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Functional imaging of chemo-brain: usefulness of Nuclear Medicine in the fog coming after cancer

Running title: imaging chemotherapy-related cognitive impairment

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Abstract

The impact of chemotherapy on brain functionality has been widely investigated from a clinical perspective and there is a consensus on a significant impairment of multiple cognitive domains affecting cancer patients after treatment. Nuclear medicine offers a variety of biomarkers for the evaluation of possible effects of chemotherapy on the brain and for depicting brain changes after chemotherapy treatment. This review aims to summarize the most relevant findings on brain imaging in patients treated with chemotherapy for the most common oncological diseases. The literature published to date offers exciting results with several radiolabeled compounds, from the more common imaging of glucose metabolism to neuroinflammation. In this review, a general overview of the literature concerning clinical features and the physiopathological basis of chemotherapy-related cognitive impairment is reported as well.

Keywords: chemobrain; functional imaging; PET; FDG; DAT; neuroinflammation.

INTRODUCTION

Chemotherapy (CHT) is associated with debilitating side effects that affect the quality of life of patients(*1,2*). Chemotherapy-related cognitive impairment (CRCI) is a term that describes a clinical condition characterized by memory and concentration impairment, difficulties in information processing, and executive functions, and mood and anxiety disorders(*3,4*), with a high variable prevalence that could be estimated in a range from 17% to 75% in patients treated with CHT(*5*). There is evidence that demonstrates the neurotoxicity of CHT drugs such as cisplatin, carboplatin, paclitaxel, cyclophosphamide, vincristine, and lenalidomide (*6*): at a molecular level, cytokine dysregulation and oxygen radical production are suspected to be responsible for CRCI (*7*). Despite several studies on CRCI, there is no consensus concerning the implication of specific brain areas(*8*). In this context, in recent years molecular neuroimaging techniques have revealed interesting aspects regarding the underlying mechanisms of CRCI. This review aims to highlight the contribution of neuroimaging in this field, underlining findings and information resulting from the most important studies.

CLINICAL FEATURES OF CRCI

Recognition of an association between cancer-related treatment and cognitive changes in long-term survivors is not something new in oncology, since the first reports on this topic date back to the 80-90s(*9*). Post-cancer-therapy cognitive changes, namely CRCI, may include a wide spectrum of symptoms, ranging from problems in attention, concentration, working memory, and executive function (Table 1) (*10*).

According to longitudinal neuropsychological studies, up to 35% of patients are affected by cognitive impairment months or years later after the completion of oncological therapy(*11*). However, CRCI can differently affect the distinct populations of cancer patients according to the different tumor histology, biological behavior, location, and growth rate(*12*).

There is no definitive consensus on the tools to be utilized for diagnosing and measuring cognitive impairment in cancer patients submitted to CHT. However, according to the existing literature, the 2 main modalities of assessment, further to neuroimaging are the following:

1) *Neuropsychological Tests*: a wide range of neuropsychological batteries have been recommended (i.e. the Hopkins Verbal Learning Test-Revised, Trail Making Test, The International Cognition and Cancer Task Force, and the Controlled Oral Word Association that is part of the Multilingual Aphasia Examination).

2) *Self-Reported Cognitive Impairment*: this way of assessment is mainly based on the patient's subjective perception, performed through several available tools such as the European Organization for Research and Treatment of Cancer QLQ-C30 (EORTC QLQ-C30) or the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-COG) Questionnaire.

CRCI PHYSIOPATHOLOGICAL BASIS

The incidence of cognitive impairment may affect up to 50 % of the patients treated with CHT (*13*). CHT may lead to encephalopathy with highly complex and heterogeneous molecular mechanisms. The damage induced by CHT affects neurons and microglia. Drug-induced damage to neurons elicits a cascade of events that culminate in the activation of microglia and astrocytes as well as disrupting the normal homeostatic relationship between myelinating cells (oligodendrocytes) and oligodendrocyte precursor cells(*13*). In addition, an increase of pro-inflammatory cytokines is observed that together with activation of astrocytes that promote the release of paracrine factors, significantly hamper the maturation of oligodendrocytes(*13*). Direct involvement of CHT in the release of cytokines need to be further investigated. Instead of local increase, it is more probable that the circulating cytokines induced by CHT penetrate the blood-brain barrier to directly act on the central nervous system activating microglia and astrocytes to secrete further cytokines(*14*). CHT may affect brain tissue by modifying the shape of neurons, neurotransmitter release and blood brain barrier integrity(*1*) and may slow neurotransmitter uptake and release into neurons (*15*-*17*). These finding could partially explain some of the clinical features of CRCI mentioned above and in particular those symptoms related to alteration in emotion, learning, and memory.

SEARCH STRATEGY

Two separate literature searches in PubMed/Medline databases were carried out according to the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) guidelines for assessing 1) the effects on cognitive function of the most commonly used chemotherapeutic drugs; 2) the results of SPECT and PET examination available on the field of interest.

