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Review article

Impact of gut microbiota dysbiosis on cancer-related cognitive impairment

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Abstract

Advances in cancer treatment have significantly improved survival rates among patients. However, many also experience cognitive changes as an adverse effect of both the disease and its therapies. This phenomenon is observed not only in patients with central nervous system (CNS) tumors but also in those with tumors located outside the CNS, and across all age groups.

Studies of patients with non-CNS malignancies have shown that cancer-related cognitive impairment (CRCI)—including deficits in memory, attention, executive function, and processing speed—affects up to 75% of patients during treatment and up to 30% prior to treatment. The gut–brain axis (GBA) is a complex, bidirectional communication system that has been identified as a potential link between neurodegeneration and alterations in the gut microbiota, influencing various brain functions. Gut microbes can produce a range of molecules, such as neurotransmitters, that enable neurochemical interactions with the host's enteric, central, and autonomic nervous systems. While the specific changes may vary, cancer treatment-induced disruptions in the gut microbiota can compromise its protective and immunomodulatory roles, leading to increased production of harmful metabolites by pathogenic microbes. The role of the gut–brain axis and gut microbiota in CRCI remains largely unknown among many cancer care specialists. CRCI is often overlooked by healthcare professionals. The primary objective of this review is to highlight this underrecognized issue. Research into the cancer microbiota is an emerging field gaining importance in clinical oncology. Several studies have documented significant changes in gut microbial composition following cancer treatments, with reduced microbial diversity being the most reported alteration. This review synthesizes current clinical and preclinical evidence linking gut microbiota to CRCI, with a particular focus on future research directions—especially concerning disruptions in the gut–brain axis.

Keywords: Cancer-related cognitive impairment, cancer, chemotherapy, hormonotherapy, targeted therapy, microbiota-gut-brain axis, Dysbiosis; Neuroinflammation; Cancer treatment toxicity

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1. Introduction

Advances in cancer therapies have significantly enhanced the overall survival of patients. However, anticancer therapies such as surgery, chemotherapy, radiotherapy, hormonotherapy, targeted therapies and recently immunotherapy are commonly associated with various toxicities. In this context, many cancer patients experience neuropsychological side effects that persist beyond treatment and negatively impact their quality of life. One of the frequently reported issues is cognitive decline during treatment [1].

Cancer-related cognitive impairment (CRCI) is defined as the neurocognitive deficiencies encountered by cancer survivors that may be a consequence of cancer and anticancer treatments. Cognitive impairment associated with cancer treatment is marked by a deterioration in cognitive abilities affecting learning, memory, executive function, attention, processing speed and multitasking [2,3]. CRCI is one of the common factors that weaken the quality of life for cancer survivors [4]. CRCI intensity is usually mild to moderate but can negatively impact on patient's treatment adherence, reduce job performance, and negatively influence the quality of everyday tasks such as cooking and driving [4]. As the number of cancer survivors continues to rise due to enhanced diagnostics and therapeutics, understanding the mechanisms underlying long-term CRCI has become increasingly important [3]. Recent studies have suggested a potential relationship between neuro-cognitive symptoms and gut microbiota. These micro-organisms appear to impact various physiological processes, particularly cognitive, neurological, metabolism, inflame-mation, and immune response [5]. The gut-brain microbiota

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axis is a complex communication infrastructure that links alterations in gut microbiome to brain degeneration, potentially disrupting various brain functions [5]. Gut microbiota CRCI and the role of the gut brain axis remain unknown for most specialists involved in cancer care. CRCI are well overlooked by healthcare professionals. Indeed, the main objective of this review is to highlight this issue [5].

Studies of prospective neuropsychological assessments of patients involved by cancer have concluded that up to 30% of patients experience CRCI before starting treatment, up to 75% experience CRCI concomitantly with treatment, and up to 35% experience CRCI months or years after completing cancer treatment [6,7]. This overview highlights current knowledge around CRCI, explores its underlying mechanisms, and underscores the role of dysregulation in the microbiota-gut-brain axis in the pathophysiology of CRCI.

