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Systematic Review for Psycho-Oncology

Is there a relationship between objectively measured cognitive changes in patients with solid tumours undergoing chemotherapy treatment and their health related quality of life outcomes? A SYSTEMATIC REVIEW

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Abstract

Objective: This systematic review examines whether there is a relationship between objective measures of chemotherapy-related cognitive impairment in patients with solid cancer tumours and health related quality of life (HRQoL).

Methods: Multiple online databases were searched (including Ovid MEDLINE, EMBASE, PsycINFO, PsycARTICLES, CINAHL, PubMed and Web of Science) in order to identify articles published between 1980 and 2016 examining the extent of chemotherapy-related cognitive deficit and its relationship with HRQoL in cancer patients. Of 2769 potentially relevant articles, 17 studies met the inclusion criteria for the current review.

Results: Evidence for the presence of cognitive impairment in patients treated with chemotherapy was found in 15 of the 17 studies. Out of the 15 studies finding some sort of cognitive impairment, 12 were in female breast cancer patients, 2 in bowel cancer, and 1 each in ovarian and lung cancer. Three of the 15 studies found a significant relationship between various objectively measured cognitively impaired domains and specific HRQoL outcomes. There was, however, only limited testing of the relationships between quantifiable cognitive dysfunction and HRQoL domains.

Conclusions: This review suggests that in patients with solid tumours, where there is a relationship between chemotherapy treatment and cognitive impairment, the type and level of cognitive decline does not consistently appear to have an impact on such patients' HRQoL. This could be partly explained by variations in study design, measures used, definitions of cognitive impairment, varying measurement time frames, small sample sizes and differences in disease severity and type of treatment regimes.

Key Words

Cognitive impairment, cognition, chemotherapy, cancer, oncology**,** health related quality of life.

Background

The effectiveness of chemotherapy drugs in treating a range of cancers has improved significantly in recent decades. Whether used alone, or in combination with other treatments, the result has been a marked reduction in disease recurrence and an increase in survival rates [1] doubling in the United Kingdom (UK) in the last 40 years [2]. This has been most notable in the treatment of female breast cancer and colorectal cancer (CRC), with an increase in absolute survival between 1971/72 and 2010/11 of 38% and 35% respectively [2]. UK survival at 5 years for colon cancer patients diagnosed between 2005–2009 and followed up to 2010 rose to 54% for men and 55% for women from 26% and 25% respectively for those diagnosed between 1971-75 and followed up to 1995. Similar increases were found in rectal cancer where 5-year survival was 55% for men and 57% for women compared to 27% and 29% respectively over the same time periods [3]. There has also been an increase in the 10-year relative survival for both sexes in CRC from just over 30% among those followed up during 1981-1986 to over 45% among those followed **up** during 1997-2001 [4].

These achievements have been attributed to screening, early detection and treatments. Nonetheless the pharmaceutical treatments used in these conditions do have side effects. The most common side effects of chemotherapy drugs are nausea, vomiting and fatigue [5]. Additionally, a decline in cognitive function, colloquially known as “chemofog” or “chemobrain”, has been reported by some patients following chemotherapy with estimates of patient numbers affected by this self-report of cognitive decline varying widely [6, 7]. Individuals report experiencing problems with concentration, memory, learning and language in their everyday life [8]. However, the number of patients reporting cognitive problems exceeds those with objectively measurable impairment, and even when present, the two do not necessarily co-occur [8, 9].

Studies have demonstrated that some degree of objectively measured post-chemotherapy cognitive difficulty is experienced by 16%-75% of adult patients with solid tumours [5, 10]. The majority of studies are of breast cancer patients, with a smaller number for lung, prostate, CRC and ovarian cancer patients [10-19]. It is possible that the large degree of variation is due to a range of confounders such as patient population diversity, cancer stage and treatment regimes as well as methodological differences between studies, including inconsistent definitions of cognitive impairment and the use of different measures to assess such impairment [20-22]. Early studies also suffer from methodological limitations such as small sample sizes, many using cross-sectional designs and some failing to conduct pre-treatment cognitive function evaluations [22]. Later studies used longitudinal designs, although sample sizes remained small and few studies used a comparison group. All of this has limited the conclusions that may be drawn from the data.