For topic 1), the terms used were a combination of the most utilized chemotherapeutic agents (i.e. cisplatin, carboplatin, oxaliplatin, cyclophosphamide, methotrexate, fluorouracil, doxorubicin, etoposide, irinotecan, taxanes) AND “chemotherapy-related cognitive impairment” OR “CHEMOBRAIN”. The following types of studies were considered: head-to-head comparative series, matched-pair studies, clinical trials, case series, prospective studies, and retrospective cohorts. Case reports, conference proceedings, editorial commentaries, interesting images, and letters to the editor were excluded. Only studies published from 2012 up to June 2022, limited to humans, in the English language with a cohort of ≥ 20 enrolled patients were selected (Supplemental Figure 1).

For topic 2), we used a combination of the following terms: “positron emission tomography” OR “PET/CT” OR “single photon emission tomography” OR “SPECT” OR “translocator protein” OR “dopamine transporter imaging” AND “chemotherapy-related cognitive impairment”. Studies’ selection was performed as previously described; nevertheless, due to the shortage of published papers on this topic, we decided not to apply any temporal filter and to include studies performed in humans, with a cohort of at least 10 patients, in the English language (Supplemental Figure 2).

Two reviewers (A.C., L.F.) conducted the literature search and independently appraised each article using a standard protocol and data extraction. The reference lists of the selected studies were carefully checked to identify any additional relevant literature.

From each study extracted data were, respectively, for topic 1 (chemotherapeutic agents and CRCI): type of the study (prospective, retrospective, etc...), year and location of the study, sample size, tumor, type of chemotherapy, timing of CRCI assessment concerning chemotherapy completion; for topic 2 (PET and SPECT imaging): type (prospective, retrospective, etc...), year and location of the study, sample size, employed radiopharmaceuticals, utilized device (SPECT or PET only, or hybrid devices), modality of image assessment (qualitative/ quantitative), the type of chemotherapeutic agent, eventually performed neuropsychological tests.

Studies with incomplete technical or clinical data were considered ineligible. In the case of studies from the same group of researchers, only the report with the highest number of enrolled patients was considered. Any discrepancy was resolved by discussion among authors. As this was not a meta-analysis, no statistical analysis was performed.

RESULTS

In total, 142 non-duplicate studies were retrieved from the database for topic 1 and 30 for topic 2, respectively. After duplicate records' removal and screening based on title and abstract, the remaining studies underwent full-text eligibility assessment, which resulted in the identification of 22 relevant studies (topic 1, n = 14; topic 2, n = 8), whose results are discussed in each of the following paragraphs. The main findings of the selected papers for topics 1 and 2 are summarized in Table 2 and Table 3, respectively.

CHEMOTHERAPEUTIC AGENTS AND CRCI

An overall number of 14 studies encompassing 2390 patients, focused on the effects of various chemotherapeutic agents on cognitive function, were selected(*18-31*). Great heterogeneity in study design was registered since only 4 out of 14 papers (28.5%) were prospective and 1 (7.1%) was a randomized trial, while the remaining 10 manuscripts (71.4%) were retrospective observational studies. Great variability in timing and modalities of CRCI assessment was also noted among the different research groups. Additionally, it has to be underlined that the time-point of CRCI assessment meaningfully varied among selected studies, since it ranged from "interim" assessment during CHT cycles to 20 years after therapy completion.

Notably, the majority of selected papers were focused on breast cancer (53.3%), most probably concerning relevant advances in prevention, diagnosis, and therapy in this field and the relatively good prognosis of this malignancy concerning others, allowing the 80% of women with primary breast cancer to survive for at least 10 years after surgery (mastectomy or breast-conserving surgery) (*32*).

In 5 cases (35.7%) taxanes were used alone or in combination with other chemotherapeutic agents, while in 4 cases (28.5%) patients were submitted to platin-based therapies. Except for 1 study that analyzed the potential impact of R-CHOP on cognitive function(*21*), none of the analyzed manuscripts was focused on recently implemented immunotherapeutic regimens, either those consisting of monoclonal antibodies (mAbs) targeting tumor-associated biomarkers or those aimed to remove negative immune regulation(*33*).

All but 1 selected paper registered a decline in cognitive function after CHT: in particular, 4 studies (28.5%) (*20*,*23*,*26*,*27*,*29*,*31*,*34*) reported a more relevant impairment of executive functions, three manuscripts (21.4%)(*27*) documented self-reported-or-perceived-cognitive-impairment-or-mood changes (anxiety, trouble sleeping), while 1 research (7.1%)(*24*) registered reduced social attainment and poor quality of life in cancer survivors (Supplemental Figure 3).