This review critically evaluates clinical and preclinical evidence linking the gut microbiota-gut-brain axis to CRCI, focusing on mechanistic insights, treatment-induced dysbiosis, and potential therapeutic implications

2. Materials and methods

This review synthesizes data from multiple research studies that explore the relationship between cancer treatments, cognitive decline, and microbiota dysregulation. It is a narrative review. The studies covered in this review were selected based on their relevance to the microbiota-gut-brain axis and its potential role in the onset and progression of CRCI. Clinical and preclinical articles published between January 1, 2000, and January 15, 2025, were included. A comprehensive literature review was conducted referring to the official scientific publication, basically, PubMed and Scopus. The search terms included "cancer-related cognitive impairment," "microbiota-gut-brain axis," "chemotherapy," "radiotherapy," "hormonotherapy," "microbial dysbiosis," and "neurocognitive decline." The inclusion criteria studied were the relationship between microbiota alterations and CRCI. An additional inclusion criteria as human participants or animal models of cancer, with specific reference to the consequences of cancer treatments on gut microbiota and cognition, were discussed.

3. Results and Discussion

Our review showed that CRCI is a prevalent and major issue for cancer patients, with up to 75% of patients experiencing cognitive changes during treatment. These cognitive disorders, which affect attention, memory, processing speed and executive function, significantly influence the quality of life and treatment adherence for cancer survivors. Additionally, our analysis highlights the emerging role of the microbiota-gut-brain axis in the development and evolution of CRCI, suggesting that disruptions in the gut microbiota may contribute to neurocognitive decline in malignancy patients. Several studies included in this review report alterations in gut microbiota diversity following anticancer therapies such as surgery, chemotherapy, radiotherapy, hormonotherapy and targeted therapies. In this section we will address the following questions namely, (I) Cancer-related Cognitive Impairment after Surgery, (II) Cancer-related Cognitive Impairment after Chemotherapy, (III) Cancer-related Cognitive Impairment after Radiotherapy, (IV) Cancer-related Cognitive Impairment after Hormone Therapy, (V) Cancer-related Cognitive Impairment after Targeted Therapy; (VI) Mechanisms of Cancer-Related Cognitive Impairment as well as (VII) Role of Microbiota-gut-brain Axis Dysregulation in CRCI .

Cancer-related Cognitive Impairment after Surgery

CRCI, commonly known as chemobrain or chemofog, primarily refers to chemotherapy induced cognitive disorders that can lead to nerve toxicity. Recent research reinforces the idea that CRCI exists after surgery and before chemotherapy. Malignant tumors and surgery are thought to increase cytokine levels, causing inflammation and tissue damage, contributing to cognitive impairment [4,8]. Various studies have documented cognitive disorders in patients with non-CNS cancers, occurring both before and after anticancer treatments. For example, breast malignancy patients with stage I-III disease (N = 110; mean age = 54.1 ± 8.1 years) exhibited significantly decreased overall cognitive abilities ($p = 0.002$) on neuropsychological tests after surgery but before adjuvant treatment, compared to those with non-invasive breast cancer and healthy controls [9]. Lange et al. conducted research on cognitive functions in elderly patients with early-stage breast cancer (N = 123; average age = 70 ± 4 years) preceding the beginning of adjuvant treatment. Their findings revealed that 41% of the patients exhibited significant cognitive dysfunction when compared to data from the healthy population ($p < 0.0001$). Specifically, 21% of patients exhibited impaired verbal episodic memory [10].

Cognitive impairment has also been noted in colorectal cancer patients prior to starting systemic therapy. Cruzado et al. reported that 37% (30 out of 81) of patients affected by colorectal cancer exhibited cognitive impairment during pre-chemotherapy evaluations, with effects on psychomotor executive functions and processing speed [11]. Vardy et al. reported that 45% (126 out of 281) of patients with early-stage colorectal neoplasm and 47% (31 out of 66) of patients with metastatic disease experienced cognitive impairment either before or after surgery, in contrast to 15% (11 out of 72) of healthy controls ($p < 0.001$, $p < 0.001$ respectively) [12]. The most affected cognitive domains covered attention, working memory, verbal learning/ memory, and complex processing speed [11,12]. In the current study of newly orchiectomized testicular cancer patients (N = 40), poorer performance was observed on 6 out of 15 neuropsychological tests compared to healthy controls (N = 22). The percentage of cognitive disorders was much higher in the patient group (65% vs. 36%; $p = 0.04$) [13].

