Neurological Sciences (2019) 40:1759–1774
https://doi.org/10.1007/s10072-019-03898-0

REVIEW ARTICLE

Neuropsychological disorders in non-central nervous system cancer: a review of objective cognitive impairment, depression, and related rehabilitation options

Fulvia Di Iulio[1] · Luca Cravello[2] · Jacob Shofany[1] · Stefano Paolucci[1] · Carlo Caltagirone[1,3] · Giovanni Morone[1]

Received: 6 June 2018 / Accepted: 12 April 2019 / Published online: 2 May 2019

Abstract

Aim The objective of the present review was to systematically characterize the types of cognitive impairment that are found in different non-brain types of cancer as measured by objective and validated tests, and also to further examine depression and cognitive function in cancer patients and explore their available rehabilitation treatments.

Results A total of 29 articles were reviewed. Most of these studies suggest that chemotherapy as well as the combination of chemotherapy and hormonal therapy can influence cognition in different types of cancer patients. Breast cancer patients appear to be the most affected in neuropsychological function, specifically in terms of cognitive impairment and reduced quality of life, as compared to other non-brain solid tumours. Overall, the most impaired functions were verbal ability, memory, executive function, and motor speed.

Conclusion Chemotherapy-related cognitive dysfunction remains under-recognized and undertreated. The various studies reported differing and non-homogenous findings with mixed results, obtained by self-reporting and web-assisted assessment, with other confounding factors such as age and depression during both cancer diagnosis and treatment. An objective neuropsychological assessment is fundamental to avoid underestimation of the extent of chemobrain. Self-reported and web-assisted assessment may ultimately result in confusion between the neuropsychological signs of chemobrain versus those of depression.

Keywords Chemobrain · Rehabilitation · Neuropsychological disorders · Depression · Cancer

Introduction

Cancer is an important cause of death throughout the world and its incidence is dramatically increasing [1]. In the last few decades, screening programmes have improved detection of cancer at earlier stages, leading to greatly increased chances of successful treatment and longer life expectancy. The prolonged lifespan of cancer patients has however resulted in the onset of long-term sequelae, such as cognitive impairment, psychological distress, and reduced quality of life, which are related to both disease evolution and side effects of antineoplastic agents [2, 3]. In fact, cognitive disorders are frequently associated with the effects of chemotherapy [4]. This cognitive impairment, commonly called "chemobrain" or "chemofog", is typically characterized by deficits in memory, attention, language and visuospatial functions, and occurs in 17–75% of treated patients [5, 6] of which one third may suffer long-term effects. Moreover, recent studies have also found that cognitive impairment may manifest prior to chemotherapy [7, 8]. Many other studies have suggested an association between cognitive impairment and chemotherapy, although other factors associated with the diagnosis and treatment of cancer may contribute [9], such as biological and psychological factors [10]. Furthermore, recent magnetic resonance imaging (MRI) studies investigating cognitive impairment in cancer patients found reduced grey matter density in the frontal and temporal brain areas of these

✉ Giovanni Morone
g.morone@hsantalucia.it

[1] IRCCS Fondazione Santa Lucia, Rome, Italy

[2] Centro Regionale Alzheimer ASST Rhodense, Passirana di Rho Hospital, Milan, Italy

[3] Università degli Studi di Roma Tor Vergata, Rome, Italy

patients [11] and also in the left caudal lateral prefrontal region, which is correlated to the effects of chemotherapy and/or disease severity [12]. In addition, some authors also observed that in pre-treated (prior to chemotherapy) patients, there is a widespread decrease in white matter volume in the bilateral orbital frontal regions. This finding is indicative of subtle frontal hypometabolism and is consistent with the results of neuropsychological testing in particular in the cognitive domains of executive functioning: working memory, and divided attention [13].

Although emerging evidence indicates that cancer and cancer treatments such as chemotherapy may contribute to cognitive impairment, it is still unclear whether chemobrain is related to the disease itself or is an effect of chemotherapy. Numerous reviews have focused attention on self-perceived cognitive deficits or web-based assessments that occur in breast cancer [9, 14]. However, the validity of self-perceived and web-based assessments is highly questionable. As recently demonstrated, patients' self-perception of mental decline is unrelated to objective cognitive deficits. Cancer patients negatively judge their cognitive performances if they have a negative emotional functioning [15]. Indeed, a previous review highlighted the failure to consistently find an association between subjective and objective measures of cognition [16]. Nevertheless, there are no reviews that have analysed the neuropsychological deficits found in different types of cancer with objective (not self-perceived) instruments. This lack of objective measures encourages reflection and consideration of the best direction and methodologies for this research. Given that both chemotherapy and the pre-treatment disease are associated with cognitive impairment in different types of cancer patients, understanding these factors and their associations with cognitive disorders and depression is a main goal of oncological research [17]. The aim of this paper was to review the existing literature on cognitive impairment focusing specifically on different types of cancer and then examine depression and cognitive function in cancer patients as measured with objective and validated tests.

Methods

Search limits

In order to clarify the status of the evidence for the topic of neuropsychological disorders in patients with cancer, we conducted detailed searches of the published medical literature with a review of the Medline (PubMed and the Cochrane library) databases between January 1995 and December 2016.

For our purposes, we used various combinations of the following keywords: "cognitive disorders", "chemobrain", "neuropsychological disorders", "cancer" and "depression".

Article inclusion criteria were as follows: (1) types of studies: randomized controlled trials (RCTs) were eligible, as were observational studies only if they were published as full paper; (2) types of participants: studies enrolling adult (older than 18 years) patients with a history of non-brain cancer and treated by adjuvant therapy; (3) types of interventions: studies enrolling patients with cancer and treated by adjuvant therapy and/or radiotherapy and/or surgery; (4) types of outcome measures: articles with a specific outcome with regard to cognitive disorders and/or articles with a specific outcome with regard to depression in cancer. Exclusion criteria were as follows: (1) articles not written in English; (2) articles on paediatric cancer; (3) articles with a primary focus on brain tumours due to the direct consequences on cognitive impairment; (4) articles on chemotherapy effects in mouse models; (5) articles regarding cognitive post-cancer impairment assessed with self-perceived instruments.

Selection process

Search terms were used to extract records limited to the subject of cognitive disorders in patients with cancer. An additional search was performed to identify papers specifically focused on chemobrain in elderly patients with cancer. The criterion of "adherence to the keywords" of a paper was defined as the presence of all the above-mentioned keywords in either the text or the abstract. Further studies were sought by means of manual search of secondary sources, including references from primary articles. Conceptually related articles were included as well. Heterogeneous studies on paediatric oncology, brain tumours, articles with scarce methodology and using a self-rating memory scale were excluded. All the articles were initially selected and judged by F.d.I. and L.C as possible candidates for the review because they met the above-mentioned criteria. To find additional publications, we also hand-searched relevant journals and the bibliographies of all the important articles. We found 29 articles suitable for review due to their adherence to the keywords. All other articles cited in the review were conceptually correlated to the topic of neuropsychological disorders in cancer patients.

Neuropsychological disorders in cancer patient

A total of 29 studies evaluating neuropsychological functions in cancer patients were selected (Fig. 1). Among these, one paper investigated neurocognitive functions in long-term survivors of ovarian cancer [18]. Three studies evaluated neurocognitive abilities of small cell lung cancer (SCLC) patients before and