PET AND SPECT IMAGING OF CRCI

Eight studies, concerning the applications of SPECT or PET imaging in CRCI and including an overall number of 198 patients, were selected. Only 3 tumor types were the object of evaluation: lymphoma (n = 4, 50%), breast cancer (n = 3, 37.5%), and acute myeloid/ lymphoid leukemia (n = 1, 12.5%), SPECT was utilized in 2 cases(*24*,*35*), while PET/CT was used in the remaining 6 papers. As expected concerning its availability and its capability to give an accurate insight into brain metabolism, ^{18}F-FDG was the most commonly used radiopharmaceutical (n = 6, 75%). It has to be underlined that a meaningful heterogeneity in PET evaluation was noted since the various authors employed, aside from qualitative evaluation, quantitative analysis by VOI in 4 cases(*36*-*39*) and a statistical parametric map (SPM) in 2 papers(*40*,*41*). As regards SPECT studies, one utilized image visual evaluation (*42*), while another 1 employed quantitative analysis of dopamine transporter (DAT) density(*35*).

Finally, only a minority of selected studies (n = 3, 37.5%)(*35*,*39*,*42*) reported a correlation between imaging findings and neuropsychological assessment. Selected manuscripts focused on PET or SPECT imaging are discussed in detail in each of the following paragraphs.

SPECT tracers for CRCI imaging

Cerebral Blood Flow (CBF) measurement

It has been postulated that CHT-induced microvascular damage in the brain might be one of CRCI's causative factors (*43*). SPECT with technetium-99m (^{99m}Tc)-hexamethyl-propylene-amine oxime (HMPAO) has been employed for the assessment of changes in cerebral blood flow (CBF) (*44*), despite its well-known limitations in terms of spatial resolution and quantitation accuracy.

In a cohort of 12 pediatric patients, treated with high-dose cytarabine for acute myeloid leukemia (AML, n = 11) or acute lymphoid leukemia (ALL, n = 1), Véra et al. investigated changes in CBF through ^{99m}Tc-HMPAO SPECT after the induction phase, immediately after the first intensification, and during follow-up (*42*). SPECT results were correlated with neuropsychological assessment and

serial brain MRI. At the induction phase, brain SPECT was carried out in 8 cases and resulted in slightly heterogeneous in 4 and normal in the remaining 4 children, while in all the 8 examined patients brain MRI was normal. At the high-dose consolidation phase, five patients presented CHT-related neurotoxicity: in such cases, MRI was normal in 4/5 subjects, while SPECT resulted diffusely heterogeneous in 4/5 cases and slightly heterogeneous in 1 child. In children presenting neurotoxicity (n = 5), follow-up was available in 4 cases: all regressed over time; of note, one patient presented particularly prolonged (60 months) neurological symptoms that resulted associated with persistent abnormalities at SPECT and brain MRI.

DAT imaging

Molecular imaging of dopamine transporters (DAT) through SPECT has been extensively applied in clinical practice to diagnose and monitor Parkinson's Disease (PD) and other extrapyramidal syndromes (*45*,*46*). SPECT with ^{99m}Tc-TRODAT-1 was performed by Vitor and colleagues to investigate DAT integrity in 28 women reporting cognitive impairment related to CHT for breast cancer, and in 22 healthy female controls, matched for age and level of instruction(*35*). Calculation of tracer concentration in the striatum, carried out by dedicated software (DaTQUANT, GE Healthcare) in both groups, demonstrated a significantly reduced striatal uptake (both at the analysis of the overall striatum and the separate analysis of caudate and putamen) in breast cancer patients experiencing CRCI than in healthy controls, indicating that toxic damage to basal ganglia might be involved in the complex mechanisms leading to CRCI. Of note, subjects developing parkinsonism after CHT are generally characterized by strong responsiveness to levodopa and tend to improve over time(*47*) (Supplemental Figure 4).

^{18}F-FDG PET imaging in CRCI

When approaching PET imaging of the brain using ^{18}F-FDG, one should consider that under normal conditions the brain uses glucose as its sole source of energy(*48*); hypometabolism may not correspond to areas with the greatest changes in routine neuropathology(*49*); hypometabolism is not directly affected by intracellular or extracellular inclusions(*50*) and that glucose metabolism primarily reflects synaptic activity(*51*).

To date, few studies have been carried out to investigate the potential role of ^{18}F-FDG in patients with CRCI. One of the first studies was carried out in 2015 in 49 subjects affected by Hodgkin's disease(*40*) evaluated at the diagnosis and during the treatment. Surprisingly, the authors reported a significantly higher metabolic activity after the first cycles in the right angular gyrus (Brodmann area 39) while a significant metabolic reduction was found in Brodmann areas 10, 11, and 32 bilaterally. All these changes disappeared at the end of the therapy course(*40*). The authors concluded that the results are consistent with a transient and limited impact on brain metabolism of CHT in Hodgkin lymphoma. In agreement with the report previously(*40*), Shrot S. et al found an increased ^{18}F-FDG uptake in the parietal and cingulate cortexes in fourteen pediatric patients diagnosed with lymphoma; a decreased fluorodeoxyglucose uptake was demonstrated in deep gray matter nuclei and the brainstem(*52*).