Cancer-related Cognitive Impairment after Chemotherapy

Several researches have studied the influence of chemotherapy on cognitive functions in cancer patients, particularly focusing on breast cancer treatments such as CMF (Cyclophosphamide, Methotrexate, 5-Fluorouracil). Early studies indicated that patients treated with CMF exhibited impaired mental functioning compared to standard test norms [5,14]. More recent research has reinforced these findings, revealing that individuals treated with CMF not only performed worse in cognitive assessments but also

exhibited smaller gray matter volumes compared to healthy controls [5,15]. Longitudinal studies further highlight the progressive nature of chemotherapy-induced cognitive impairment in breast cancer patients treated by anthracycline-based and taxane chemotherapy. Over a 15-month period, these patients experienced worsening cognitive deficits alongside symptoms of anxiety and fatigue [16]. The cognitive domains affected include attention, short-term memory, long-term memory, overall executive functioning and processing speed [5,17].

Several studies have revealed that decreased verbal memory, verbal fluency, visuospatial ability, and executive function are frequently found before or after chemotherapy for small cell lung cancer [18]. Whitney et al. (2008) reported that > 60% of non-small cell lung cancer (NSCLC) patients presented cognitive damage both before and one month after chemotherapy [18]. Thus, chemotherapy not only influences anticancer treatments outcomes but also significantly affects cognitive functions and emotional well-being through complex mechanisms involving both direct neurotoxic consequences and indirect pathways via the gut microbiota.

Cancer-related Cognitive Impairment after Radiotherapy

Treatment strategies for both primary and secondary brain tumors frequently involve brain. Irradiation techniques, including limited or total brain irradiation, have been historically linked to cognitive changes. These changes may present themselves months to years after radiotherapy and can gradually deteriorate over time [19]. The cognitive fields most altered by whole brain radiotherapy include learning and memory, attention, executive function and processing speed [20-21]. Radiotherapy has been a cornerstone of cancer treatment for both localized and locally advanced diseases for decades. However, its influence on cognitive function has been relatively underexplored compared to the focus on chemotherapy or combined chemo-radiotherapy in patients with early-stage breast cancer. Research conducted by Quesnel et al. has studied the cognitive impacts of adjuvant chemotherapy in comparison to adjuvant radiotherapy in patients with breast cancer. The study, which included 81 participants, found that both groups those receiving chemotherapy followed by radiotherapy and those receiving radiotherapy alone exhibited poorer performance on neuropsychological tests compared to healthy controls [22]. Shibayama et al. similarly demonstrated cognitive impairments in breast cancer patients exposed to adjuvant regional radiotherapy, which improved approximately three years post-treatment [23,24]. Radiotherapy targeting retroperitoneal lymph nodes in patients with seminomatous testicular germ cell tumors (GCT) has traditionally been employed for stage I or II disease [25]. Although adjuvant radiotherapy is previously considered the preferred treatment option, the irradiation of retroperitoneal lymph nodes measuring up to 3 cm is still deemed supportable for stage II disease [26]. A prospective study conducted by Chovanec et al. evaluated long-term cognitive functioning in survivors of germ cell tumors (GCT) with a median follow-up period of 10 years. This study compared those receiving cisplatin-based chemotherapy, radiotherapy, or a combination of both to survivors who underwent orchiectomy alone, utilizing FACT-Cog questionnaires. The findings indicated that radiotherapy was linked to decreases in overall cognitive function scores and in two specific cognitive fields. Survivors who received radiotherapy, either alone or in conjunction with chemotherapy, revealed statistically significant declines across all cognitive fields when compared to patients treated exclusively with orchidectomy (all $p < 0.05$), as well as in the overall cognitive function score ($p = 0.01$) [27].