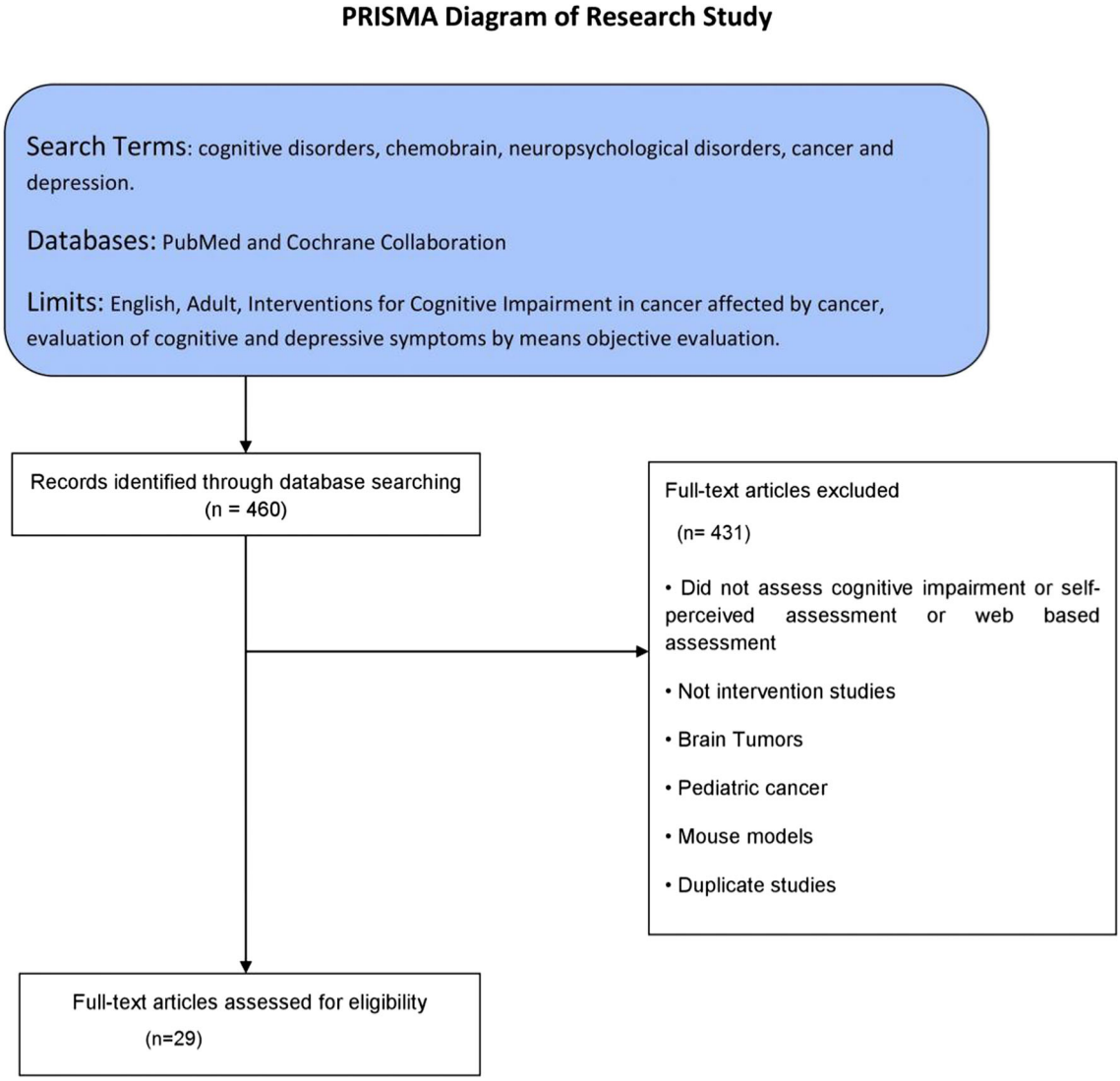

Fig. 1 PRISMA diagram of the research study

after receiving chemoradiation and prophylactic cranial irradiation (PCI) [19–21]; four studies were on assessing patients with testicular cancer with neuropsychological tests prior and after adjuvant therapy [22–25]; the remaining 21 papers were on breast cancer and all the studies assessed patient before chemotherapy, hormonal therapy or radiation [7, 26–44]. For the characteristics of the selected studies, see Table 1. Some researchers investigated neuropsychological abilities just after chemotherapy, while others investigated both before and after chemotherapy to explore the manifestation of cognition deficits during treatments. Other studies compared patients with standard-dose versus high-dose chemotherapy and/or after different types of therapy to investigate their effects on cognition. Finally, some articles have compared patients at different stages of cancer (stage 1-2-3). The neuropsychological domain was evaluated using different methods in the different studies reviewed herein (Table 1).

Adjuvant therapy and cognitive impairment: an effect of the disease or the treatment?

Exploration of the relationship between cognitive function, health/disease and treatment-related factors in cancer patients is limited. Patients with cancer may develop cognitive deficits more frequently than in healthy subjects, whether induced by disease-related factors, such as psychological factors (depression, anxiety, fatigue), or related to the effects of chemotherapy.

There is some evidence that patients exhibit cognitive dysfunction before receiving chemotherapy [8–35], which suggests that certain pre-treatment factors may play an important role, in particular fatigue, depression, anaemia, genetic variability, tumour biology and the reaction of the immune system to a tumour, which were all associated to cognitive dysfunction [45, 46].

Table 1 Study characteristics

Author	Sample	Mean age	Type of cancer	Therapy	Timing (before and/or after therapy)	% of patients of cognitive impairment	Neuropsychological test	Abilities evaluated
Correa et al. (2010) [18]	48 women (22 patients disease free 26 with recurrent disease)	61.8 60.3	Invasive epithelial ovarian cancer	Chemotherapy Hormonal therapy Treatment-induced menopause	5–10 years from diagnosis	28% Attention, executive function and memory	Digit Span BTA TMT A-B Trails A & B HVLTR	Attention Executive function Learning and memory
Meyers et al. (1995) [19]	46 patients (21 untreated 25 treated)	54.7 54.9	Small cell lung cancer	Chemotherapy and Radiation therapy	Before chemoradiation	70–80% Memory deficit 38% Frontal lobe executive functions	WAIS Verbal and non-verbal reasoning TMT A-B WCST VSR BVRT GS, GP	Intellectual Visual-perceptual Frontal lobe executive function Language Memory Motor dexterity
Komaki et al. (1995) [20]	30 patients	61	Small cell lung cancer	Chemotherapy and thoracic irradiation PCI	After chemotherapy and thoracic irradiation After 1 year of PCI	95% Visual and verbal memory Frontal lobe dysfunction Fine motor incoordination No decline	WAIS Verbal and non-verbal reasoning TMT A-B WCST Token Test VSR BVRT GS, GP	Intellectual Visual-perceptual Frontal lobe executive function Language Memory Motor dexterity
Grosshans et al. (2008) [21]	96 patients	59	Small cell lung cancer	Chemotherapy Thoracic radiation (3 patients treated with irradiation, chemotherapy)	After chemotherapy and thoracic irradiation 450 days after PCI	40% Executive function and learning memory	VSTR BVR WCST TMT A-B Similarity Block Design WAIS COWAT Token Test GS, GP, FT	Learning and memory Executive function Verbal and visual Reasoning Attention Processing speed Motor coordinator
Schagen et al. (2008) [22]	182 patients (70 treated with chemotherapy 57 treated with radiotherapy 55 surgery only untreated)	32.1 38.9 34.4	Testicular cancer	Chemotherapy Radiotherapy	After chemotherapy and radiotherapy	No significant difference between three patients groups	Not reported	Attention Visual and verbal memory Processing speed Verbal/motor functioning
Pedersen et al. (2009) [23]	72 (36 treated 36 untreated)	38.3 42.0	Testicular cancer	Chemotherapy	2–7 years after chemotherapy	No significant different between two groups	RAVLT RCFT WAIS-III LM-CD-SS-DS-LN TMT A-B ANIMALS Fwords Nwords SCWT Interference Score	Learning and memory Processing speed Working memory Visuospatial construction Verbal fluency Response inhibition

Table 1 (continued)

