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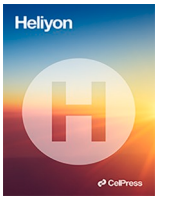

Research article

Correlation between cancer-related cognitive impairment and resting cerebral glucose metabolism in patients with ovarian cancer

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ABSTRACT

Background: An increasing number of research have applied neuroimaging techniques to explore the potential neurobiological mechanism of Cancer-related cognitive impairment (CRCI).
Purpose: To explore the correlation between resting brain glucose metabolism and CRCI using ^{18}F-FDG PET/CT in ovarian cancer (OC) patients.
Methods: From December 2021 to March 2022, 38 patients with OC were selected as the study group, and 38 healthy women of the same age (±1 year) who underwent routine physical examination using PET/CT were selected as the control group. Patients received further assessment with the Montreal Cognitive Assessment Scale (MoCA) and Perceived Deficit Questionnaire (PDQ). Independent sample *t*-test and Spearman correlation were conducted for data analysis.
Results: The resting brain glucose metabolism in the OC group was significantly lower than in the healthy controls. 60.52 % patients had neuropsychological impairment and retrospective memory were the most serious perceived cognitive impairments. The resting brain glucose metabolism in OC patients did not significantly correlate with neuropsychological performance but had significant positive correlation with subjective cognitive evaluation.
Discussion: Resting glucose metabolism was low in OC patients and associated with subjective cognitive impairment but not objective neuropsychological test results. ^{18}F-FDG PET/CT can be used to evaluate brain function in OC patients and provide reliable imaging indicators for early recognition of and intervention for changes in cognitive function.

Abbreviations: 18F-FDG, 18-fluorodeoxyglucose; OC, ovarian cancer; CRCI, cancer-related cognitive impairment; MoCA, Montreal Cognitive Assessment Scale; PDQ, Perceived Deficit Questionnaire; SUV, standardized uptake value.

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1. Introduction

Cancer-related cognitive impairment (CRCI) refers to cognitive dysfunction caused by cancer, cancer-related treatments, and symptoms (such as fatigue, emotional disorders, and insomnia) in patients with non-central nervous system cancer [1,2]. Patients with CRCI experience a decline in memory, attention, processing speed, and execution, which affects their daily routine and quality of life [3,4]. An increasing number of scholars have applied neuroimaging techniques in CRCI research, including magnetic resonance imaging (MRI) and positron emission tomography (PET), to explore the potential neurobiological mechanism of the symptoms [5,6]. PET/computerized tomography (CT) integrates multimodal functional and structural imaging procedures and provides the anatomic location of metabolic changes in patients. The most commonly used radiopharmaceutical in PET imaging is 18-fluorodeoxyglucose (^{18}F-FDG); it is used to examine the glucose metabolism of cells and organs in vivo [7,8]. Owing to its unique diagnostic and predictive advantages in function and morphology, ^{18}F-FDG PET/CT has been widely used in cancer and neuropsychology, which lays a good foundation for its application in CRCI research to understand the biological mechanism of neuropsychological changes in cancer patients [5,9–11]. Ovarian cancer (OC) is one of the most common gynecological malignancies. Due to the characteristics of the disease, treatment, and related symptoms, including high recurrence, extensive tumor reduction, multiple rounds of chemotherapy, especially platinum/paclitaxel, and surgical menopause, nearly 69 % of OC patients reported suffering from cognitive dysfunction, which is higher than previous reports on breast cancer patients [12,13]. Numerous prior neuroimaging studies on CRCI have demonstrated alterations in brain metabolism, function, and structure among tumor patients compared to healthy individuals [9,14]. However, there is a scarcity of literature utilizing PET/CT imaging technology. Moreover, due to variations in diagnostic and evaluation methods employed by different research studies, the conclusions drawn from these investigations exhibit significant heterogeneity. Furthermore, previous studies have not comprehensively evaluated CRCI using comprehensive assessment methods; instead focusing only on specific dimensions of objective cognitive function. Additionally, limited attention has been given to the discussion of subjective and objective cognitive dysfunction alongside corresponding changes observed in patients' brain imaging. Lastly, while several studies have primarily focused on cognitive function tasks within breast cancer patient populations, there remains a dearth of research pertaining to other high-risk non-central nervous system tumor groups such as ovarian cancer cohorts, including patients with OC [15,16], especially regarding cerebral glucose metabolism. This study aimed to compare the differences in resting brain glucose metabolism between OC patients and healthy individuals using ^{18}F-FDG PET/CT and explore the correlation between resting glucose metabolism and cognitive performance in OC patients to provide a biological basis for better understanding cognitive function changes in patients diagnosed with OC.