Cancer-related Cognitive Impairment after Hormone Therapy

Numerous studies have revealed a negative influence of hormonotherapy on cognition in man with prostate cancer and women with breast cancer [28-34]. Castellon conducted a comparison of cognitive functioning among breast cancer remainders who underwent adjuvant chemotherapy (N = 18) or a combination of chemotherapy and tamoxifen (N = 18) against those who were treated solely with surgery (N = 17). The group that received only chemotherapy demonstrated significantly poorer abilities in verbal learning ($p = 0.03$), visual memory ($p = 0.01$) and visual-spatial functioning ($p = 0.005$), and when compared to the surgery only group. Furthermore, patients who received both chemotherapy and tamoxifen displayed the most pronounced cognitive impairment in neuropsychological assessments [28]. These findings were corroborated by Wagner et al., who conducted a comparison of patient-reported cognitive impairment among women with early breast cancer (N = 552) receiving chemotherapy in conjunction with hormonotherapy and those receiving hormonotherapy alone (58% acquired an aromatase inhibitor as primary endocrine therapy, while 37% were administered Tamoxifen). Their results indicated that the combination of adjuvant chemotherapy and hormonotherapy was linked to a significantly greater cognitive decline compared to hormonotherapy alone at both 3 and 6 months ($p < 0.001$ and $p = 0.02$, respectively). Nevertheless, no notable differences were noted in 12 months and thereafter [31]. Schilder et al. conducted a comparison of the consequences of adjuvant Tamoxifen and Exemestane on cognitive function in postmenopausal breast cancer patients. The study involved 80 participants using Tamoxifen and 99 using Exemestane, who were evaluated with neuropsychological tests both prior to and one year after the starting of adjuvant hormonotherapy. The findings indicated that after one year of treatment, Tamoxifen was correlated with notably inferior scores in verbal memory ($p < 0.01$) and executive functions ($p = 0.01$) when compared to healthy controls. Additionally, Tamoxifen users exhibited reduced scores in information processing speed ($p = 0.02$) compared to Exemestane users. However, those using Exemestane did not exhibit significantly poorer performance than healthy controls across any cognitive domain [29]. Bender et al. conducted an evaluation of the consequences of Anastrozole on cognitive function in early-stage breast cancer patients in the initial 18 months of treatment, comparing those receiving chemotherapy in conjunction with Anastrozole (N = 114) to those receiving Anastrozole alone (N = 173). The study revealed that patients exhibited deprived executive functioning in comparison to healthy controls ($p = 0.09$). Additionally, women receiving Anastrozole alone experienced a decrease in working memory and concentration between 12 and 18 months following the begin of therapy ($p < 0.0001$ and $p =$

0.02, respectively) [30].

However, not all studies have shown a significant negative influence of hormonal treatment. A recent prospective longitudinal study conducted by Van Dyk et al. assessed the cognitive functions of early-stage breast cancer survivors (N = 189) who were treated with hormonal therapy (Tamoxifen or Aromatase inhibitors) at intervals of 6 months, 12 months, and 3-6 years. The authors found no cognitive differences during the follow-up period between women receiving hormonal therapy and those who did not [35]. Hurria et al. concluded that there was no significant decline in cognitive function among elderly breast cancer patients receiving Aromatase inhibitors (N = 32) when compared to healthy controls [36]. The consequences of androgen deprivation therapy (ADT) on cognitive functions in patients with prostate cancer have been examined. Although several studies did not identify significant adverse effects of ADT on cognition [37, 38]. Multiple studies have reported a relation between ADT and cognitive impairment in prostate cancer patients [39-41]. Several retrospective studies have notably investigated a potential link between ADT and neurodegenerative diseases, particularly Alzheimer`s disease. Two large analyses conducted by Nead et al. identified a positive association between ADT and the risk of Alzheimer's disease ($p = 0.021$) as well as all forms of dementia ($p < 0.001$) [42,43]. The largest population-based cohort study, which evaluated 1.2 million prostate cancer patients with a mean follow-up period of 5.5 years, found no increased risk of Alzheimer's disease or dementia among men undergoing ADT [44].

Cancer-related Cognitive Impairment after Targeted Therapy

Several trials have investigated the potential consequences of targeted therapies on cognition. Galvan et al. conducted a review on the significance of vascular endothelial growth factor (VEGF) in CNS functioning, emphasizing its role in neurogenesis and neuroprotection, as well as the potential neurotoxic effects of VEGF inhibitors on cognitive functions in cancer patients [45]. Mulder et al. assessed cognitive impairment in patients with metastatic renal cell carcinoma (RCC) or gastrointestinal stromal tumors (GIST) who were undergoing treatment with VEGFR tyrosine kinase inhibitors, specifically Sunitinib or Sorafenib (N = 30). This was compared to metastatic RCC patients who were not receiving systemic treatment (patient controls, N = 20) and healthy controls (N = 30). The study revealed a significant cognitive decline in both patient groups, particularly in executive abilities ($p = 0.005$ and $p = 0.049$, respectively) and in the domains of memory and learning ($p = 0.019$ and $p = 0.0001$ respectively). These findings suggest potential unlucky effects of VEGFR tyrosine kinase inhibitors on cognitive function [46]. Another study evaluated the cognitive effects of anti-angiogenic therapies in metastatic RCC patients (N = 75) and their liaison with fatigue. Cognitive alterations were observed in 31% of patients, particularly affecting working memory and information-processing speed [47].