Author	Sample	Mean age	Type of cancer	Therapy	Timing (before and/or after therapy)	% of patients of cognitive impairment	Neuropsychological test	Abilities evaluated
Skaali et al. (2009) [24]	122 (31 NO CHEMO, 38 ONE CHEMO, 53 MULTIPLE CHEMO)	32.0 35.0 30.0	Testicular cancer	Chemotherapy	Before treatment 1 year after end of treatment	No negative effect of systemic chemotherapy at 1 year follow-up	HVLT-R SWM PAL CRT GP TMT A-B C-W-I 1-2 C-W-I 3-4 Word Fluency SOC IED Set Shift	Learning and memory Attention, concentration and working memory Speed of information processing Executive functions Motor function
Wefel et al. (2011) [25]	69	31.0	Testicular cancer	Chemotherapy	Baseline, 1 week after completion of chemotherapy 3 months after baseline for no chemotherapy patients, 12 months after baseline for all patients	46% impaired at baseline on fine motor dexterity verbal learning and executive function	HVLT T 1-3 WAIS-R DSpan WAIS-R DSymbol TMT A-B COWA GPD GPND	Learning and memory Attention, Psychomotor speed Executive and motor function Language
Van Dam et al. (1998) [26]	104 (34: high-dose chemotherapy, 36: standard-dose chemotherapy, 34: untreated)	45.5 48.1 46.1	Breast cancer	Chemotherapy	After chemotherapy	The high-dose chemotherapy group had 3.5 times elevated risk in comparison with the patients treated with standard-dose chemotherapy	REY 15 words Complex Figure WAIS-R DSpan WAIS-R DSymbol TMT A-B Stroop test Word Fluency FFT	Memory attention and concentration, Mental flexibility, Speed of information processing, Verbal function, Visuopatial motor function
Brezden et al. 2000 [27]	107 (31: during chemotherapy, 40: at least 1 year after chemotherapy, 36: healthy controls)	49.0 46.0 41.5	Breast cancer	Chemotherapy	During chemotherapy and 1 year after chemotherapy	Memory and language domains Significant difference between first group and controls. An higher number of moderate or severe cognitive impairment in groups A and B than in controls	High Sensitivity Cognitive Screen	Memory Language Visual-motor Spatial Attention and concentration Self-regulating and planning
Tchen et al. 2003 [28]	100	48	Breast cancer	Chemotherapy and hormonal therapy	After chemotherapy	Patients scored worse on language attention and concentration, self-regulation and planning	High Sensitivity Cognitive Screen Trail Making A-B Conner's Continuous Performance Test	Memory Language Visual-motor Spatial Attention and concentration Self-regulating and planning

Table 1 (continued)

Author	Sample	Mean age	Type of cancer	Therapy	Timing (before and/or after therapy)	% of patients of cognitive impairment	Neuropsychological test	Abilities evaluated
Castellon et al. 2004 [7]	17: local therapy 36: adjuvant therapy (−/+ tamoxifen)	48.3 46.8	Breast cancer	Chemotherapy and hormonal therapy	After chemotherapy	Subject treated with chemotherapy scored significantly worse than those treated with surgery only on visual memory, visuospatial and verbal learning domain	COWAT (F-A-S) Animal Fluency Logical memory I-II CVLT WMS-R, Rey Complex Figure, Recall Block Design, Rey Complex Figure Copy Digit Symbol, Trails A-B CalCAP PASAT, Stroop interference	Verbal fluency Verbal memory Verbal learning Visual memory Visuospatial function Psychomotor speed Reaction time Executive attention
Shilling et al. (2003) [29]	94	63.1	Breast cancer (early stage)	Hormonal therapy plus radiotherapy (67%)	After therapy (hormonal and radiotherapy)	Specific impairment on verbal memory	WAIS-R DSpan, AVLT 1-7, Complex Fig. C-R, Letter-number WAIS-R DSymbol Stroop test NARD KDCT	Verbal and visual memory Working memory Executive function Working memory IQ Processing speed
Shilling et al. (2005) [30]	50	51.10	Breast cancer (early stage)	Chemotherapy	Baseline 6 months after 18 months after	Verbal and working memory	WAIS-R DSpan, AVLT 1-7, Complex Figure C-R WAIS-R DSymbol Stroop test NARD	Verbal and visual memory Working memory Executive function Working memory FSIQ Processing speed
Scherwarth et al. (2006) [31]	47 (24 high-dose and 23 standard-dose therapy)	53.3 51.8	Breast cancer	Chemotherapy	Baseline 5 years after chemotherapy	8% of high-dose and 13% of standard-dose chemotherapy patients had globalimpairment Standard-dose slightly more impaired of high-dose patients	VLMT, ROCFT WMS-R TMT, TAP RWTLPS HAWIE-R	Memory Attention Executive function
Jansen et al. (2008) [32]	30	49.6	Breast cancer	Chemotherapy	Before chemotherapy and After 4 cycles of chemotherapy	13% cognitive impairment Significant decrease in visual spatial skill and in total cognitive scores following chemotherapy (significant improvement in executive function)	RBANS Stroop Test GP	Memory, Visuospatial skill, Language, Attention Executive function Motor function

Table 1 (continued)

Author	Sample	Mean age	Type of cancer	Therapy	Timing (before and/or after therapy)	% of patients of cognitive impairment	Neuropsychological test	Abilities evaluated
Jansen et al. (2010) [33]	71 (22 only AC, 49 AC + taxane)	50.9 50.7	Breast cancer	Chemotherapy, Chemotherapy plus taxane	Before chemotherapy 1 week after AC and 1 week after taxane 6 months after all type chemotherapy	23% cognitive impairment 52% decline in visuospatial skill, motor function, attention, immediate memory and language improvement to baseline levels	RBANS Stroop Test GP	Memory, Visuospatial skill, Language, Attention Executive function Motor function
Ahles et al. (2010) [34]	110 patients Stage 1–3 22 Patients Stage 0	54.1 58.8	Breast cancer	Chemotherapy Radiation or Hormonal therapy	Before therapy	All groups scored within normal range Patients with Stage 1–3 scored significantly lower than healthy controls on the Reaction Time domain	CVLT-II, WMS-III PASAT ST WASI, WRAT-3, VF WAIS-R DSymbol, TMT, CWIT GP, CPT CPT WASI	Verbal and visual memory Working memory Sorting Verbal ability Processing speed Distractibility Reaction time Block design
Ahles et al. (2008) [35]	60 chemotherapy patients 72 no chemotherapy patients	51.7 56.6	Breast cancer	Chemotherapy	Baseline 1 month after treatment 6 months after treatment 18 months after treatment	Processing speed	CVLT-II, WMS-III PASAT ST WASI, WRAT-3, VF WAIS-R DSymbol, TMT, CWIT GP, CPT CPT WASI	Verbal and visual memory Working memory Sorting Verbal ability Processing speed Distractibility Reaction time Block design
Vernacombe et al. (2009) [36]	136 chemotherapy patients	49.38	Breast cancer	Chemotherapy	Baseline After chemotherapy	16% verbal learning and memory, abstract reasoning and motor coordination	AVLT, WMS-III WMS-III D Backword SDMT TEA WMS-III, Stroop Test, DKEFS, COWAT PP	Verbal learning and visual memory Working memory Processing speed Attention Executive function Motor coordination
Schilder et al. (2009) [37]	30 using tamoxifen 50 using exemestane	57.9 58.5	Breast cancer	Chemotherapy	Two years after completion of chemotherapy	Tamoxifen use is possible related worse verbal functioning Exemestane use is possibly related to slower manual motor speed	RAVLT, WMS-III WMS-III STROOP CARD1-2, TMT A STROOP CARD3, TMT B FR-TIME FR-TAPPING LF, CF	Verbal and visual memory Working memory Attention and concentration Mental flexibility Speed of information processing Manual motor speed Verbal fluency
	41 chemotherapy	50.3	Breast cancer	Chemotherapy	Before and post treatment		RAVLT, CFT, VFT	Learning and memory

Table 1 (continued)

Author	Sample	Mean age	Type of cancer	Therapy	Timing (before and/or after therapy)	% of patients of cognitive impairment	Neuropsychological test	Abilities evaluated
Quesnel et al. (2009) [38]	40 radiotherapy	57.7		and Radiotherapy		Significant declines of both groups on learning and verbal memory. Chemotherapy group have a specific negative effect on verbal fluency	WAIS-R D Span, DSymbol, TMT A TMT B, VFT	Attention and Executive function Processing Speed
Wefel et al. (2004) [39]	84	50.4	Breast cancer	Radiotherapy	Before therapy	18% verbal learning 25% memory function	HVLT, VSRT, NVSRT, ROCFT WAIS-R D Span, DSymbol, Arith, WAIS-III LN, MC, TMT A MAE-COWA, BNT, MAE-SC TMT B, CT, WAIS-III Sim WAIS-R BD, ROCFT Copy, JLO GS, GP	Memory Attention Language Executive Visuospatial Motor
Wefel et al. (2004) [39]	18	43.7	Breast cancer	Chemotherapy Radiotherapy	Before Short-term after Long-term after chemotherapy	33% cognitive impairment 61% cognitive impairment 50% cognitive impairment and 50% remained stable	VSRT, NVSRT, ROCFT WAIS-R DSpan, DSymbol, Arith, TMT A MAE-COWA, BNT, MAE-SC TMT B, CT, WAIS-III Sim BD GS, GP	Memory Attention Language Executive Visuospatial Motor
Wefel et al. (2010) [40]	42	48.8	Breast cancer	Standard-dose chemotherapy	Before During Shortly after chemotherapy 1 year after completion chemotherapy	21% cognitive impairment 65% cognitive impairment 61% cognitive impairment 71% cognitive impairment and 29% new onset decline	HVLT WAIS-R DSpan MAE-COWA, TMT B WAIS-R DSymbol, TMT A	Learning and Memory Attention Executive Processing speed
Schagen et al. 2002 [41]	22 high-dose patients 23 standard-dose patients 31 conventional chemotherapy patients	47.0 50.4 50.3	Breast cancer	Chemotherapy	Baseline 4 years after chemotherapy	23% impaired 13% impaired 26% impaired Improvement in performance in all chemotherapy groups	RAVLT, WMS-III, ROCFT WAIS-R DSpan, DSymbol, TMT A TMT B, Stroop Test, WF FFTT, FVR, FBCT, FVST, DART	Learning and memory Attention Executive Processing speed
	101	48.6	Breast cancer	Chemotherapy	Baseline		WMS-I,	Memory