2. Methods

2.1. Participants

A total of 38 patients diagnosed with OC at Fudan University Shanghai Cancer Center were selected as the patient group from December 2021 to March 2022, and 38 healthy women were enrolled in the study as the healthy group. The inclusion criteria included patients between 18 and 65 years of age, diagnosed with OC, having undergone complete body or brain PET/CT examination, in a stable condition, and being able to communicate in Mandarin normally. Inclusion criteria for the healthy group included age ($\pm$1 year) matched with the OC patients, female sex, and having received routine physical examination with PET/CT during the same period. The exclusion criteria were as follows: patients with brain metastasis, potential psychiatric disorders, and previous severe cognitive disorders; the healthy group included those diagnosed with cancer, potential psychiatric disorders, and previous severe cognitive disorders. The study was approved by the ethics committee of the Fudan University Shanghai Cancer Center (approval #2103232-25).

2.2. Instruments

2.2.1. The Montreal Cognitive assessment scale (MoCA)

The scale was first developed by Canadian scholar Nasredine in 1996. It covers seven cognitive functions: visuospatial/executive, naming, attention, language, abstraction, delayed recall, and orientation. It is a rapid objective neuropsychological screening tool for mild cognitive impairment that can be used by neurologists, psychologists, and nurses [17]. The scale has been translated and revised into at least 35 languages [18]. There are four Chinese versions of MoCA (the version of Changsha, Beijing, Peking Union Medical College Hospital, and Hong Kong). Among them, the Changsha version by Tu Qiuyun et al. which we used in this research has the most cultural revisions and has changed the named animals and memory phrases with more detailed and scientific instructions. For this version, Cronbach's α, retest reliability, and investigator reliability were 0.846,0.974, and 0.969, respectively. According to the instrument, a score $\geq$27 points was considered cognitively normal, and one point was added to the score if education years were $\leq$6 years. The sensitivity and specificity of the diagnostic criteria were 90.0 % and 70.9 %, respectively. It is considered suitable for promotion and application in the mainland Chinese population [19].

2.2.2. Perceived Deficit Questionnaire (PDQ)

This questionnaire was developed by Sullivan et al., in 1990 for multiple sclerosis patients, aiming to provide patients with self-reports of cognitive dysfunction [20]. This questionnaire has good reliability and validity and has been widely used in other populations, including patients with depression and schizophrenia [21]. The questionnaire consisted of 20 items. Each item was rated on a five-point scale from zero (never) to four (almost always), with a higher score indicating more severe subjective cognitive impairment

in the past week. The scale assesses four cognitive functions: attention/concentration, retrospective memory, prospective, and planning/organization. The Chinese version of the PDQ by Song et al. has been widely applied, with a structural validity of 0.867, internal reliability α of 0.932, and retest reliability R of 0.476 [22].

2.3. PET imaging method

2.3.1. Methods

Before the examination, patients fasted for more than 6 h with blood glucose controlled below 8.3 mmol/L and rested for 60 min. They were then administered an intravenous injection of 0.1 mCi/kg (3.7 MBg/kg) of ^{18}F-FDG. PET/CT was then performed after 60 min in a quiet, dark environment.

2.3.2. Image acquisition

Siemens mCT-Flow PET/CT scan was used, with imaging agent ^{18}F-FDG and radiochemical purity ≥95 %. CT scanning parameters were: voltage 120 kV, current 100 mA, 0.8 s/revolution, bed speed 22.5 mm/s, scanning layer thickness 3.75–4.00 mm. PET adopts three-dimensional scanning and 512 × 512 matrix; for image fusion, it is converted to 128 × 128 matrix with a bed speed of 2.2 mm/S.

2.3.3. Image fusion and analysis

The neurologic analysis module of Siemens syngo.via workstation was used to read, fuse and analyze the images. The corrected PET and CT images were fused to obtain PET, CT, and fusion images of the whole body in axial, sagittal, and coronal positions. The observed brain region's standardized uptake value (SUV) was obtained using this module's standard database analysis method. With the method of regions of interest (ROI) and whole brain semi-quantitative analysis, the brain regions of syngo.via standard region group were defined as ROIs, involving nine regions including the frontal lobe, temporal lobe, parietal lobe, cingulate and paracingulate gyri, central region (including precentral gyrus, postcentral gyrus, and Rolandic operculum), occipital lobe, calcarine fissure, surrounding cortex, basal ganglia, mesial temporal lobe (amygdala, hippocampus and gyrus parahippocampalis) and cerebellum, and covering 41 brain anatomical locations. ROIs were marked at different levels on each area's left and right sides, taking average SUVs.