Goldfarb L et al. and Tauty A et al. (*53*) found a reduced metabolism in the bilateral anterior cingulate cortex and left inferior frontal and insular cortex soon after 2 cycles and hypometabolic areas in the left anterior cingulate cortex, in the left inferior frontal and insular cortex and finally in the left temporal lobe after 6 cycles of CHT(*54*); a reduction of glucose metabolism was found in the frontal, cingular, and temporoinsular regions after two cycles of CHT(*53*). The differences with other studies cited previously could be partially explained by the differences in the CHT agents used. In non-Hodgkin lymphoma, a general reduction in the overall cerebral cortical metabolism of around 20% was found after CHT(*36*). These findings suggest a diffuse and severe impairment of brain functionality after CHT in these patients(*36*). In a population of 10 subjects with breast cancer, Ponto L. et al found a reduced metabolism in bilateral orbital frontal regions as compared to healthy subjects(*37*). Interestingly, this finding is consistent with cognition and executive function impairment found by neuropsychological assessment(*37*).

PET with tracers other than ^{18}F-FDG: translocator protein (TSPO) ligands for CRCI imaging

In recent years, translocator protein (TSPO), an 18 kDa protein mainly expressed on the outer mitochondrial membrane of several cells of the CNS (microglia, astrocytes, and endothelial cells), has emerged as a relevant target for the molecular imaging of neuroinflammation, since its expression is minimal in the healthy brain, but strongly overexpressed when microglia are activated as a response to an injury(*55*). The development of positron-emitting ligands selectively binding to TSPO has allowed the *in vivo* assessment of neuroinflammation through PET/CT or PET/MRI technology (*56,57*). Notably, the binding of second-generation tracers to TSPO is strongly influenced by a single polymorphism (rs6971) in exon 4 of the TSPO gene(*58*), according to which subjects can be stratified into 3 categories: high, mixed, and low-affinity binders.

Schroyen et al. have recently investigated the potential of TSPO PET for the *in vivo* imaging of neuroinflammation in breast cancer patients submitted to CHT, also through the correlation among PET findings, neuropsychological tests, and inflammatory markers(*59*). The authors prospectively enrolled subjects distributed into 3 different cohorts: breast cancer patients treated with CHT, breast cancer patients not scheduled for CHT, and a control group of healthy women. CHT-cohort exhibited higher ^{18}F-DPA714 uptake in occipital and parietal lobes, in comparison with CHT-naive and healthy controls. Furthermore, subjects treated with CHT showed altered neuropsychological tests and increased inflammatory markers concerning the other 2 cohorts. Among inflammatory biomarkers, neurofilament light chain protein (i.e. NfL), an axonal damage indicator, resulted particularly increased in CHT patients and strongly correlated with TSPO-PET findings. Of note, despite positive ^{18}F-DPA714 incorporation, CHT-treated patients did not show relevant alterations of brain white matter micro- and macrostructure at MRI analyzed through pixel-based analysis of diffusion-weighted images.

Conclusions and future outlook

Nuclear medicine techniques are not commonly considered in the work-up of patients with CRCI-related manifestations, despite their high potential to investigate different physiopathological

phenomena (i.e. cortical metabolism, dopamine transporter integrity, neuroinflammation) through specific imaging probes(*60*). From the careful analysis of the selected papers, some considerations on the role of functional neuroimaging in CRCI can be made.

Firstly, few studies have explored ^{18}F-FDG PET/CT's usefulness for the imaging of CRCI, and an even more limited number of papers employed SPM technique to quantitatively assess changes in cortical metabolism before and after CHT. In this perspective, it is mandatory to implement SPM in future clinical trials concerning the use of ^{18}F-FDG for CRCI imaging, since this parametric analysis entails a voxel-level statistical parametric mapping at the whole-brain level, comparing each subject concerning images belonging to a reference control group utilizing a two-sample t-test, thus generating a contrast t-map for areas of relative hypometabolism in the study group compared to the controls(*61*). On this path, novel technology innovations might be of great value to further improve the imaging approach to CRCI: hybrid PET/MRI, as an example, is still a few explored tool for correlating eventual changes in T1- or T2-weighted images with metabolic abnormalities detected by ^{18}F-FDG, while the emerging applications of artificial intelligence (AI) and radiomics might find an interesting application in the field to extract potentially useful data, undetectable to the naked eye, from ^{18}F-FDG PET images' texture analysis(*62*). Notably, PET tracers other than ^{18}F-FDG, such as TSPO-ligands, can provide an interesting opportunity to investigate *in vivo*, at a molecular level, the inflammatory landscape associated with CRCI, but their widespread use is still hampered by the high cost, the lack of authorized compounds and dependence of image-quality on genetic polymorphism.