Table 1 (continued)

Author	Sample	Mean age	Type of cancer	Therapy	Timing (before and/or after therapy)	% of patients of cognitive impairment	Neuropsychological test	Abilities evaluated
Hermelink et al. (2007) [43]					After the end of neoadjuvant chemotherapy	Patients means below the test norms 5/12 cognitive test Overall improvement	WMS-R DSpan, TMT A RWT TMT B, CT, WAIS-WMS-R DSymbol	Attention Language Executive Psychomotor function
Donovan et al. 2005 [42]	60 chemotherapy plus radiotherapy patients 83 radiotherapy patients	52.33 57.65	Breast cancer	Chemotherapy and radiotherapy	6 months after completion treatment	No statistically differences between women who received chemotherapy and those who did not	CVLT, WMS-III WAIS-R DSpan, TMT A WAIS-R DSymbol, TMT B FOT COWA	Episodic Memory Attention Complex cognition Motor Language
Debess et al. (2010) [44]	75 patients chemotherapy 26 patients tamoxifen 19 patients no medical treatment	47.2 56.2 49.7	Breast cancer	Chemotherapy or adjuvant tamoxifen	Baseline After 6 months completion of chemotherapy	No difference between patients and healthy controls	VLT CST LDCT SCWT LDCT	Episodic memory Simple and complex attention Cognitive speed and flexibility Visual scanning Executive function

Legend: *Digit Span*, Digit Span of the Wechsler Intelligence Scale; *BTA*, Brief Test of Attention; *Trails A & Trails B*, Trail Making Test Parts A & B; *HLVTR*, Hopkins Verbal Learning Test-Revised; *WCST*, Wisconsin Card Sorting Test; *VSR*, Verbal Selective Reminding; *BVRT*, Benton Visual Retention Test; *VSRT*, Verbal Selective Reminding Test; *BVR*, Benton Visual Retention Test; *COWAT*, Controlled Oral Word Association; *RAVLT*, Rey Auditory Verbal Learning Test; *RCFT*, Rey Complex Figure Test; *WAIS-III*, Wechsler Adult Intelligence Scale third edition; *CD*, subtests Digit Symbol-Coding; *SS*, Symbol Search; *A*, Arithmetic; *DS*, Digit Span; *LN*, Letter-Number Sequencing; *LM*, Wechsler Memory Scale third edition subtest Logical Memory; *SCWT*, Stroop Color and Word Test; *SWM*, Spatial Working Memory; *PAL*, Paired Associates Learning; *CRT*, Choice Reaction Time; *CW*, Color-Word Interference Test; *SOC*, Stockings of Cambridge; *IED*, Intra-Extra Dimensional; *CVLT*, California Verbal Learning Test; *CalCAP*, California Computerized Assessment Package; *PASAT*, Paced Auditory Serial Addition Test; *AVLT*, Auditory-Verbal Learning Test; *NART*, National Adult Reading Test; *KDCT*, Kendrick Digit Copying Task; *VLMT*, Verbaler Lern- und Merkfähigkeitstest- Auditory Verbal Learning Test—German modified version; *WMS-R*, Wechsler Gedächtnistest-revidierte Fassung—German adaptation of the Wechsler Memory Scale-Revised; *ROCFT*, Rey-Osterrieth Complex Figure Test; *RWT*, Regensburg Word Fluency Test; *LPS*, Leistungsprüfsystem—Achievement Measure System; *HAWIE-R*, Hamburg-Wechsler-Intelligenztest für Erwachsene, German Version; *RBANS*, Repeatable Battery for the Assessment of Neuropsychological Status Update; *CVLT-II*, California Verbal Learning Test-II; *WMS-III*, Wechsler Memory Scale-III; *PASAT*, Paced Auditory Serial Addition Test; *CPT*, Continuous Performance Test; *WASI*, Verbal Fluency Test; *CWIT*, Color-Word Interference Test; *TEA*, Test of Everyday Attention; *SDMT*, Symbol Digit Modalities Test; *DKEFS*, Delis-Kaplan Executive Function Scale; *COWAT*, Controlled Oral Word Association Test; *HLVT*, Hopkins Verbal Learning Test; *MAE*, Multilingual Aphasia Examination; *COWA*, Controlled Oral Word Association; *NVSRT*, Nonverbal Selective Reminding Test; *LDCT*, Letter Digit Coding Test

On the other hand, there is also evidence of chemotherapy having a direct effect on neurological function, as imaging studies have identified cerebral atrophy, cortical calcification [47] and decreased metabolic activity in numerous brain regions after chemotherapy [48].

Among the factors associated with cognitive functional impairment in cancer, one of the most well-known is serum haemoglobin levels, which significantly predicted impairment of multiple cognitive measures [36]. It was further found in another study that anaemia may detrimentally affect cognitive performance [49]. Indeed, the loss of cognitive function may be due to anaemia-induced cerebral hypoxia. Systemic hypoxia (evaluated in terms of haemoglobin levels) and proneoangiogenic cytokines (evaluated in terms of circulating bFGF-Fibroblast Growth Factor values) were recently well described as the mechanism that cause anaemia in patients with solid cancer [50], underlying that there are mechanisms involving malnutrition, low iron levels and cytokine-mediated factors. The authors argued that there is anaemia with reduced iron availability due to alterations in the levels of hepcidin, the key regulator of iron homeostasis. Increased hepcidin levels block the ferroportin-mediated release of iron from enterocytes and macrophages [51]. One study examined the acute effect of chemotherapy on cytokine levels founding an increased level of IL6, IL8 and IL 10 [52]. Thus, the cytokine mechanism could explain the manifestation of cognitive impairment in cancer patients before undergoing treatment [8, 52]. Inflammatory cytokines inhibit proliferation and differentiation of erythroid progenitor cells and blunt endogenous erythropoietin production in the kidney. In addition, reduced sensitivity to erythropoietin, a reduced life span of erythrocytes, solid tumours or metastases infiltrating the bone marrow, and myelosuppressive effects of chemotherapies can impair normal hematopoiesis [51]. In some cases, a specific paraneoplastic syndrome has been reported that might lead to cancer-related microangiopathic haemolytic anaemia with Coombs-negative haemolytic anaemia with schistocytes and thrombocytopenia [53]. On the other hand, decline of cognitive function is also present after or during chemotherapy. Chemotherapy and chemotherapy-related neurotoxicity is associated with the release of proinflammatory cytokines, substances related to sickness behaviour (e.g. decreased ability to concentrate). Cytokine-induced sickness behaviour is associated with cognitive disturbance, fatigue and depression [54]. Although not extensively studied, there is evidence that standard-dose chemotherapy is associated with increases in cytokine levels.