Nevertheless, some studies have examined a range of cognitive abilities and reported memory, processing speed and executive function as being the most likely to be adversely affected by adjuvant chemotherapy treatment [15, 17, 20, 22, 23]. The degree of impairment observed is

usually mild to moderate [24–27]. Even so, these cognitive deficits may have implications for patients' health related quality of life (HRQoL) [28] as well as their daily functioning, work performance and health care [29, 30].

HRQoL is an independent predictor of survival and response to therapy in cancer patients [31-33]. With the increase in survival times HRQoL has become a meaningful outcome measure for cancer patients [34]. An understanding of any link between chemotherapy-related cognitive impairment and HRQoL domains (e.g. emotional, physical, functional, social, financial and spiritual status) will provide medical teams and patients' with a broader picture of the related consequences of chemotherapy treatment. Such knowledge may be a helpful catalyst in the development of interventions, which aim to improve coping and adjustment [35].

This review's primary aim is to identify and synthesise research concerned with the relationship between objectively measured chemotherapy-related cognitive impairment and HRQoL in adult patients who received chemotherapy for treatment of solid tumours. It also aims to establish whether particular chemotherapy-related cognitive deficits are associated with specific aspects of HRQoL. As far as the authors are aware this is the first review of its type.

Methods

Inclusion and exclusion criteria

The search was limited to papers published in English post 1980, as this period coincides with a prevalence of reporting and systematic investigation of post-chemotherapy cognitive impairment [20].

Articles were restricted to those that had recruited patients' aged 18+ with a solid tumour such as breast, ovarian, CRC, prostate and lung treated with chemotherapy. Studies of patients with brain tumours and central nervous system tumours were excluded because of the inherent effects of the tumour on cognition, as well as the fact that the treatments often involve brain irradiation and surgical interventions which are known to cause additional direct effects on brain tissue secondary to the lesions [36,37], and consequent changes in neuropsychological functioning [38].

Included studies were required to be full papers that assessed both cognition and HRQoL using standardised measures. In addition, to be included, studies needed to examine (by quantitative measurement) and/or report on the relationship between such objectively measured cognitive deficits (global cognitive deficits and/or domain specific ones) and (global or domain specific) measures of HRQoL. Reviews, commentaries, case reports, dissertations and conference abstracts were all excluded.

Search strategy

An electronic search was performed using Ovid MEDLINE, EMBASE, PsycINFO, PsycARTICLES, CINAHL, PubMed and Web of Science on 6 June 2016, using a combination of search terms that

included all known terms for cancer such as, neoplasms and oncology, treatment terms including chemotherapy and “systemic treatment”; HRQoL terms and terms referring to cognition and cognitive impairment (please see detailed search strategy in Supplementary File 1). The first author (MRD) agreed the search terms with a specialist librarian and the third author (CH). A combination of both text words and indexed terms (such as MeSH) were applied in each database. Search terms were modified as necessary for each electronic database. The reference lists of all included articles were also searched for additional studies.

Study selection

Once the duplicates had been removed, retrieved articles were screened by title and, if eligibility was unclear from the title alone, the abstracts were screened (by MRD and 10% by CH). All articles potentially satisfying the inclusion criteria were retrieved in full and screened for eligibility (again by MRD and 10% by the second author (LR)).

Quality assessment

As there is currently no agreed “gold standard” appraisal tool for observational studies, a quality-scoring tool was developed based on methodological quality assessment checklists from the NICE “Methods for the development of NICE public health guidance” (Appendix 1) [39, 40]. Valid criteria (items) were selected from the NICE checklists and adapted for the purposes of this review in order to ensure that the 5 recommended aspects of internal validity (i.e. a clearly focused question, selection of subjects, assessments, confounders and statistical analysis), together with an overall assessment of the study were addressed in the evaluation of quality. A total of 16 items were included which covered all aspects considered necessary to evaluate the quality of the evidence in relation to the research question. [See Supplementary File 3.] Authors were emailed to obtain any missing data or details to ensure the study quality could be evaluated.