2.4. Data collection

The investigators received professional neuropsychology test training from the Shanghai Mental Health Center and the MoCA official online training and were required to pass the examinations. For subjects' recruitment, the purpose and process of the study were explained in detail to patients who initially met the inclusion criteria. The participants signed informed consent, and the appropriate time and place for the investigation were selected according to the patient's wishes, either in a hospital conference room or at their home. A relatively comfortable, closed, undisturbed, and quiet environment was selected. Trained investigators then conducted one-to-one and face-to-face assessments. The subjects completed the PDQ first. The MoCA test was then carried out strictly per the MoCA guidelines.

Table 1
Sample characteristics of patients (n = 38).

Characteristics		N(%)
Education	Primary school or below	8(21.05)
	Middle school	11(28.95)
	High school	6(15.79)
	University or above	13(34.21)
Comorbidity	None	30(78.95)
	One	6(15.79)
	Two or more	2(5.26)
Employment status	Employed full time	3(7.89)
	Employed but on medical leave	15(39.47)
	Retired	12(31.58)
	Unemployed	3(7.89)
	Homemaker	5(13.16)
Disease stage (FIGO criteria)	Phase III/IV	30(78.95)
Recurrence	Yes	12(31.58)
Previous treatment	Surgery	5(13.16)
	Chemotherapy	5(13.16)
	Surgery + chemotherapy	13(34.21)
	Surgery + chemotherapy + Targeted therapy	8(21.05)
	None	7(18.42)
Current treatment status	Regular follow-up	3(7.89)
	Waiting further treatment	25(65.79)
	Chemotherapy and/or targeted therapy	10(26.32)
	PARPi	2(5.26)

2.5. Data analysis

SPSS software version 24.0 was used to input data independently, and the data were cross-checked and analyzed. Frequency and constituent ratios were used for enumeration data description, and mean ± standard deviation and range were used to describe the data distribution for the measurement data. The differences in the SUVs in each brain region between the patient and control groups were analyzed using linear regression with adjusting age, chemotherapy. Pearson or Spearman correlation was used to explore the correlation between SUVs in each brain region of the study group and the performance of the MoCA test based on whether the variables were normally distributed. The same method was used to explore the correlation between each brain region's SUVs and the patient group's PDQ test results. A multiple linear regression analysis was conducted on two statistically significant dimensions identified in the correlation analysis. This involved primarily adjusting for education background, age, and chemotherapy history in order to further investigate the relationship between cognitive function and SUV in different brain regions. All tests were two-sided with a test level of $\alpha = 0.05$.

3. Results

3.1. Sample characteristics

The mean age of the patient group (n = 38) was (50.18 ± 8.379) years, while that of the control group (n = 38) was (50.05 ± 8.428) years, and the difference was not statistically significant (P = 0.946). Other patient information is presented in Table 1.

3.2. Comparison of resting cerebral glucose metabolism between the patient group and the healthy group

The results showed that the SUV of ^{18}F-FDG in all brain regions was significantly lower than in the healthy group (P<0.05). The top five brain regions with the most significant differences included the parietal lobe (right), occipital lobe (right), temporal lobe (right), central region (right), and cerebellum (right), as shown in Table 2.

3.3. Cognitive performance in OC patients

The mean MoCA score was 23.53 (standard deviation [SD] 5.31), and 23 (60.52 %) patients screened positive for cognitive impairment, as defined by MoCA scores <26. According to the average score/total score, delayed recall, abstraction, and visuospatial/executive functions were the worst. The mean PDQ score was 17.15 (SD 10.63), and retrospective memory scored the highest, leading to the most severe cognitive complaints, followed by prospective memory and organization.

3.4. Correlations between neuropsychological impairment and resting cerebral glucose metabolism in OC patients

In OC patients, the score on the MoCA test was normal or did not significantly correlate with SUVs in each brain region (P > 0.05). In contrast, there was a positive correlation between SUVs in seven regions, including the frontal lobe (left and right), right temporal lobe, right parietal lobe, right central region, right basal ganglia, right medial temporal lobe, and the abstraction function score (P <

Table 2
Comparison of resting cerebral glucose metabolism between the patient group and the healthy group.