Some other probable mechanisms for chemotherapy-associated changes in cognitive function have been considered. Firstly, chemotherapy has been associated with DNA damage and telomere shortening, both of which have been implicated in neural degeneration and development of neurodegenerative disorders with cognitive components. There is evidence for oxidative DNA damage in peripheral blood lymphocytes after chemotherapy for breast cancer and increased number of point mutations in mitochondrial DNA in patients with various cancer diagnoses treated with chemotherapy with or without radiation therapy [55]. Secondly, oestrogen and testosterone levels can be reduced following to chemotherapy and as a result of hormonal treatments for cancer such as tamoxifen for breast cancer, and androgen ablation in prostate cancer. Reduction in hormonal levels has been associated with cognitive decline even in cases without chemotherapy [56, 57]. Research also supports the neuroprotective and antioxidant effects of both oestrogen and testosterone and the importance of oestrogen for maintaining telomere length [58, 59]. Even a particular genetic feature has been studied as mechanism induced cognitive changes. In particular, the *APOE* E4 allele has been associated with worse cognitive performance in cancer survivors, in particular with regard to the visual memory and spatial domains. The reduced ability to repair micro blood vessels was indicated as a possible explanation for the relationship between APOE e4 and the reduced cognitive response to brain damage [60].

Neuropsychological symptoms and depression

Cognitive function could be influenced by the presence of depression. One out of two cancer patients reports psychiatric disorders, especially depression [2]. Despite the high prevalence of depressive disorders in cancer patients, the topic of depression in cancer is still not well explored. Depression can occur in the form of major depressive disorder or minor depressive disorder and depression is equally distributed across the genders [61]. There are, however, forms of depression which may be present in patients with medical comorbidity, but which are "subsyndromal" or "subthreshold". Subthreshold depression is below the threshold of even a minor depressive disorder diagnosis and thus may be under-recognized. In fact, the average rate of major depressive disorder in cancer is around 25% during the clinical course of the illness and is accompanied by a small number of symptoms. Also, for the diagnostic assessment of mood in cancer patients, it should be considered that many somatic symptoms, such as anorexia, weight loss, low energy and sleep disturbances, are similar to those of cancer itself [62, 63]. Therefore, they may be easily misattributed to cancer and not to depression [64]. For this reason, several authors have proposed exclusion of these somatic symptoms from a depression diagnosis in cancer patients or substitution of them with other non-somatic symptoms [65, 66]. It becomes apparent that depression in cancer patients may have a peculiar phenomenology, and psychological depression is thought to be a predictor of poor survival among cancer patients.

Interestingly, anxiety seems to be the symptom that characterizes cancer diagnosis, whereas depression is more common after medical treatment [67].

Relationship between neuropsychological disorders and depression

Cognition may be affected by the presence of depression. Indeed, a diminished ability to think or concentrate, or make decisions, is among the depressive symptoms. Thus, due to the overlap between cognitive deficits and depressive symptoms, the former might be misattributed to depression. Although many research groups have assessed depression in cancer patients since the 1960s, studies that have explored the relationship between depression and cognition are sparse. Vearncombe et al. suggested that psychological factors might increase the vulnerability of breast cancer patients to cognitive impairment after chemotherapy [36]; however, several prospective studies have generally found no significant association between psychological distress and objective cognitive performance [40, 43, 68]. In fact, many studies have explored the association between depression and self-reported cognitive function, but in most cases self-impression did not correlate with objective neuropsychological testing [33, 57]. In particular, one study found that the 26% of patients that had distress (due to depression and anxiety) were more likely to be cognitively impaired [39]. Recently, some studies have found that depressive symptomatology was present in patients, but not significantly correlated with any cognitive tests at baseline [38] or in the acute and late intervals between patients with and without decline [40]. In line with this evidence, cognitive test performance was not related to anxiety and depression [32, 37], even when high Beck Depression Interview scores were significantly associated with self-reported cognitive failure [7, 29, 37]. In contrast, a recent study found higher levels of psychological distress were associated with poor cognitive function in breast cancer patients receiving chemotherapy [69]. However, the authors did note that the discrepancy of their results with previous studies could be due to the small number of participants in the study. Even in patients with testicular cancer, mood (depression and anxiety) appears to have a limited impact on decline of cognitive function [22, 24, 25]; one single study found that depression (evaluated with BDI-II) associated with poorer performance for working memory (WAIS-III LN) following chemotherapy [23]. However, according to several researches in the area of SCLC, depressive illness is significantly associated with diagnoses of lung cancer and should not be underestimated [70], and moreover this depression is common and persistent, especially in patients with more severe symptoms or functional limitations [71]. These last studies highlight the need to recognize psychological morbidity in order to improve the quality of life of lung cancer patients, but the question of a possible association between cognition and depression in this type of cancer remains unresolved. There may be a different explanation for these inconsistencies. Firstly, depression symptomatology is assessed with different scales, and often some of the psychological assessments used are not able to diagnose major or minor depressive disorder or subclinical depression. Thus, it is necessary to begin evaluation of depression with instruments able to diagnose clinical mood disorders. Secondly, even if depressive symptoms are actually assessed, in several studies they are mostly analysed and significantly associated with cognitive self-impression [34]. However, no relationship has been found between neuropsychological evaluations and self-reported cognitive difficulties [27, 44, 72]. In fact according to Shilling and Jankins, the proportion of patients receiving chemotherapy reporting problems with cognitive functions after chemotherapy was far greater than those objectively identified to have cognitive impairment [72]. However, it is possible that perceptions of cognitive difficulties are in fact correlated with psychological distress, in cancer patients receiving chemotherapy, and may also occur in depressive disorders in terms of memory and concentration abilities. Such information could help clinicians, neuropsychologists to better understand patients' cognitive difficulty, as they can then feel and adjust to them more effectively [73, 74]. Finally, certain cancer populations might be more vulnerable to depression than others population: patients with oropharyngeal, pancreatic, breast and lung cancer have higher reported rates of depression than those with colon, gynaecologic or lymphoma cancer [75]; however, it should be noted that these research studies did not all assess depression and neuropsychological functions at the same time point. Studies on the effect of chemotherapy and other therapies on cognitive function and mood are important to better understand their relationship and their impact on the quality of life in cancer survivors. Taken together, these finding seem to indicate that depression is frequent, but under-recognized and undertreated among cancer patients [76], despite its prevalence and the degree of suffering it inflicts on cancer patients. Moreover, depression seems to be associated with minimal cognitive impairment, and as such, cognitive dysfunction in cancer patients cannot be explained exclusively by the presence of depression [77]. Cognitive impairment and depression influence the quality of life of cancer patients as well as the course of their treatment. The prevalence of depression in cancer is now recognized to be high, and is thought to influence both morbidity and the course of cancer treatment in patients [78]. Brain dysfunction in cancer patients, is indeed, complicated by chemotherapy-related depression, and anxiety, which can also contribute to poor cognitive performance [79]. Risk factors that have been described for cognitive impairment after cancer and cancer treatments are as follow: age, lower pretreatment intelligence quotient and the apolipoprotein E genotype (which is also associated with Alzheimer disease) [60].

For all these reasons, a neuropsychological and depression assessment should be considered before and during the course of cancer treatment as separate conditions that they need to be addressed with a neuropsychological and psycho-diagnostical battery.