Kang et al. explained the neural psychological performance and psychosoma of NSCLC patients among 113 patients. Depending on the variety of cancer therapy, the patient was classified as chemotherapy (n = 40), target therapy (n = 33), and non -treatment (n = 40). In the group that received chemotherapy or targeted therapy, 30-35% performed worse in at least one cognitive domain. There were no major differences between the three patient groups with concern to subjective or objective measures of cognitive impairment [18]. Specific cognitive impairments have not been thoroughly documented in patients undergoing cancer immunotherapy with immune checkpoint inhibitors (CPI) or chimeric antigen receptor T-cell therapy (CAR T-cell therapy). Joly et al. completed a review of the potential biological and pathophysiological consequences of immunotherapy on cognitive functions in cancer patients [48]. Immune-related neurological unlucky events associated with CPI are infrequent and varied, generally classified as grade 1–2. These events may include meningoradiculoneuritis, encephalopathies, Guillain-Barré-like syndromes, myasthenic syndromes, among others. The overall incidence of immune-related neurological unlucky events has been reported to be less than 4% with anti-CTLA-4 agents, 6% with anti-PD-1 agents, and 12% with combination therapy [49]. Studies combining precision radiotherapy and immunotherapy (CPI) in animal models have shown behavioral alterations and cognitive impairment, associated to enhanced microglial activity and modifications in proinflammatory cytokines [50].

Mechanisms of Cancer-Related Cognitive Impairment

Several mechanisms have been suggested to explain the heightened rates of cognitive alteration and emotional fluctuations observed in patients after chemotherapy. These mechanisms include systemic inflammation, disruption of neurotransmission, blood-brain barrier disruption, and functional alterations in brain regions like the amygdala and hippocampus [2,5,51]. Recent investigations have also explored the responsibility of the gut microbiota in chemotherapy-induced cognitive impairments (Fig.1).

Studies have indicated that alterations in the gut microbiota can impact physiological processes, including metabolism, cognitive and neurological functions, inflammation, and immunity [52,53]. The microbiota-gut-brain axis, a complex communication system, facilitates neurochemical connections between gut microbes and the host`s central, enteric, and autonomic nervous systems via neuro-transmitter fabrication and other pathways [53-59].

Dysregulation of this axis due to chemotherapy-induced microbial disruption can damage the microbiotas protective and immunomodulatory functions, potentially increasing the presence of harmful products from pathogenic microbes [60]. Changes in gut microbial diversity are commonly observed after chemotherapy, with a consistent trend towards decreased microbial diversity reported in several studies [61,62].

Proposed mechanisms contributing to the development of CRCI incorporate the inhibition of hippocampal neurogenesis, damage to white matter, oxidative damage, inflammatory and immune functions, decreased activity of the hypothalamic-pituitary-adrenal axis, and diminished brain vascularization and blood flow [63,64]. Additional potential mechanisms encompass direct neurotoxicity from

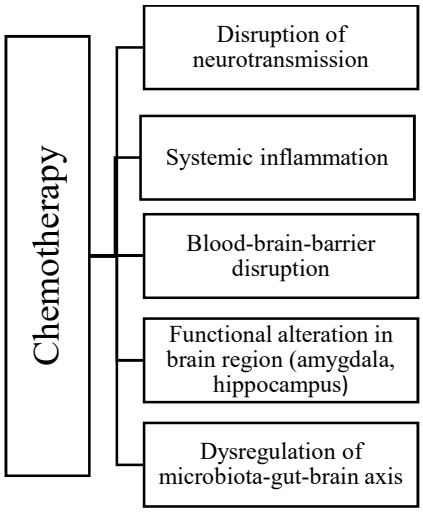

Fig. 1. Potential mechanisms of Cancer-Related Cognitive Impairment.

cytostatic agents able of crossing the blood-brain barrier, as well as hormonal changes induced by chemotherapy, which may result in cognitive impairment [65,66].

