emerged hypermetabolism is mostly caused by cerebral functional compensation.

## 6. Effects of Other Causes on Cerebral Metabolism

Zhu *et al.* [45] evaluated the effect of chemotherapy on cerebral glucose metabolism (FDG uptake) in DLBCL patients. The study found that during the middle and end of chemotherapy, the brain metabolic state of patients changed significantly compared with the baseline level, and almost the entire brain showed a significant increase in FDG uptake. The researchers proposed that this extensive increase in brain metabolism may be related to the significant reduction of tumor load in the body due to effective treatment, so that FDG originally taken up in large quantities by lymphoma lesions can be "redistributed" or "transferred" to brain tissue.

The risk of metabolic abnormalities and cognitive impairment in elderly cancer patients after chemotherapy is more significant, suggesting that the aging process and cancer treatment (such as chemotherapy)-related cognitive decline may have the same neurobiological mechanism. Ahles *et al.* [46] found that, compared with cancer patients who did not receive chemotherapy and healthy controls, elderly breast cancer patients who received chemotherapy had lower baseline cognitive reserve levels and experienced more severe CRCI, with the damage being particularly prominent in information processing speed.

Multiple studies have consistently shown that elevated blood glucose status (in-

cluding diabetes, non-diabetic hyperglycemia, and prediabetes) is significantly associated with decreased cerebral glucose metabolism (FDG uptake). Kawasaki *et al.* [47] found, by comparing FDG PET images before and after blood glucose control in diabetic patients, that mild hyperglycemia leads to decreased FDG uptake in the frontal lobe, temporal lobe, and parietal association cortex; Chen Hailong *et al.* [48] found, by comparing the hyperglycemia non-diabetic group with the normal blood glucose group, that the standardized uptake value (SUV) of each brain region in the hyperglycemia non-diabetic group was significantly reduced; Jiang Donglang *et al.* [49] further revealed that even in the prediabetic stage, compared with normal groups with different blood glucose levels, patients had decreased glucose metabolism in multiple brain regions, suggesting that brain function abnormalities occur in the preclinical stage of diabetes.

## 7. Intervention and Relief Strategies

For cancer-related cognitive impairment (CRCI), clinical and preclinical studies have confirmed that a variety of interventions can exert ameliorative effects by regulating cerebral glucose metabolism, inhibiting neuroinflammation, and other pathways, which specifically include two major categories: pharmacological treatment and non-pharmacological intervention. As a neuroprotective drug, metformin regulates CRCI-related pathological processes through multiple mechanisms: first, it directly inhibits microglial activation and reduces the release of pro-inflammatory cytokines such as IL-6 and TNF-$\alpha$, thereby alleviating central neuroinflammation; second, it triggers the nuclear factor erythroid 2-related factor 2 (Nrf2) pathway to counteract oxidative stress damage; third, it maintains the integrity of the blood-brain barrier (BBB), prevents toxic chemicals and inflammatory mediators from invading brain tissue, protects neuronal function, and indirectly improves the balance of glucose transport and metabolism in the brain [50]. Donepezil is commonly used in the treatment of Alzheimer's disease and has currently been applied in the intervention of CRCI. By inhibiting acetylcholine hydrolysis, it supplements cholinergic neurotransmitters in the brain, improves neural signal transmission, and simultaneously indirectly regulates the metabolic activity of cognition-related brain regions (such as the prefrontal cortex and temporal lobe), thereby alleviating cognitive decline caused by neuroinflammation or metabolic abnormalities [51]. For cancer patients undergoing chemotherapy, regular physical exercise has been proven to reduce the levels of inflammatory markers in the body and inhibit systemic as well as central neuroinflammatory responses. Meanwhile, exercise can promote cerebral blood circulation, optimize the expression and function of glucose transporters (such as GLUT1 and GLUT3), improve the glucose metabolism efficiency of cognition-related brain regions (e.g., the prefrontal cortex and cingulate gyrus), and ultimately achieve dual improvements in cognitive performance and quality of life. In terms of dietary intervention, a diet rich in Omega-3 fatty acids can directly exert anti-neuroinflammatory effects. By inhibiting the production of pro-inflammatory factors and regulating immune cell

activity, it alleviates inflammatory damage to brain tissue, thereby reducing the interference of inflammation on cerebral glucose metabolism and maintaining the stability of neuronal energy metabolism. Cognitive rehabilitation training has long been used for patients with dementia, and relevant research on CRCI has been extensively carried out at present. By targeted strengthening of cognitive function pathways and improving neuroplasticity, it indirectly promotes the balance of cerebral metabolism. At the same time, it reduces the impact of neuroinflammation on the function of cognition-related brain regions (such as the hippocampus and prefrontal cortex), helping patients restore cognitive function in daily environments [25].

## 8. Clinical Prospects

Studies on brain metabolism in tumor patients before and after treatment have revealed complex and dynamic glucose metabolism reorganization rules, characterized by the coexistence of metabolic inhibition in key cognitive brain regions (hippocampus, prefrontal lobe) and the reconstruction of systemic multi-organ metabolic networks. Whole-body PET/CT technology has led to the transformation of metabolic network analysis, promoting the research of "chemobrain" into the era of multi-organ interaction and precise intervention. Through research, the correlation between metabolic abnormalities and cognitive disorders (such as memory decline, decreased executive function) has been revealed, and early prediction models have been established. At the same time, PET tracers other than FDG have been developed, such as TSPO ligands, which can evaluate inflammation related to CRCI at the molecular level [3] and better dynamically monitor the metabolic repair process. Emerging new BBB imaging methods will help study BBB permeability and/or dysfunctional transcellular transport under conditions related to CRCI, although there is currently little attention to this field [5]. In addition, the emergence of artificial intelligence and radiomics may extract potentially useful data from imaging details that cannot be detected by visual evaluation. The core unresolved key question at present is whether the characteristic cerebral metabolic profiles of patients with different tumor types before treatment can serve as specific biomarkers for predicting the risk of occurrence, severity, and recovery prognosis of CRCI after chemotherapy. In the future, it is necessary to expand samples, unify scanning protocols, and integrate genomic and neuropsychological data to clarify the causal mechanism of metabolic changes and establish prediction models. Through the research of cerebral PET metabolism, it is expected to provide an important basis for the early diagnosis and risk stratification of chemotherapy-induced neurotoxicity, thereby helping tumor patients obtain precise intervention and ultimately improving their quality of life.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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