Rehabilitation for cancer- and treatment-related cognitive impairment

Several interventions to reduce cognitive dysfunction related to cancer treatment in patients were recently described: behavioural strategies, physical activity, neuromodulation strategies and pharmacotherapy [80]. Cognitive rehabilitation refers to a clinic-based, therapeutic programme aimed at improving cognitive abilities, functional capacity and real-world skills. Cognitive rehabilitation programmes can be in inpatient or outpatient setting and involve patients meeting individually and/or in groups with a trained clinician (typically a neuropsychologist, psychologist, speech and language pathologist or occupational therapist). Cognitive rehabilitation can also be effective for managing psychological comorbidities, such as anxiety and depression experienced during cancer diagnosis and treatment. Von Ah et al. evaluated the preliminary efficacy and satisfaction/acceptability of group training or improving memory or processing speed as compared to wait list control patients in cohort of 82 breast cancer survivors. Both interventions were associated with improvements in perceived cognitive functioning, symptom distress, quality of life, objective verbal memory and speed of processing [81]. Similarly, Kesler et al. showed that a novel individual cognitive rehabilitation treatment online training programme was effective for improvement of executive function in long-term breast cancer survivors. A total of 41 breast cancer survivors (21 active, 20 wait list controls) completed the 48-session training programme over 12 weeks. The participants were, at an average, of 6 years after cancer therapy. Cognitive computerized training led to significant improvements in cognitive flexibility, verbal fluency and processing speed, with marginally significant downstream improvements in verbal memory as assessed via standardized measures [82]. A qualitative study conducted with nine women concluded that occupational therapy is important to assist women in returning to daily occupations during or following their chemobrain symptoms due to cancer treatment [83]. Physical activity is associated with improved cognitive function in human studies. In healthy adults and also with several pathological conditions, exercise induces the largest and most consistent increases in executive function, which is thought to be due to increased neurogenesis and levels of neurotransmitters and neurotrophins that promote cognitive function, as well as reduction of inflammation [84]. Initial findings have shown that physical fitness activities also increased cognitive health and quality of life in patients that have undergone chemotherapy [85]. Specific multidisciplinary cognitive-based exercise programmes could improve body image related- and overall quality of life in cancer patients [86]. Neurofeedback-based methods provide the best possibility for non-invasive treatment of cognitive disorders among the neuroscience-based interventions. These are methods that involve providing participants with feedback regarding their brain activity, as a means of training them to be able to control the upregulation and downregulation of brain activity using different strategies. Neurofeedback is provided via electroencephalogram (EEG), functional near-infrared spectroscopy (NIRS) or real-time functional magnetic resonance imaging. An example of this application is the Brain Computer Interface, an EEG feedback-based mental practise that was applied in stroke survivors [87]. A recent study was conducted in breast cancer survivors that demonstrated positive effects on cognitive function using EEG neurofeedback, suggesting potential benefits for this and similar neurofeedback techniques [88]. In terms of pharmacotherapy, few psychopharmacologic agents have proven effective in reducing or preventing cognitive impairment in non-CNS cancer patients. Psychostimulants like methylphenidate, dexmethylphenidate and modafinil have produced mixed results [80]. In addition, a recent review showed that pharmacological treatments appeared to have less efficacy as compared to non-pharmacological interventions [89].

Discussion and future directions

In conclusion, most of these studies suggest that chemotherapy alone or in combination with hormonal therapy can influence cognition in patients diagnosed with different types of cancer: breast cancer patients appear to be the most affected in terms of cognitive impairment and reduced quality of life, while testicular and ovarian cancer patients seem to be less impaired. Cognitive impairment has been reported in small cell lung cancer patients, however presently there are few studies confirming these data. Overall, the most impaired functions were verbal ability, memory, executive function and motor speed. Less affected are visuospatial skills, language and abstract reasoning. Some studies have shown that mild cognitive impairment was present before chemotherapy, while others found a decline just after chemotherapy. This decline was decreased in the late post-chemotherapy stage and in standard dose-treated patients. Only a few studies, with methodological limits, have reported no effect from chemotherapy. Considering this breadth of evidence, it appears that cognitive impairment is almost ubiquitous in several different

types of cancer, most especially after adjuvant therapy. It must now be clarified whether cognitive impairment is related to the disease itself or is a direct effect of chemotherapy.

This review of the literature regarding cognitive disorders in patients with different type of cancers leads to several considerations and suggestions for future studies.

Firstly, as it is well documented, there is a high incidence of misdiagnosis and variability with this phenomenon [14], further objective guidelines should be developed for clear assessment of cognitive dysfunction in order to avoiding these issues. Further randomized controlled trials must also be done to clarify the effect structured multidisciplinary rehabilitation has on the cognitive performance and quality of life of patients.

The second problem is that chemotherapy can have short-term and sometimes even long-term cognitive effects. Studies have consistently found that a subset of cancer survivors have cognitive declines that persist after cancer treatments. Most of these studies suggest that chemotherapy and even hormonal therapy can influence cognition in different types of cancer patients, although other factors associated with the diagnosis and treatment of cancer may also contribute. Large longitudinal studies with long-term follow-up are required to determine the duration of cognitive impairment after chemotherapy.

The third problem to solve is the evaluation of depressive symptoms in patients with cancer. Depression can influence and be influenced by cancer and cancer treatments. Despite many studies assessing mood in different types of cancer patients, depression is still under-recognized. Thus, it is necessary to refine specific diagnostic criteria for depression in cancer patients and to develop instruments for the assessment of depression severity that can help to distinguish the relative contribution of somatic or psychological factors. Neuropsychological function seems to be minimally associated with the presence of depression, even if few studies assessed this association and very few researchers are able to assess and recognize clinical and subclinical depression in cancer patients. Future studies should also focus on the differential effects of clinical and subclinical depression and assess cognitive function in order to determine their impact on quality of life, medical use and adherence to medical regimens.

Fourthly, as the number of long-term cancer survivors increases, it is necessary to understand the implications of systemic interventions on cognitive function in elderly cancer patients. A diagnosis of cognitive impairment may also alter clinical decision-making in geriatric oncology. Moreover, it would be useful to understand whether cancer survivors are at greater risk for increased age-related brain changes or dementia secondary to cancer treatment, since cancer patients are at increased risk for long-term cognitive dysfunction [90, 91]. Finally, because chemotherapy might accelerate the aging process, studies on long-term survivors might be further necessary.

Conclusions

Despite increasing research in this area, the mechanisms by which chemotherapy-induced cognitive changes occur remains largely unknown. Several possible mechanisms for chemotherapy-induced cognitive changes have been proposed and it is likely that there are several pathways to cognitive decline depending on the treatment and the individual. In conclusion, with all the above-mentioned clinical and biological aspects, future research should aim to provide data on the real prevalence and severity of cognitive dysfunction and mood disorders in elderly patients with cancer, and to improve knowledge regarding the association of cognition, depression or immune function with cancer progression in different types of cancer. In this scenario, objective neuropsychological assessment is fundamental to avoid underestimation of the incidence of chemobrain. In addition, it is important to plan and tailor appropriate cognitive rehabilitation programmes that could specifically target patients' cognitive function, motor performance and related quality of life in terms of emotional and physical well-being. For all these reasons, further studies are necessary in terms of assessment and multidisciplinary treatment in order to improve the quality of life patients and their caregivers.

Funding This review has been financed by the Line of Research "Cognitive and Motor Neurorehabilitation" of Santa Lucia Foundation, Rome, Italy.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

References

1. WHO (2018) The International Agency for Research on Cancer (IARC) is part of the World Health Organization (WHO). Latest global cancer data: Cancer burden rises to 18.1 million new cases and 9.6 million cancer deaths in 2018. https://www.who.int/cancer/en/. Accessed 2 Nov 2018
2. Akechi T, Okuyama T, Sugawara Y, Nakano T, Shima Y, Uchitomi Y (2004) Major depression, adjustment disorders, and post-traumatic stress disorder in terminally ill cancer patients: associated and predictive factors. J Clin Oncol 22:1957–1965
3. Breitbart W, Rosenfeld B, Pessin H et al (2000) Depression, hopelessness, and desire for hastened death in terminally ill patients with cancer. JAMA. 284:2907–2911
4. Sioka C, Kyritsis AP (2009) Central and peripheral nervous system toxicity of common chemotherapeutic agents. Cancer Chemother Pharmacol 63:761–767
5. Ahles TA, Saykin AJ, Furstenberg CT et al (2002) Neuropsychologic impact of standard-dose systemic