Another relevant issue is when and how to assess CRCI after therapy completion. In this regard, an objective determination of CHT effects on cognitive abilities is hampered by CRCI multifaceted nature, since underlying depression or anxiety disorders can also be responsible for the symptoms complained by patients and are often classified as "CRCI". It is worth mentioning that the concept of cancer-related post-traumatic stress disorder (CR-PTSD), a complex set of symptoms affecting patients' psychosocial and physical well-being during cancer treatment and into survivorship(*63*), has been gaining consideration and should be taken into account in future clinical trials aimed to apply functional imaging for CRCI investigation.

The impact of CHT on the brain has been assessed by a relatively low number of imaging studies. Moreover, the methodology used in the studies, the most relevant of them being cited in this review, is characterized by a huge heterogeneity in terms of imaging modality, clinical evaluation, CHT used, and type of tumors. Moreover, longitudinal studies are missing to investigate the possible reversible effect of neuronal impairment induced by CHT.

In this context, nuclear medicine offers several instruments for the detailed evaluation of those physiopathological processes that underline CRCI. Based on the results of the research performed for this review, the major constraint on discoveries will not be related to the available techniques of functional imaging, which are constantly improving, but rather to the precision of our hypotheses and the creativity of our methods for testing them. In particular, longitudinal and standardized studies are requested to investigate the impact of each CHT drug on the brain (considering in particular the same

dose) or the combination of these drugs in patients affected by the tumor. Moreover, a correlation with a standardized neuropsychological assessment is mandatory to exclude the possible contribution of stress and emotional aspect, especially for functional studies.

Noteworthy:

- 18F-FDG brain PET imaging show a reduction of glucose metabolism in CRCI (page 6);
- Chemotherapy may affect DAT receptor expression in brain (page 6);
- Imaging of TSPO is a promising tool for the investigation of CRCI (page 7);

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TABLE 1

Cognitive domains and abilities more commonly involved in chemotherapy-related cognitive impairment

Cognitive Domain or Ability	
Memory	*Working memory*: transiently stores and elaborates information.
	Episodic memory: recalls and allows mentally re-experience of context-dependent events.
	Remote memory: retrieves events from the past
Executive Function	Encompasses the mental skills (e.g. flexible thinking and self-control) we use to learn, work and manage ourselves in everyday life.
Processing Speed	Indicates the efficiency and speed in elaborating information to finalize a specific task.
Attention	Indicates the capacity of focusing on a certain topic, by leaving out other coexisting data and stimuli.
Reaction Time	Time needed for a person to react to a certain stimulus
Motor Speed	Indicates the precision and speed with which a person can complete a simple motor task.

TABLE 2

The main features of selected studies focused on the effects on cognitive function of the most commonly used chemotherapeutic drugs

Authors	Year	Location	Study Design	Tumor	Sample Size	CHT Agents	CRCI Assessment Timing	Comments
Andreis et al. (*19*)	2013	Italy	Observational	Colorectal cancer	57	Oxaliplatin, 5-fluorouracil, and leucovorin (FOLFOX4)	Neuropsychological battery at T0 (baseline), T1 (end of therapy) and T2 (6 months after CHT)	No cognitive impairment, only some changes in emotional performance during CHT.
Khan et al. (*21*)	2016	India	Prospective cohort study	Non-Hodgkin's lymphoma	68	CHOP vs R-CHOP	Neuropsychological assessment performed after the 1st (TP0), 2nd (TP1), 3rd (TP2) and 4th (TP3) cycle	R-CHOP patients were found to present a more profound cognitive decline than subjects who underwent CHOP alone
Lange et al. (*22*)	2016	France	Observational	Breast cancer	123	Doxorubicin ± docetaxel	Evaluation before CHT and after the end of treatment	CHT-treated (n= 58) and RT-treated (n = 61) pts were compared with healthy controls (n = 61) for cognitive performance: in 49% of RT and CHT-treated subjects a cognitive decline was observed after adjuvant therapy, with CHT-group having more subjective complaints
Miao et al. (*23*)	2016	China	Comparative	Breast cancer	23	Docetaxel/adriamycin/cyclophosphamide	Assessment carried out at 36.6 ± 4.4 mo after their chemotherapy treatment	Functional connectivity (i.e. executive function) of anterior cingulate cortex in the BC group is significantly lower than that in the control group
Amidi et al. (*18*)	2017	Denmark/The Netherlands	observational	Testicular Cancer	64	Bleomycin, etoposide, and cisplatin	Neuropsychological battery at 6 mo after CHT	22 patients received surgery plus CHT, while 42 underwent only surgery and were on active surveillance. CHT-treated patients experienced relevant CRCI
Cerulla et al. (*20*)	2017	Spain	Prospective, longitudinal	Breast cancer	51	Fluorouracil, epirubicin and cyclophosphamide (FEC) + taxanes vs FEC alone	Assessment at baseline, short term and long-term	Short-term assessment demonstrated cognitive decline (i.e. executive function) in both groups, with a greater number of affected cognitive measures in "taxane-group"; long-term assessment confirmed cognitive impairment in both groups
Ehrhardt et al. (*24*)	2018	USA	Retrospective cohort analysis	NHL	187	Methotrexate, cytarabine, anthracyclines	Evaluation in long term (more than 10 years) survivors	NHL-survivors presented impaired neurocognitive function, associated with lower social attainment and poor quality of life with respect to age-matched controls
Sales et al. (*25*)	2018	Brazil	observational, prospective	Colorectal cancer	85	fluoropyrimidine	Assessment at T0 (baseline) and T1 (after 12 months)	CRC pts treated with adjuvant CHT showed a decline in executive function after 12 months, with respect to those who did not undergo CHT
van der Willik et al. (*30*)	2018	The Netherlands	Cohort study	Breast cancer	166	cyclophosphamide, methotrexate, and fluorouracil (CMF)	Assessment at 20 years after chemotherapy	Survivors had lower cognitive performance than non-CHT exposed matched controls, furthermore, survivors had higher levels of inflammatory markers than non-exposed population. A significant association was registered between cognitive impairment and inflammatory biomarkers
Phillips et al. (*29*)	2020	USA	Cross-sectional study	Acute lymphoblastic leukemia (ALL)	176	methotrexate	Evaluation at 2 years after diagnosis	No meaningful brain volume discrepancy between ALL survivors and controls, but cerebellar volume was reduced in ALL survivors. At neuropsychological assessment, female survivors showed impaired executive function
Wagner et al. (*31*)	2020	USA	Cohort study	Breast cancer	454	docetaxel, cyclophosphamide and anthracycline	Evaluation of self-reported CI carried out at baseline and every 3 months	Pts treated with CHT+endocrine therapy (n = 218) showed significant self-reported cognitive impairment compared to subjects treated with endrocrine therapy alone
Keetile et al. (*28*)	2021	South Africa	Randomized, time-based series study	Breast cancer	30	CMF (cyclophosphamide, methotrexate, fluorouracil) and FAC (fluorouracil, adriamycin,	Assessment carried out at baseline (T0, 3rd cycle [T1], 6th cycle (T2)	Significant cognitive decline was registered from baseline (T0) to completion (T2) of chemotherapy