The overall assessment for each paper was calculated by considering all 16 items and then attributing scores between 0-4 to the overall assessment of the study; considering the extent to which each study was internally and externally valid. The higher the score the less bias in the study and the more external validity. Two studies had the highest overall rating score of 4 [39 & 42], five studies scored 3 [10/14, 20, 43, 44/45,46]; nine scored 2 [11, 19, 29, 47, 48, 49, 50,51, 52] and one was rated 0 [53]. MRD assessed each included study and LR independently coded the quality of the studies to check the reliability of the quality assessment. Agreement between the coders was substantial (kappa = 0.675) and MRD’s final score was used. Although the methodological quality of each study was evaluated and discussed, studies were not eliminated from this review because of poor quality.

Results

Literature search results

Database searches identified 2796 citations, and 36 additional citations were retrieved from

reference lists. Screening of titles and abstracts identified 365 potentially eligible articles (Figure 1).

The full texts of 59 papers were reviewed, 20 satisfied the inclusion criteria. An examination of the reference lists did not identify any additional papers that met the inclusion criteria. Several papers were linked and consequently treated as a single study ([10 and 14], [44 and 45] and [54 and 42]). This resulted in the final inclusion of 17 studies, whose main characteristics are presented in the Supplementary File 2.

Defining Cognitive Impairment

The calculation and operational definition of what constitutes cognitive impairment varied widely across studies (See Table 1). More than half of the studies (n = 10) converted raw scores into standardised z-scores (mean = 0, SD = 1) using published normative data adjusted for age, education, and gender. However, the number of tests and the extent to which these z-scores had to deviate to constitute cognitive impairment varied across the studies. Definitions of cognitive impairment included z-scores of ≤ −1.4, -1.5 and -2 standard deviations (SD) below the mean on between 1-4 tests. (See Supplementary File 2 for the full list of operational definitions used.) The extent of impairment has been shown to be dependent on the method of analysis [55]. As a consequence of the differences across the studies it is not possible to provide a simple estimate of the prevalence of cognitive impairment in patients treated with adjuvant chemotherapy. Ignoring these methodological differences, all but two studies [50, 53] reported statistically significant cognitive dysfunction in some patients undergoing adjuvant chemotherapy treatment.

Affected Cognitive Domains and Assessment of Objective Cognitive Impairment

The cognitive domains most affected varied widely across studies. Four studies [11, 41, 42& 44] reported verbal memory as being most affected whereas [42, 43, 46 & 47] and [29, 48] found that the most common domains showing decline were processing speed and executive function. Two studies [50 & 53] reported that objective cognitive performance remained constant throughout treatment.

As shown in Table 1 multiple tools were used and many different cognitive domains (as reported by the authors of the articles) were measured. Not only did the studies assess different areas of cognition but they also used different tests to assess the same domains. Overall there were more than 54 different measures used across 17 studies to tap a variety of cognitive domains. The majority of studies (n = 15) used a battery of neuropsychological tests assessing a range of domains. It is worth noting that the different psychometric qualities of each of the measures may have influenced the conclusions drawn regarding the cognitive domains most affected by chemotherapy treatment. For example, no impairment was reported by [53] who used the Mini-Mental State Examination (MMSE), which has been criticised for not being sensitive enough to detect subtle cognitive changes [56, 57].

This problem of diversity of assessments used has been recognised as an issue that needs consideration in future research by the International Cognition and Cancer Task Force (ICCTF) [58]. In an attempt to bring some homogeneity to all studies, the ICCTF recommended that in future trials 3 core neuropsychological assessments (the Hopkins Verbal Learning Test-Revised (HVLT-R), Trail Making Test (TMT), and the Controlled Oral Word Association (COWA) of the Multilingual Aphasia Examination)[59-63] be used to measure learning and memory, processing speed and executive function, supplemented with additional tests of working memory capacity, based on the researchers own preferences [58]. This was justified by the assertion that research has shown that the domains assessed by these tests are most affected by chemotherapy treatment [58]. However no study undertaken post ICCTF's recommendations used the entire core battery to assess neuropsychological impairment although 3 earlier studies did [48, 49, 50].