Chronic inflammation and neuroinflammatory pathways are likely leading processes in cognitive impairment. Chemotherapy disrupts cellular mechanisms and cell division, potentially increasing concentrations of inflammatory components, especially proinflammatory cytokines (e.g., TNF-alpha and IL-1, IL-6) and cytokine receptors (e.g., sTNFRI and sTNFRII), during and after treatment administration. Several reports have highlighted a relationship between cancer patients` reduced cognitive performance and inflammatory indicators [7, 67-70]. Preclinical research has assessed alterations in the expression of genes related to inflammation and the onset of CRCI [71-74]. In a recent clinical study, Oppegaard et al. assessed altered inflammatory pathways and differentially expressed genes in two separate samples of cancer patients who either announced or did not announce cognitive issues. They evaluated self-reported CRCI using the 16-item Attentional Function Index (AFI). Low cognitive function was indicated by AFI scores in about half of the patients in each group. For 357 patients (Sample 1), total RNA extracted from peripheral blood was measured by RNA-sequencing, and for 360 patients (Sample 2), microarray. A total of twelve signaling pathways exhibited significant alterations between individuals with low and high AFI scores, including five pathways connected to inflammatory processes: mTOR (mechanistic target of rapamycin), cytokine-cytokine receptor interaction, IL-17 (interleukin-17), MAPK (mitogen-activated protein kinase), and TNF (tumor necrosis factor) signaling pathways (all $p < 0.05$). This study was the first to recognize irregularities in inflammatory pathways linked to CRCI, emphasizing the significant role of inflammation in its development [74].

Role of Microbiota-gut-brain Axis Dysregulation in CRCI

The gut microbiota-gut-brain system is a complex reciprocal communication system involving gut bacteria, the enteric nervous system (ENS), and the CNS via neural, endocrine, immune, and humoral pathways [3,5,75,76]. Chemotherapy has been shown to negatively influence the composition of gut microbiota in both pediatric and adult cancer patients. Gastrointestinal (GI) issues, a common and often limiting adverse event of chemotherapy, can reduce treatment adherence and impact survival. Chemotherapy-induced gastrointestinal toxicity is caused by disruption of the intestinal flora (dysbiosis), inflammation (intestinal and systemic), and mucositis, including ulceration of the oral and gastrointestinal mucosa. Mucositis affects more than 80% of malignancy patients receiving high-dose chemotherapy [3,77,78].

Huang et al. analyzed alterations in gut microbiota configuration in 36 pediatric patients having acute lymphoblastic leukemia (ALL) treated with high-dose methotrexate (MTX), compared to 36 healthy age-matched controls. They found a 29.6 % decrease in intestinal microbes in stool samples from the ALL-group post-chemotherapy completion compared to controls [79]. Another study of ALL survivors showed MTX-induced changes in gut microbiota configuration persisting at least 9 months after chemotherapy cessation [80]. Additional studies indicate that chemotherapy reduces gut microbiota variety, contributing to mucositis, inflammation, and long-term dysbiosis [5, 81-83].

Recent interest has concentrated on the role that the gut microbiota plays in CNS function, cognition, and behavior; and alterations in the gut microbiota are believed to play a role in the development of various neurological disorders, including Alzheimer`s disease, that are accompanied by alterations in cognition and emotional behavior [84], autism spectrum disorders [85], Major Depressive Disorder, Parkinson`s disease, and schizophrenia [86-89] (Fig. 2). These disorders are similarly connected with neuroinflammation. Similarly, chemotherapy-induced intestinal mucositis and reduced GI microbiota variety may influence CNS functions and contribute to CRCI through various pathways, including neural and endocrine signaling via the enteric nervous system, and systemic inflammation [83, 90-95].

Conclusion

The microbiota-gut-brain axis performs a leading role in the advancement of many neurological disorders. Present studies have illustrated that chemotherapy can initiate toxicities within the enteric apprehensive framework and lead to changes in gut microbiota, possibly impacting neurocognitive work. Further investigation is essential to fully understand the impacts of cancer and its treatments such as radiotherapy, chemotherapy, and immunotherapy on the composition of gut microbiota in both cancer patients and pre-clinical rodent models. : The furthers studies must be undertaken as (i) Clinical trials testing probiotics, prebiotics, or fecal microbiota transplantation in mitigating CRCI, (ii) Longitudinal microbiome profiling in cancer patients to identify dysbiosis patterns linked to cognitive decline, (iii) Mechanistic studies in animal models to establish causality between specific microbial alteration and neuroinflammation.

Declaration of Competing of Interest

The authors declare that they have no conflicts of interest.

Author Contributions

SA wrote the manuscript. NBA was responsible for the critical revision. All authors contributed to the article and approved the submitted version.

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