						cyclophosphamide)		
Beesley et al. (*26*)	2022	Australia	Prospective	Ovarian cancer	726	At least 3 cycles of platinum	Assessment completed every 3 mo, starting 6 mo after diagnosis up to 4 years	Long-term moderate-to-severe fatigue (32%), trouble sleeping (31%), and anxiety (18%) were common
Durán-Gómez et al. (*27*)	2022	Spain	Observational, cross-sectional, non-probability study	Breast cancer	180	docetaxel, cyclophosphamide and anthracycline	Assessment performed in newly diagnosed patients under chemotherapy	Perceived cognitive impairment was present in 41.7% of patients, being significantly associated with CHT exposure. Furthermore, spectroscopy (NIRS) demonstrated meaningfully decreased oxygen saturation in the frontal cortex of CHT BC group (n = 90) with respect to no-CHT BC group (n = 90)

mo = months; pts = patients; NIRS = near-infrared spectroscopy

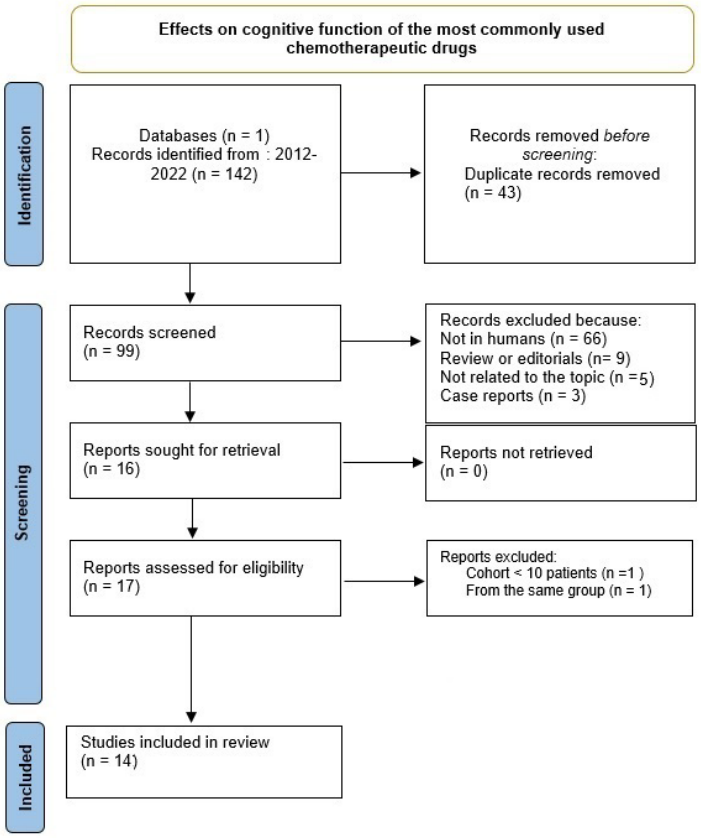
TABLE 3

Summary of main manuscripts focused on PET and SPECT imaging in CRCI

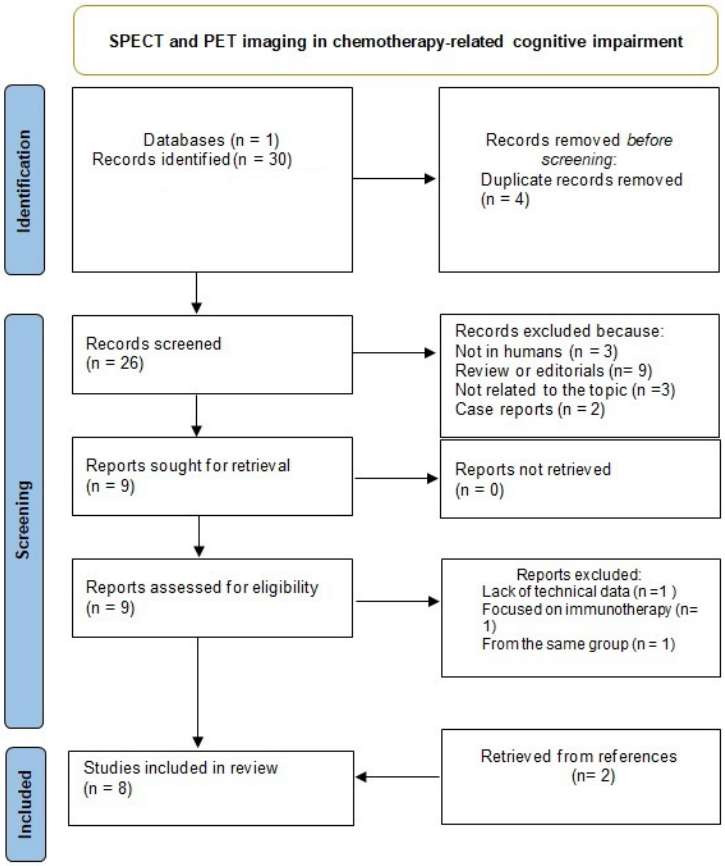
Authors	Year	Location	Study Design	Tumor	CHT Agents	Sample Size	Radioph.	Imaging Target	Device	Image Assessment	Neuropsy. Assessment	Comments
Véra et al et al. (*42*)	1999	France	Prospective	Acute myeloid/ lymphoid leukemia	Cytarabine	12	99mTc-HMPAO	Cerebral blood flow (CBF)	SPECT	QUAL	Performed at baseline	99mTc-HMPAO SPECT can detect CBF abnormalities associated with CHT toxicity
Sorokin et al. (*36*)	2014	USA	Retrospective	Hodgkin Disease	ABVD scheme	21	18F-FDG	Metabolism	PET/CT	QUAL+QUANT (VOI analysis)	N.P.	Reduced metabolism in whole grey matter