Brain region		Resting cerebral glucose metabolism(M±SD)		β (95 % CI)	*P values*
		Patient group(n = 38)	Healthy group (n = 38)		
Frontal lobe	right	78.97 ± 24.43	99.25 ± 22.24	0.490(11.778,37.581)	0.000
	left	83.82 ± 25.45	99.76 ± 23.87		
Temporal lobe	right	30.33 ± 8.85	39.76 ± 8.53	0.349(4.165,31.604)	0.011
	left	35.34 ± 10.62	41.30 ± 9.32		
Parietal lobe	right	26.46 ± 8.08	35.67 ± 7.46	0.556(6.066,15.685)	0.000
	left	29.66 ± 8.92	36.21 ± 7.97		
Cingulate gyrus and paracingulate gyrus	right	16.60 ± 4.84	20.70 ± 4.30	0.285(0.308,11.417)	0.039
	left	17.06 ± 5.05	20.94 ± 4.39		
Central part	right	15.56 ± 4.62	20.31 ± 4.19	0.590(6.252,14.860)	0.000
	left	17.52 ± 5.15	20.64 ± 4.32		
Occipital lobe	right	38.55 ± 11.51	51.38 ± 10.99	0.379(2.084,11.520)	0.005
	left	41.32 ± 12.40	51.99 ± 11.93		
Basal ganglia	right	16.58 ± 4.96	19.94 ± 4.26	0.471(2.130,7.205)	0.000
	left	17.72 ± 5.42	21.06 ± 4.70		
Medial temporal lobe	right	12.05 ± 3.89	14.78 ± 2.88	0.388(1.303,6.541)	0.004
	left	13.62 ± 3.72	15.52 ± 2.96		
Cerebellum	right	36.56 ± 10.24	46.36 ± 9.48	0.562(3.140,8.012)	0.000
	left	40.20 ± 11.72	50.51 ± 10.78		

0.05). In addition, a significant positive correlation was also observed between the SUV of the left basal ganglia and language score ($P < 0.05$). Further details are provided in Table 3. However, after adjusting for age, chemotherapy, and education, the multiple linear regression analysis revealed that there was no statistically significant correlation between the two variables.

3.5. Correlation between self-perceived cognitive deficit and resting cerebral glucose metabolism in OC patients

There was a significant positive correlation between the total PDQ score and SUVs of all brain regions except the cingulate and paracingulate gyrus (right). Retrospective memory also significantly correlated with the SUVs of 14 brain regions, including the frontal and temporal lobes. Prospective memory significantly correlated with the left temporal and frontal lobes. In addition, the left central region significantly correlated with the attention dimension. Further details are provided in Table 4.

After controlling for age, chemotherapy, and education, correlations between self-perceived cognitive deficit and resting cerebral glucose were examined. Multiple linear regression analysis was conducted on the two indexes with a significance level of $P \leq 0.01$ in metabolism correlation analysis. The results were found to be consistent with the findings of the correlation analysis. A significant positive correlation was observed between the total PDQ score and SUVs of many brain regions. Further details are provided in Table 5.

4. Discussion

The present study is the first to compare the resting brain glucose metabolism of OC patients with that of healthy controls. The results showed that the resting brain glucose metabolism rates in patients are significantly lower than those in healthy women of the same age. Previous studies on cancer patients have also reported decreased glucose metabolism in extensive brain areas, while some even reported increased metabolism in different areas. Studies by Li Yangyang et al. [23], Yao Shulin et al. [24] and Jordan Sorokin et al. [25] showed that compared with healthy controls, lymphoma patients showed decreased resting glucose metabolism in several brain areas. Li et al. [23] also found increased metabolism in the bilateral hippocampal amygdala of the hippocampus, bilateral globus pallidus, and gray matter of the cerebellar tonsil region, while the latter two studies did not find increased metabolism in brain regions. High local metabolism may represent a compensatory response to lower resting metabolism in patients with treatment damage [15, 26]. According to the retrospective analysis of Li Wei-Ling et al., compared with healthy people of the same age and sex, lung cancer patients showed decreased brain resting glucose metabolism in some regions, mainly the frontal and temporal lobes. The extent of reduced metabolism was related to the cancer tissue type [27]. Differences between reports may be due to variability in the diagnosis, disease course, treatment, sample size, and analysis methods.