chemotherapy in long-term survivors of breast cancer and lymphoma. J Clin Oncol 20:485–493
6. Wieneke MH, Dienst ER (1995) Neuropsychological assessment of cognitive functioning following chemotherapy for breast cancer. Psycho-Oncology 4:61–66
7. Castellon SA, Ganz PA, Bower JE, Petersen L, Abraham L, Greendale GA (2004) Neurocognitive performance in breast cancer survivors exposed to adjuvant chemotherapy and tamoxifen. J Clin Exp Neuropsychol 26:955–969
8. Wefel JS, Lenzi R, Theriault R, Buzdar AU, Cruickshank S, Meyers CA (2004) 'Chemobrain' in breast carcinoma?: a prologue. Cancer. 101:466–475
9. Vardy J, Rourke S, Tannock IF (2007) Evaluation of cognitive function associated with chemotherapy: a review of published studies and recommendations for future research. J Clin Oncol 25: 2455–2463
10. Vardy J, Wefel JS, Ahles T, Tannock IF, Schagen SB (2008) Cancer and cancer-therapy related cognitive dysfunction: an international perspective from the Venice cognitive workshop. Ann Oncol 19: 623–629
11. McDonald BC, Conroy SK, Ahles TA, West JD, Saykin AJ (2010) Gray matter reduction associated with systemic chemotherapy for breast cancer: a prospective MRI study. Breast Cancer Res Treat 123:819–828
12. Kesler SR, Kent JS, O'Hara R (2011) Prefrontal cortex and executive function impairments in primary breast cancer. Arch Neurol 68: 1447–1453
13. Ponto LL, Menda Y, Magnotta VA, Yamada TH, Denburg NL, Schultz SK (2015) Frontal hypometabolism in elderly breast cancer survivors determined by [(18)F] fluorodeoxyglucose (FDG) positron emission tomography (PET): a pilot study. Int J Geriatr Psychiatry 30:587–594
14. Selamat MH, Loh SY, Mackenzie L, Vardy J (2014) Chemobrain experienced by breast cancer survivors: a meta-ethnography study investigating research and care implications. PLoS One 9(9): e108002
15. Biglia N, Bounous VE, Malabaila A et al (2012) Objective and self-reported cognitive dysfunction in breast cancer women treated with chemotherapy: a prospective study. Eur J Cancer Care (Engl) 21: 485–492
16. Hutchinson AD, Hosking JR, Kichenadasse G, Mattiske JK, Wilson C (2012) Objective and subjective cognitive impairment following chemotherapy for cancer: a systematic review. Cancer Treat Rev 38:926–934
17. Craig CD, Monk BJ, Farley JH (2014) Chase DM (2014). Cognitive impairment in gynecologic cancers: a systematic review of current approaches to diagnosis and treatment. Support Care Cancer 22:279–287
18. Correa DD, Zhou Q, Thaler HT, Maziarz M, Hurley K, Hensley ML (2010) Cognitive functions in long-term survivors of ovarian cancer. Gynecol Oncol 119:366–369
19. Meyers CA, Byrne KS, Komaki R (1995) Cognitive deficits in patients with small cell lung cancer before and after chemotherapy. Lung Cancer 12:231–235
20. Komaki R, Meyers CA, Shin DM et al (1995) Evaluation of cognitive function in patients with limited small cell lung cancer prior to and shortly following prophylactic cranial irradiation. Int J Radiat Oncol Biol Phys 33:179–182
21. Grosshans DR, Meyers CA, Allen PK, Davenport SD, Komaki R (2008) Neurocognitive function in patients with small cell lung cancer: effect of prophylactic cranial irradiation. Cancer. 112:589–595
22. Schagen SB, Boogerd W, Muller MJ et al (2008) Cognitive complaints and cognitive impairment following BEP chemotherapy in patients with testicular cancer. Acta Oncol 47:63–70
23. Pedersen AD, Rossen P, Mehlsen MY, Pedersen CG, Zachariae R, von der Maase H (2009) Long-term cognitive function following chemotherapy in patients with testicular cancer. J Int Neuropsychol Soc 15:296–301
24. Skaali T, Fossa SD, Andersson S et al (2011) A prospective study of neuropsychological functioning in testicular cancer patients. Ann Oncol 22:1062–1070
25. Wefel JS, Vidrine DJ, Veramonti TL et al (2011) Cognitive impairment in men with testicular cancer prior to adjuvant therapy. Cancer. 117:190–196
26. van Dam FS, Schagen SB, Muller MJ et al (1998) Impairment of cognitive function in women receiving adjuvant treatment for high-risk breast cancer: high-dose versus standard-dose chemotherapy. J Natl Cancer Inst 90:210–218
27. Brezden CB, Phillips KA et al (2000) Cognitive function in breast cancer patients receiving adjuvant chemotherapy. J Clin Oncol 18: 2695–2701
28. Tchen N, Juffs HG, Downie FP et al (2003) Cognitive function, fatigue, and menopausal symptoms in women receiving adjuvant chemotherapy for breast cancer. J Clin Oncol 21:4175–4183
29. Shilling V, Jenkins V, Fallowfield L, Howell T (2003) The effects of hormone therapy on cognition in breast cancer. J Steroid Biochem Mol Biol 86:405–412
30. Shilling V, Jenkins V, Morris R, Deutsch G, Bloomfield D (2005) The effects of adjuvant chemotherapy on cognition in women with breast cancer—preliminary results of an observational longitudinal study. Breast. 14:142–150
31. Scherwath A, Mehnert A, Schleimer B et al (2006) Neuropsychological function in high-risk breast cancer survivors after stem-cell supported high-dose therapy versus standard-dose chemotherapy: evaluation of long-term treatment effects. Ann Oncol 17:415–423
32. Jansen CE, Dodd MJ, Miaskowski CA, Dowling GA, Kramer J (2008) Preliminary results of a longitudinal study of changes in cognitive function in breast cancer patients undergoing chemotherapy with doxorubicin and cyclophosphamide. Psychooncology. 17: 1189–1195
33. Jansen CE, Cooper BA, Dodd MJ, Miaskowski CA (2010) A prospective longitudinal study of chemotherapy-induced cognitive changes in breast cancer patients. Support Care Cancer 19:1647–1656
34. Ahles TA, Saykin AJ, McDonald BC et al (2010) Longitudinal assessment of cognitive changes associated with adjuvant treatment for breast cancer: impact of age and cognitive reserve. J Clin Oncol 28:4434–4440
35. Ahles TA, Saykin AJ, McDonald BC et al (2008) Cognitive function in breast cancer patients prior to adjuvant treatment. Breast Cancer Res Treat 110:143–152
36. Vearncombe KJ, Rolfe M, Wright M, Pachana NA, Andrew B, Beadle GJ (2009) Predictors of cognitive decline after chemotherapy in breast cancer patients. J Int Neuropsychol Soc 15:951–962
37. Schilder CM, Eggens PC, Seynaeve C et al (2009) Neuropsychological functioning in postmenopausal breast cancer patients treated with tamoxifen or exemestane after AC-chemotherapy: cross-sectional findings from the neuropsychological TEAM-side study. Acta Oncol 48:76–85
38. Quesnel C, Savard J, Ivers H (2009) Cognitive impairments associated with breast cancer treatments: results from a longitudinal study. Breast Cancer Res Treat 116:113–123
39. Wefel JS, Lenzi R, Theriault RL, Davis RN, Meyers CA (2004) The cognitive sequeale of standard-dose adjuvant chemotherapy in women with breast carcinoma: results of a prospective, randomized, longitudinal trial. Cancer 100:2292–2299
40. Wefel JS, Saleeba AK, Buzdar AU, Meyers CA (2010) Acute and late onset cognitive dysfunction associated with chemotherapy in women with breast cancer. Cancer 116:3348–3356
41. Schagen SB, Muller MJ, Boogerd W et al (2002) Late effects of adjuvant chemotherapy on cognitive function: a follow-up study in breast cancer patients. Ann Oncol 13:1387–1397