Assessing HRQoL

HRQoL was assessed at the same time points as cognition in all included studies. As with the neuropsychological assessments some studies reported having analysed only global HRQoL scores [14, 19, 48, 53] whereas others extended the analysis to the subscales of the HRQoL measure [11, 20, 41, 43, 46, 47, 52].

Five studies assessed HRQoL using the European Organization for Research and Treatment of Cancer Quality of Life questionnaire (EORTC–QLQ C30); the remaining studies used one or more of the questionnaires from the Functional Assessment of Cancer Treatment (FACT) battery. Both the EORTC–QLQ C30 and FACT-G are generic core HRQoL questionnaires supplemented by disease specific modules (e.g. the FACT-B for breast cancer). Both have subscales measuring key aspects of HRQoL (physical, emotional, social and functional), however the EORTC–QLQ C30 also provides brief scales for cognitive functioning, financial impact and a range of symptoms which are either not assessed by the FACT-G or are embedded within its wellbeing scale [64, 65]. The EORTC-QLQ C30 also provides 5 "functioning" scales and 10 symptom scores compared to FACT-G, which gives 5 summary scales (4 "well-being" and 1 overall scale) [65]. There are also differences between the 2 batteries' social domains. EORTC QLQ–C30's social functioning scale assesses the impact on social activities and family life whereas the FACT–G social well-being subscale focuses on social support and relationships [66]. As both scales are widely used but measure markedly different aspects of HRQoL, a direct comparison of results between studies using different scales is not possible [67].

The Relationship Between Objective Cognitive Dysfunction and HRQoL

Table 1 shows that 3 [51, 41, 43] of the 17 studies found a significant relationship between objectively assessed cognitive impairment and HRQoL. Two studies [51, 43] demonstrated that the greater the cognitive impairment related to chemotherapy the worse the patient's self-reported HRQoL as measured by the EORTC-QLQ C30 or the FACT battery. The third study [41] suggested patients with lower functional well-being at baseline are at greater risk of cognitive impairment after chemotherapy. All 3 studies examined the inter-relationships between various

domains of HRQoL and specific impaired cognitive domains, with 2 of them [51 and 43] specifically examining the presence of post-treatment cognitive deficits whereas the third study [41] examined deficits over the course of treatment.

The significant relationships were different in all 3 studies. For example, one study [51] found that objective measures of verbal memory were associated with poorer HRQoL (as measured by EORTC-QLQ C30) 5 years after treatment. Another [43] reported that poorer functional well-being (as measured by FACT-B) was significantly associated with verbal fluency at 12 months post-chemotherapy (although only a small proportion of participants' demonstrated objective cognitive decline). The third study [41] found that lower functional well-being at baseline (pre-chemotherapy treatment) significantly contributed to changes over the course of treatment in the cognitive domains of attention and executive function rather than declines in well-being affecting cognitive functioning shortly after finishing chemotherapy treatment.

The remaining studies included in this review found no correlation between overall objective cognitive impairment and overall HRQoL or between any of the specific domains. One study [49] did observe that those with the most dysfunction who improved also showed an improvement in overall global HRQoL. Unfortunately no statistics or specific details were provided to back up this assertion.

Methodological Quality

It is noteworthy that 11 studies (65%) [10/14, 29, 41, 43, 44/45, 46, 47, 48, 49, 50 & 51] were exclusively on breast cancer, one was with a mixed solid tumour patient group [53], 2 examined CRC patients [11,42], another examined patients with ovarian cancer [19] and one examined lung cancer patients [52]. In addition to variations in study samples, there were many differences in the designs and measurement points across the studies (Figure 2) which make it difficult to draw overall conclusions from this body of work. Twelve studies [11, 14, 19, 29, 41, 42, 43, 45, 48, 49, 52, 53] were longitudinal, with 10 (59%) having pre-chemotherapy baseline assessments. Four of the longitudinal studies with pre-treatment assessments [11, 19, 42, & 48] also examined cognition during chemotherapy treatment. Follow-up periods varied across the studies, ranging from end-of-treatment [53] to 2 years post-treatment [14]. One longitudinal study assessed cognition at 3 time-points post-chemotherapy [43].