According to the studies, the most common factors affecting brain glucose metabolism in cancer patients include paraneoplastic syndrome, psychiatric illness, cancer, and cancer treatment. Paraneoplastic syndrome is an auto-cross immune reaction between tumor antigen and nervous system-expressed protein, commonly seen in small cell lung cancer, OC, breast cancer, etc. [23,24]. The incidence of psychological symptoms in patients with malignant tumors, including OC, is very high, with at least 1/3 having significant anxiety and 1/4 having severe depressive symptoms [28]. A prospective study by Li Pei et al. showed that depression/anxiety scores in lung cancer patients were significantly higher than those in healthy people and correlated with decreased glucose metabolism in multiple brain regions, mainly in the bilateral frontal and temporal lobes [29]. The psychological symptoms in OC patients that can affect their brain metabolism, mainly include anxiety, depression, stress, fear of recurrence, and hopelessness, which medical staff may often

Table 3
Correlations between neuropsychological impairment and resting cerebral glucose metabolism in OC patients.

Brain region		MoCA						
		Naming	Attention	Language	Visuospatial/ Executive	Orientation	Delayed recall	Abstraction
Frontal lobe	right	−0.102	0.214	0.213	0.227	0.011	0.108	0.403[a]
	left	−0.085	0.131	0.259	0.206	0.072	0.154	0.361[a]
Temporal lobe	right	−0.013	0.160	0.187	0.203	0.011	0.075	0.349[a]
	left	−0.093	0.113	0.264	0.161	0.146	0.132	0.315
Parietal lobe	right	−0.022	0.250	0.221	0.265	−0.031	0.080	0.381[a]
	left	−0.031	0.214	0.187	0.197	0.063	0.003	0.300
Cingulate gyrus and paracingulate gyrus	right	0.111	0.259	0.268	0.303	0.045	0.098	0.309
	left	0.120	0.162	0.287	0.269	0.146	0.108	0.248
Central part	right	−0.040	0.168	0.191	0.210	0.004	0.043	0.369[a]
	left	−0.085	0.125	0.174	0.158	0.099	0.083	0.316
Occipital lobe	right	−0.085	0.126	0.058	0.133	−0.025	−0.023	0.313
	left	−0.085	0.131	0.147	0.156	−0.012	0.039	0.290
Basal ganglia	right	−0.071	0.258	0.251	0.223	0.042	0.111	0.370[a]
	left	0.120	0.126	0.398[a]	0.313	0.083	0.247	0.309
Medial temporal lobe	right	−0.156	0.184	0.078	0.063	0.087	−0.003	0.332[a]
	left	−0.174	0.180	0.111	0.079	0.183	0.009	0.314
Cerebellum	right	−0.200	−0.084	−0.085	−0.121	0.126	−0.117	0.170
	left	−0.174	−0.034	−0.038	−0.087	0.085	−0.101	0.165

**$P \leq 0.01$.
[a] $P \leq 0.05$.

Table 4
Correlations between self-perceived cognitive deficit and resting cerebral glucose metabolism in OC patients.

Brain region		PDQ				
		Total score	Attention/ concentration	Retrospective memory	Prospective memory	Planning/ Organization
Frontal lobe	right	0.422[a]	0.264	0.399[b]	0.201	0.509[a]
	left	0.519[a]	0.335[b]	0.497[b]	0.289	0.567[a]
Temporal lobe	right	0.356[b]	0.233	0.354[b]	0.160	0.444[a]
	left	0.516[a]	0.297	0.520[a]	0.325[b]	0.531[a]
Parietal lobe	right	0.377[b]	0.217	0.395[b]	0.169	0.446[a]
	left	0.444[a]	0.219	0.489[a]	0.265	0.467[a]
Cingulate gyrus and paracingulate gyrus	right	0.242	0.032	0.333[b]	0.136	0.299
	left	0.282	0.063	0.383[b]	0.173	0.344[b]
Central part	right	0.374[b]	0.217	0.383[b]	0.181	0.458[a]
	left	0.515[a]	0.325[b]	0.500[a]	0.298	0.558[a]
Occipital lobe	right	0.421[a]	0.257	0.419[a]	0.171	0.489[a]
	left	0.500[a]	0.313	0.514[a]	0.259	0.514[a]
Basal ganglia	right	0.318	0.153	0.283	0.156	0.438[a]
	left	0.344[b]	0.172	0.434[a]	0.181	0.391[b]
Medial temporal lobe	right	0.271	0.180	0.201	0.110	0.362[b]
	left	0.391[b]	0.250	0.345[b]	0.194	0.454[a]
Cerebellum	right	0.400[b]	0.280	0.380[b]	0.117	0.467[a]
	left	0.294	0.223	0.274	0.032	0.407[b]

[a] $P \leq 0.01$.
[b] $P \leq 0.05$.