Ponto et al. (*37*)	2015	USA	Retrospective	Breast Cancer	Cyclophosphamide, methotrexate and 5-fluorouracil or an anthracycline	10	18F-FDG	Metabolism	PET/CT	QUAL+QUANT (VOI analysis)	N.P.	Reduced metabolism in bilateral orbital frontal regions as compared to healthy subjects
Chiaravalloti et al. (*40*)	2015	Italy	Prospective	Hodgkin Disease	ABVD scheme	74	18F-FDG	Metabolism	PET/CT	QUAL+QUANT (SPM)	N.P.	Significantly higher metabolic activity after the first cycles in the right angular gyrus, while metabolic reduction was found in Brodmann areas 10, 11, and 32 bilaterally
Shrot et al. (*52*)	2019	Israel	Observational	Non-Hodgkin Lymphoma	Schemes: LMB-group B, Euro-LB-02, ALCL-99	14	18F-FDG	Metabolism	PET/CT	QUAL+QUANT (ROI analysis)	N.P.	Reduced metabolism in deep gray matter nuclei and in the brainstem
Tauty et al. (*41*)	2019	France	Retrospective	Hodgkin Disease	ABVD or BEACOPP scheme	20	18F-FDG	Metabolism	PET/CT	QUAL+QUANT (SPM)	N.P.	Reduced metabolism in frontal, cingular, and temporoinsular regions after 2 cycles, with less extent when compared to adults
Vitor et al. (*35*)	2019	Brazil	Prospective	Breast Cancer	Doxorubicin, cyclophosphamide	28	99mTc-TRODAT	Dopamine Transporters (DAT)	SPECT	QUAL+QUANT (DATQUANT)	FACT-Cog Mini Mental	Cognitive impairment resulted associated with reduced DAT density in striatum
Schroyen et al. (*39*)	2021	Belgium	Prospective	Breast Cancer	Epirubicin. Cyclophosphamide, paclitaxel	19	18F-DPA714	Translocator Protein (TSPO)	PET/CT	QUAL+QUANT (VOI analysis)	Questionnaires to derive cognitive failure score	PET detected neuroinflammation in in parietal and occipital brain regions in chemotherapy-treated patients.