Eight studies [14, 20, 41, 42, 45, 46, 50, 51] included more than one group. Three compared groups with different types of treatment or stages of disease (e.g. standard dose chemotherapy compared to high dose [51, 20, 41]). Two studies [42 & 51] compared the different chemotherapy groups to an early stage cancer group who did not need chemotherapy; and 3 studies compared chemotherapy patients to healthy controls [45, 10/14, 42]. The healthy control groups studies were peer-nominated (i.e. friends and family of the patient participants). The healthy controls were a useful comparator as they were matched for age and socioeconomic status. However, it should be noted that the cognitive evaluation in the patient group may be confounded by the stress associated with a cancer diagnosis and consequent surgery [12]. This raises the question as to

whether a healthy control group is the ideal comparison group in this context. Two studies used two comparison groups [55, 42] a non-chemotherapy group (post-surgery and had commenced endocrine therapy) as well as healthy controls (friends and family of the patient participants) [42, 58].

Eight studies recruited participants from a single hospital site [11, 20, 29, 46, 48, 49, 50 & 53] and the remaining 9 studies recruited from 2 or more sites making these results potentially more generalisable. Of the 8 single-site studies, 4 had sample sizes of fewer than 50 participants despite long recruitment periods. For example, one study recruited only 28 breast cancer participants over 2 years [49] and [50] was a pilot study with only 17 participants. In contrast, 2 single site studies [11 & 53] recruited over 80 participants each but both had high attrition rates (33% & 21%) and neither was sufficiently powered. Overall 59% of studies [11, 20, 41, 43, 47, 48, 51, 52, 50, 53] were underpowered and/or did not provide sample size justifications.

Of the studies with the most robust methodological designs [14, 20, 41, 48, 45, 19, 42], 3 were longitudinal and had the largest sample sizes [41, 45, 14, 19, 42] a total of 159, 177, 206, 231 and 434 participants respectively, with one or more comparison group as outlined above.

Six studies were graded as having high internal validity (i.e. unbiased) [14, 41, 42, 43, 45 & 46]; 10 as moderate [11, 19, 20, 29, 45, 47, 48, 49, 50, & 52] and one as poor [53]. Only 3 studies were graded as having high external validity [20, 41, & 42], 13 as moderate and one as having poor external validity [53].

Methodological shortcomings mainly concerned 3 studies [48, 49, 44/45] which were exploratory in nature with no focussed objective, 7 studies [11,19, 42, 43, 47, 49 & 50] which failed to report the acceptance rate of invited participants and 8 of the longitudinal studies [11,14,19, 42,43,48,52 & 53] (60%) which had attrition rates exceeding 20%.

Of the 3 studies that reported a relationship between objectively measured cognitive deficits and HRQoL one was cross-sectional [51] and 2 longitudinal in design [41, 43]. The focus of each was slightly different. For example, one study [51] examined neuropsychological impairment and HRQoL in high-risk breast cancer survivors 5 years after treatment. A second [43] examined the relationship one month after treatment and followed up the participants for another 12 months and the third study [41] investigated whether HRQoL significantly contributed to cognitive dysfunction reported after chemotherapy, examining cognition pre-treatment and 4 weeks post-treatment.

In interpreting the quality of the studies that found a significant relationship between cognitive decline and HRQoL, the cross-sectional study [51] had a low quality rating (1), and therefore the results should be treated with caution. Both longitudinal studies [41,43] received a higher overall quality score (3 and 4 respectively) suggesting that the results are more robust. All 3 studies examined cognitive impairment post-treatment, although one [41] also assessed pre-treatment

cognition. The results of these studies are difficult to compare because of their different aims, designs, participants and measures.