Table 5
Multiple linear regression analysis of **self-perceived cognitive deficit in OC patients**.

Brain region		PDQ					
		Total score		Retrospective memory		Planning/Organization	
		β(95 % CI)	*P values*	β(95 % CI)	*P values*	β(95 % CI)	*P values*
Frontal lobe	right	0.520(0.006,0.015)	0.000			0.470(0.024,0.076)	0.000
	left	0.526(0.006,0.015)	0.000			0.474(0.024,0.072)	0.000
Temporal lobe	right					0.432(0.054,0.202)	0.001
	left	0.487(0.012,0.033)	0.000	0.496(0.077,0.224)	0.000	0.418(0.042,0.158)	0.001
Parietal lobe	right					0.432(0.054,0.202)	0.001
	left	0.488(0.014,0.039)	0.000	0.496(0.093,0.267)	0.000	0.418(0.042,0.158)	0.001
Central part	right					0.453(0.118,0.398)	0.001
	left	0.537(0.030,0.072)	0.000	0.527(0.180,0.480)	0.000	0.466(0.112,0.348)	0.000
Occipital lobe	right	0.461(0.010,0.031)	0.000	0.453(0.057,0.209)	0.001	0.447(0.046,0.161)	0.001
	left	0.482(0.010,0.029)	0.000	0.486(0.064,0.195)	0.000	0.435(0.040,0.142)	0.001
Basal ganglia	right					0.421(0.087,0.349)	0.002
	left			0.472(0.133,0.430)	0.000		
Medial temporal lobe	left					0.472(0.153,0.519)	0.001
Cerebellum	right					0.529(0.071,0.207)	0.000
	left					0.407*	

ignore [30]. Chemotherapy is a widely discussed treatment that affects patients' brain structure and cognitive function. It is related to increased levels of cytokines in vivo, which lead to neurotoxicity, glial cell changes, decreased nerve repair, and accelerated aging/oxidative stress [4]. The earliest study by Silverman et al., in 2007 showed that chemotherapy affected resting brain metabolism in breast cancer, especially in specific areas of the frontal lobe and cerebellum [26]. Two prospective studies by McDonald et al. showed that gray matter density in the bilateral, frontal, and temporal lobes was reduced in breast cancer patients who received one month of chemotherapy compared with those who did not yet receive chemotherapy [31,32]. Tingting et al. reported that compared with the healthy group, patients in the chemotherapy group showed a diffuse decrease in ^{18}F-FDG uptake in both cerebral hemispheres, which was synchronous in the cerebral cortex and basal ganglia [33]. Multiple platinum-based chemotherapies are one of the main treatment approaches for OC patients, and nearly 70 % of the patients received chemotherapy in this study. Correa et al. showed that the brain structure and function of OC patients receiving paclitaxel/platinum chemotherapy changed, mainly in the frontal and parietal lobes, involving space and working memory, but this change did not correlate with neuropsychological test results [34].

This study showed that CRCI was severe in OC patients. The decreased resting glucose metabolism in most brain regions was correlated with self-perceived cognitive deficits but not neuropsychological impairment. This result is similar to that of previous reports by Keler et al. that showed changes in brain function induced by chemotherapy in breast cancer patients were related to subjective cognitive function but not objective cognitive function [35]. Correa et al. also showed no association between changes in brain metabolism and neuropsychological tests in patients undergoing chemotherapy [34]. Zeng et al. reported that changes in brain