CHT = chemotherapy; Radioph. = radiopharmaceuticals; N.P. = not performed; QUAL = qualitative; QUANT = quantitative; Neuropsy. = neuropsychological

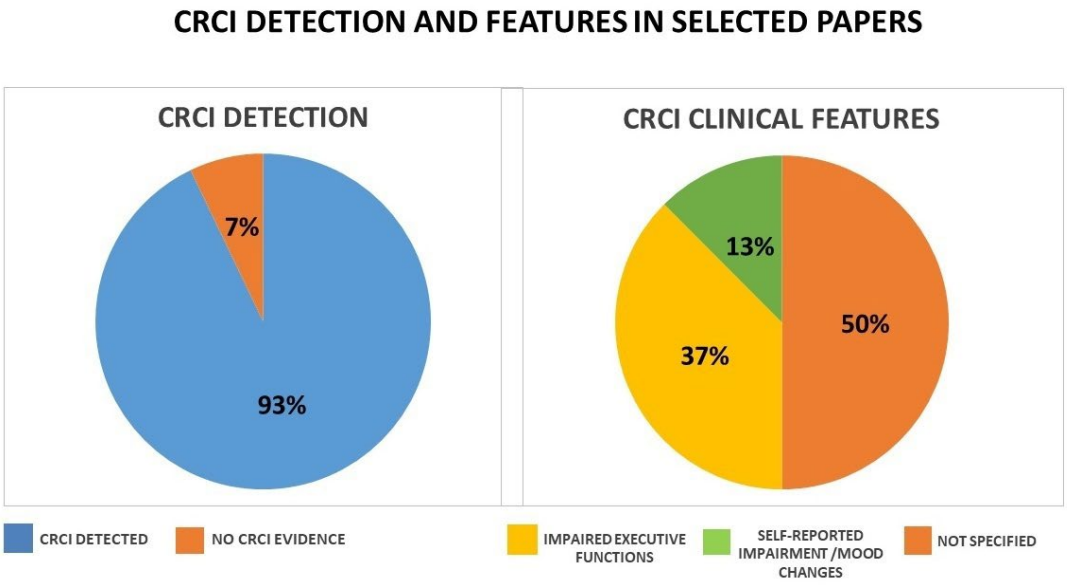
Supplemental Figure 1



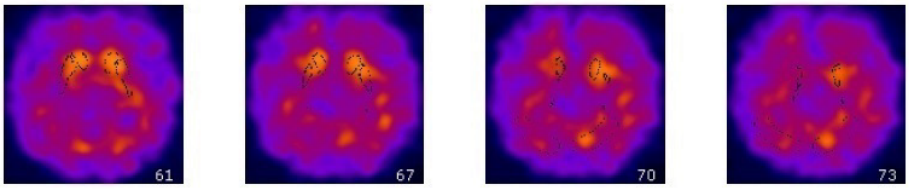
Supplemental Figure 2

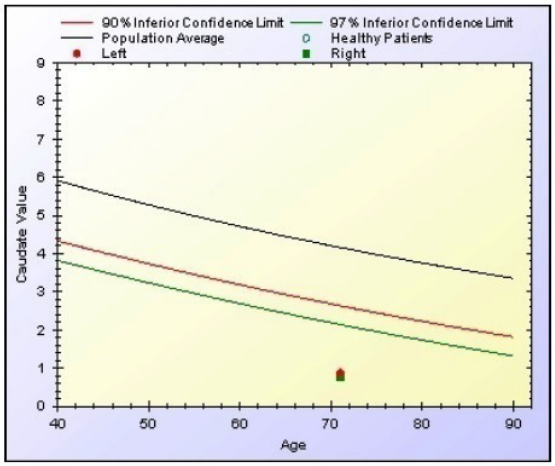


Supplemental Figure 3

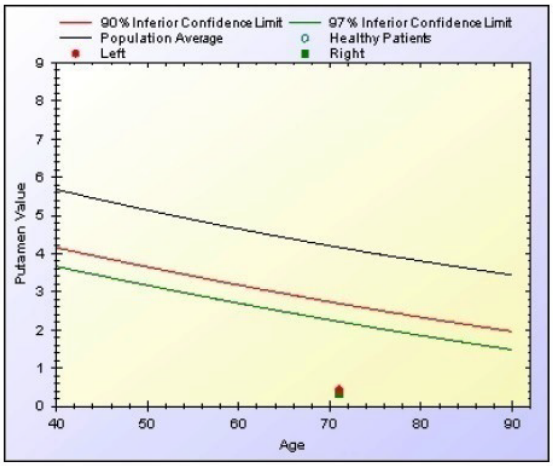


Supplemental Figure 4





Caudate: patient activity (left side in red, right side in green)



Putamen: patient activity (left side in red, right side in green)