42. Donovan KA, Small BJ, Andrykowski MA, Schmitt FA, Munster P, Jacobsen PB (2005) Cognitive functioning after adjuvant chemotherapy and/or radiotherapy for early-stage breast carcinoma. Cancer. 104:2499–2507
43. Hermelink K, Untch M, Lux MP et al (2007) Cognitive function during neoadjuvant chemotherapy for breast cancer: results of a prospective, multicenter, longitudinal study. Cancer. 109:1905–1913
44. Debess J, Riis JO, Engebjerg MC, Ewertz M (2010) Cognitive function after adjuvant treatment for early breast cancer: a population-based longitudinal study. Breast Cancer Res Treat 121: 91–100
45. Cheung YT, Ng T, Shwe M et al (2015) Association of proinflammatory cytokines and chemotherapy-associated cognitive impairment in breast cancer patients: a multi-centered, prospective, cohort study. Ann Oncol 26:1446–1451
46. Ahles TA, Saykin AJ (2007) Candidate mechanisms for chemotherapy-induced cognitive changes. Nat Rev Cancer 7: 192–201
47. Verstappen CC, Heimans JJ, Hoekman K, Postma TJ (2003) Neurotoxic complications of chemotherapy in patients with cancer: clinical signs and optimal management. Drugs. 63:1549–1563
48. Silverman DH, Dy CJ, Castellon SA et al (2007) Altered frontocortical, cerebellar, and basal ganglia activity in adjuvant-treated breast cancer survivors 5-10 years after chemotherapy. Breast Cancer Res Treat 103:303–311
49. Jacobsen PB, Garland LL, Booth-Jones M et al (2004) Relationship of hemoglobin levels to fatigue and cognitive functioning among cancer patients receiving chemotherapy. J Pain Symptom Manag 28:7–18
50. Porta C, Imarisio I, De Amici M (2005) Pro-neoangiogenic cytokines (VEGF and bFGF) and anemia in solid tumor patients. Oncol Rep 13:689–695
51. Aapro M, Osterborg A, Gascón P, Ludwig H, Beguin Y (2012) Prevalence and management of cancer-related anaemia, iron deficiency and the specific role of i.v. iron. Ann Oncol 23:1954–1962
52. Tsavaris N, Kosmas C et al (2002) Immune changes in patients with advanced breast cancer undergoing chemotherapy with taxanes. Br J Cancer 87(1):21–27
53. Lechner K, Obermeier HL (2012) Cancer-related microangiopathic hemolytic anemia: clinical and laboratory features in 168 reported cases. Medicine (Baltimore) 91:195–205
54. Kelley KW, Bluthe RM et al (2003) Cytokine-induced sickness behavior. Brain Behav Immun 17(Suppl 1):S112–S118
55. Nadin SB, Vargas-Roig LM, Drago G, Ibarra J, Ciocca DR (2006) DNA damage and repair in peripheral blood lymphocytes from healthy individuals and cancer patients: a pilot study on the implications in the clinical response to chemotherapy. Cancer Lett 239: 84–97
56. Bender CM, Paraska KK et al (2001) Cognitive function and reproductive hormones in adjuvant therapy for breast cancer: a critical review. J Pain Symptom Manag 21(5):407–424
57. Jenkins VA, Bloomfield DJ, Shilling VM, Edginton TL (2005) Does neoadjuvant hormone therapy for early prostate cancer affect cognition? Results from a pilot study. BJU Int 96:48–53
58. Unfer TC, Conterato GM, da Silva JC, Duarte MM, Emanuelli T (2006) Influence of hormone replacement therapy on blood antioxidant enzymes in menopausal women. Clin Chim Acta 369:73–77
59. Lee SA, Ross RK, Pike MC (2005) An overview of menopausal oestrogen-progestin hormone therapy and breast cancer risk. Br J Cancer 92:2049–2058
60. Ahles TA, Saykin AJ, Noll WW et al (2003) The relationship of APOE genotype to neuropsychological performances in long-term cancer survivors treated with standard dose chemotherapy. Psychooncology. 12:612–619
61. Miller S, Lo C, Gagliese L et al (2011) Patterns of depression in cancer patients: an indirect test of gender-specific vulnerabilities to depression. Soc Psychiatry Psychiatr Epidemiol 46:767–774
62. Angelino AF, Treisman GJ (2001) Major depression and demoralization in cancer patients: diagnostic and treatment considerations. Support Care Cancer 9:344–349
63. Ciaramella A1, Poli P (2001) Assessment of depression among cancer patients: the role of pain, cancer type and treatment. Psychooncology. 10:156–165
64. McDaniel JS, Musselman DL, Porter MR, Reed DA, Nemeroff CB (1995) Depression in patients with cancer. Diagnosis, biology, and treatment. Arch Gen Psychiatry 52:89–99
65. Endicott J (1984) Measurement of depression in patients with cancer. Cancer 53(10 Suppl):2243–2249
66. Bukberg J, Penman D, Holland JC (1984) Depression in hospitalized cancer patients. Psychosom Med 46:199–212
67. Gil F, Costa G, Hilker I, Benito L (2012) First anxiety, afterwards depression: psychological distress in cancer patients at diagnosis and after medical treatment. Stress Health 28:362–367
68. Stewart A, Collins B, Mackenzie J, Tomiak E, Verma S, Bielajew C (2008) The cognitive effects of adjuvant chemotherapy in early stage breast cancer: a prospective study. Psychooncology. 17:122–130
69. Ando-Tanabe N, Iwamitsu Y, Kuranami M et al (2014) Cognitive function in women with breast cancer receiving adjuvant chemotherapy and healthy controls. Breast Cancer 21:453–462
70. Montazeri A, Milroy R, Hole D, McEwen J, Gillis CR (1998) Anxiety and depression in patients with lung cancer before and after diagnosis: findings from a population in Glasgow, Scotland. J Epidemiol Community Health 52:203–204
71. Hopwood P, Stephens RJ (2000) Depression in patients with lung cancer: prevalence and risk factors derived from quality-of-life data. J Clin Oncol 8:893–903
72. Shilling V, Jenkins V (2007) Self-reported cognitive problems in women receiving adjuvant therapy for breast cancer. Eur J Oncol Nurs 11:6–15
73. Boykoff N, Moieni M, Subramanian SK (2009) Confronting chemobrain: an in-depth look at survivors' reports of impact on work, social networks, and health care response. J Cancer Surviv 3:223–232
74. Munir F, Burrows J, Yarker J, Kalawsky K, Bains M (2010) Women's perceptions of chemotherapy-induced cognitive side effects on work ability: a focus group study. J Clin Nurs 19:1362–1370
75. Massie MJ (2004) Prevalence of depression in patients with cancer. J Natl Cancer Inst Monogr 2004:57–71
76. Hotopf M, Chidgey J, Addington-Hall J, Ly KL (2002) Depression in advanced disease: a systematic review. Part 1. Prevalence and case finding. Palliat Med 16:81–97
77. Poppelreuter M, Weis J, Kulz AK, Tucha O, Lange KW, Bartsch HH (2004) Cognitive dysfunction and subjective complaints of cancer patients. A cross-sectional study in a cancer rehabilitation centre. Eur J Cancer 40:43–49
78. Croyle RT, Rowland JH (2003) Mood disorders and cancer: a National Cancer Institute perspective. Biol Psychiatry 54:191–194
79. Ganz PA (2012) Doctor, will the treatment you are recommending cause chemobrain? J Clin Oncol 30:229–231
80. Wefel JS, Kesler SR, Noll KR, Schagen SB (2015) Clinical characteristics, pathophysiology, and management of noncentral nervous system cancer-related cognitive impairment in adults. CA Cancer J Clin 65:123–138
81. Von Ah D, Carpenter JS, Saykin A et al (2012) Advanced cognitive training for breast cancer survivors: a randomized controlled trial. Breast Cancer Res Treat 135(3):799–809

82. Kesler S, Hadi Hosseini SM, Heckler C et al (2013) Cognitive training for improving executive function in chemotherapy-treated breast cancer survivors. Clin Breast Cancer 13:299–306
83. Player L, Mackenzie L, Willis K, Loh SY (2014) Women's experiences of cognitive changes or 'chemobrain' following treatment for breast cancer: a role for occupational therapy? Aust Occup Ther J 61:230–240
84. Hotting K, Roder B (2013) Beneficial effects of physical exercise on neuroplasticity and cognition. Neurosci Biobehav Rev 37:2243–2257
85. Fitzpatrick TR, Edgar L, Holcroft C (2012) Assessing the relationship between physical fitness activities, cognitive health, and quality of life among older cancer survivors. J Psychosoc Oncol 30: 556–572
86. Morone G, Iosa M, Fusco A et al (2014) Effects of a multidisciplinary educational rehabilitative intervention in breast cancer survivors: the role of body image on quality of life outcomes. Sci World J 2014:451935
87. Morone G, Pisotta I, Pichiorri F et al (2015) Proof of principle of a brain-computer interface approach to support poststroke arm rehabilitation in hospitalized patients: design, acceptability, and usability. Arch Phys Med Rehabil 96(3 Suppl):S71–S78
88. Alvarez J, Meyer FL, Granoff DL, Lundy A (2013) The effect of EEG biofeedback on reducing postcancer cognitive impairment. Integr Cancer Ther 12:475–487
89. Borghgraef C, Libert Y, Etienne AM, Delvaux N, Reynaert C, Razavi D (2014) Treatment of cognitive impairments in oncology: a review of longitudinal controlled studies. Bull Cancer 101:866–875
90. Heflin LH, Meyerowitz BE et al (2005) Cancer as a risk factor for long-term cognitive deficits and dementia. J Natl Cancer Inst 97: 854–856
91. Kurita K, Meyerowitz BE et al (2011) Long-term cognitive impairment in older adult twins discordant for gynecologic cancer treatment. J Gerontol A Biol Sci Med Sci 66:1343–1349