function in patients with gynecological malignancies are associated with self-reported cognitive dysfunction [36]. This result was mainly related to subjective cognitive dysfunction affected by psychophysiological factors such as fatigue, anxiety, stress, and sleep disorder [37]; the influences of these factors on brain metabolism have been confirmed by previous studies [28,38]. The underlying mechanisms of the effects of the cluster of psychoneurotic symptoms on cognition include pro-inflammatory cytokines, the hypothalamic-pituitary-adrenal axis, and monoamine neurotransmission system activation [39]. Studies by Liu et al. [40] [][][]and Laura et al. [41] showed that subjective cognitive impairment and emotional changes are associated with decreased brain network efficiency and glucose metabolism, mainly in the frontal and temporal lobes. Psychological factors lead to the body's stress response, which increases circulating pro-inflammatory cytokines and impairs glucose metabolism [42]. Therefore, some researchers believe that, compared with objective tests, the structural validity of the subjective cognitive assessment is not high, and easily affected by depression, anxiety, fatigue, or other emotions; it is more sensitive in detecting subtle changes in cognitive function [35,43]. Many researchers believe that subjective cognitive impairment is the earliest symptom of neurodegenerative disease [44], leading to brain function changes similar to Alzheimer's disease. Patients or the elderly with subjective cognitive impairment are at a greater risk for dementia than those without such symptoms [45].

There are several reports on structural, functional, and metabolic changes in the frontoparietal region, temporal lobe, basal ganglia, and medial temporal lobe, such as the hippocampus. These changes suggest demyelination and/or axon injury/degeneration. The frontoparietal lobe region (and cerebellum) impacts attention and executive function, and the temporal lobe region impacts episodic memory [14,34], which is similar to the results of this study. In the present study, the metabolic decline of the frontal and temporal lobes, especially the left side, affected the abstraction function in neuropsychological impairment and self-perceived cognitive deficit, suggesting that these regions are more susceptible to CRCI-related risk factors. In addition, this study showed that decreased metabolism in the left basal ganglia had a significantly positive correlation with language function, and the left central region significantly correlated with attention function. The central cuneus, a key brain region for advanced cognitive function, is involved in the rated executive network and is the main node of the brain's default mode network. Compared with other regions, the central cuneus maintains a higher resting metabolic rate in the resting state, which requires 35 % more glucose. Therefore, abnormal metabolism or function in this region indicates a decline in memory and executive function [46].

5. Recommendation

This study showed that the resting brain glucose metabolism in OC patients decreased, leading to self-perceived cognitive deficits, which enabled a better understanding of the neurobiological basis of CRCI in this population. Early "biomarkers" based on metabolic patterns can help develop and implement early interventions for patients with CRCI [8,14]. PET/CT is an essential tool for diagnosing, treating, evaluating, and following up on patients with OC. As suggested by Haut et al. an additional 4 min of head scan should be performed during each PET image acquisition of cancer patients, which neither increases the intake of radioactive substances nor the burden on patients [8], especially for patients with subjective cognitive dysfunction, to improve their quality of life and the outcome.

6. Limitations

This was a single-center study with a small sample size and did not analyze and control for the effects of other factors such as demography, cancer stage, and emotion on brain metabolism. In addition, the analysis of the correlation between brain metabolism and cognitive function did not include a control group. In the future, multicenter and prospective cohort studies should be conducted according to the recommendations of the International Cognition and Cancer Task Force [5]. In addition, different treatment regimens administered to patients with the same diagnosis should be included in the control group to dynamically understand the changes in brain metabolism and cognitive function with the progress of disease and treatment and to further identify and verify the potential imaging biomarkers related to CRCI. Simultaneously, comprehensive clinical and demographic data should be collected to explore the influence of other risk factors, including emotional disorders and chemotherapy (drug, dose, and course), on patients' cognitive function and brain glucose metabolism.

7. Conclusion

Brain resting glucose metabolism in OC patients was low and associated with subjective cognitive impairment but not objective neuropsychological impairment. ^{18}F-FDG-PET/CT can be used to evaluate the brain function of patients with OC and can provide reliable imaging indicators for early recognition and intervention in case of cognitive function changes in this population.

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Data availability statement

The data that support the findings of this study are available from the corresponding author, [Yan Ding], upon reasonable request.

CRediT authorship contribution statement

Li-ying Wang: Writing – review & editing, Writing – original draft, Software, Methodology, Investigation, Formal analysis, Conceptualization. **Si-long Hu:** Visualization, Supervision, Methodology. **Zhi-feng Yao:** Methodology, Data curation. **Mei Xue:** Investigation. **Lu Zhenqi:** Writing – review & editing, Supervision, Resources, Methodology. **Zhang Xiao-ju:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Yan Ding:** Writing – review & editing, Supervision, Methodology.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Wang Liying reports financial support was provided by Shanghai Anti Cancer Association. If there are other authors, they 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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