Conclusion

This review set out to examine studies that explored the possibility of a direct relationship between the adverse cognitive effects of chemotherapy treatment in patients with solid tumors and HRQoL. A critical examination of identified studies indicates that objective cognitive impairment is subtle and only occurs in a subset of patients. Processing speed, executive function and verbal fluency were the most commonly reported affected domains in the papers reviewed here. Although the review established that there is limited evidence to indicate that such cognitive impairment puts patients treated with adjuvant chemotherapy at greater risk of poorer HRQoL there is a suggestion that some HRQoL domains are affected.

There are a number of possible explanations for the limited number of studies reporting a significant relationship between impaired cognition and HRQoL. One explanation for some findings which failed to find any such relationship may be that the studies which used a global cognitive impairment score and/or a global HRQoL score masked the more subtle relationships or associations which possibly existed between specific cognitive domains and different aspects of HRQoL. For example, 2 studies [14 & 20] that combined test scores to produce an overall measure of cognitive impairment failed to find any correlation with HRQoL. In contrast one study [43] did find evidence of women who experienced greater executive function deficits reporting more difficulties in functioning in social roles. This however cannot account for all the failures to find a relationship between impaired cognition and HRQoL as one study [52] that did examine possible relationships between each neuropsychological test result and all HRQoL variables also did not find any statistically significant correlations at the three assessed time points.

A further caution is required when considering the number of studies that failed to find any such relationship. Most of the studies did not set out to explore this relationship; rather it typically featured as an exploratory post-hoc analysis.

Future research is needed to examine the relationship more thoroughly as more people who are diagnosed with cancer are surviving longer. If chemotherapy-related cognitive impairment is associated with feelings of low competence, survivors may encounter problems returning to work [6] and/or withdrawal from social life [30] both important consequences that need to be addressed.

An additional complication when attempting to gain clarity in this research revolves around different assessments used and the variability in the definition of cognitive impairment. Going forward, consistent use of the recommended tests and definitions should provide a clearer picture of the type and extent of deficits suffered by different cancer patients undergoing chemotherapy treatment [58].

A similar issue relates to the definition and questionnaires used to assess HRQoL. There are many instruments available for assessing HRQoL, from generic (measuring multiple concepts relevant to a wide range of patients) to specific (a disease, population or health dimension) [68]. All studies in this review used one of two instruments, the EORTC–QLQ C30 or the FACT battery. The findings indicated the difficulty in drawing meaningful comparisons between the results obtained by these two measures. There were insufficient data to examine which affected cognitive domains were related to which particular aspects of HRQoL. Even amongst the 3 studies that did find specific relationships it was not feasible to draw any meaningful comparisons between them as they used different HRQoL measures. A further complication is that in the studies on women with breast cancer some patients often received endocrine therapy as well as chemotherapy, making it difficult to distinguish the particular role of chemotherapy in relation to HRQoL.

Although almost all the studies found some type of cognitive impairment in a small subset of participants, such impairment often improved for some patients after treatment [14, 29, 49, 52]. It is common with repeated assessments of neuropsychological performance that individuals show some improvement even when alternate forms of the same test are used. This emphasizes the need for a control group so as to be able to examine and compare the practice effects when repeatedly using these tests over time [58].

If the heterogeneity between future studies can be reduced, valuable information may be gained which could effectively inform suitable interventions for decreasing the effects of chemotherapy-related cognitive deficits and potentially improving HRQoL [69]. This would help those susceptible to impairment to cope or more fully understand the implications of side effects, particularly if their diagnosis means that chemotherapy is an option rather than a requirement.

Strengths and limitations of the review

This review is not without its limitations. For example, all studies regardless of quality were included in the review because it is an under researched area. Most were of moderate quality at best and not necessarily methodologically robust enough to answer the review question.

Implication

The review highlights the need for more appropriately powered studies with suitable comparison group(s) along with greater overlap of instruments used and consistency in concepts especially the definition of cognitive deficit to advance our understanding of chemotherapy, cognition and HRQoL.

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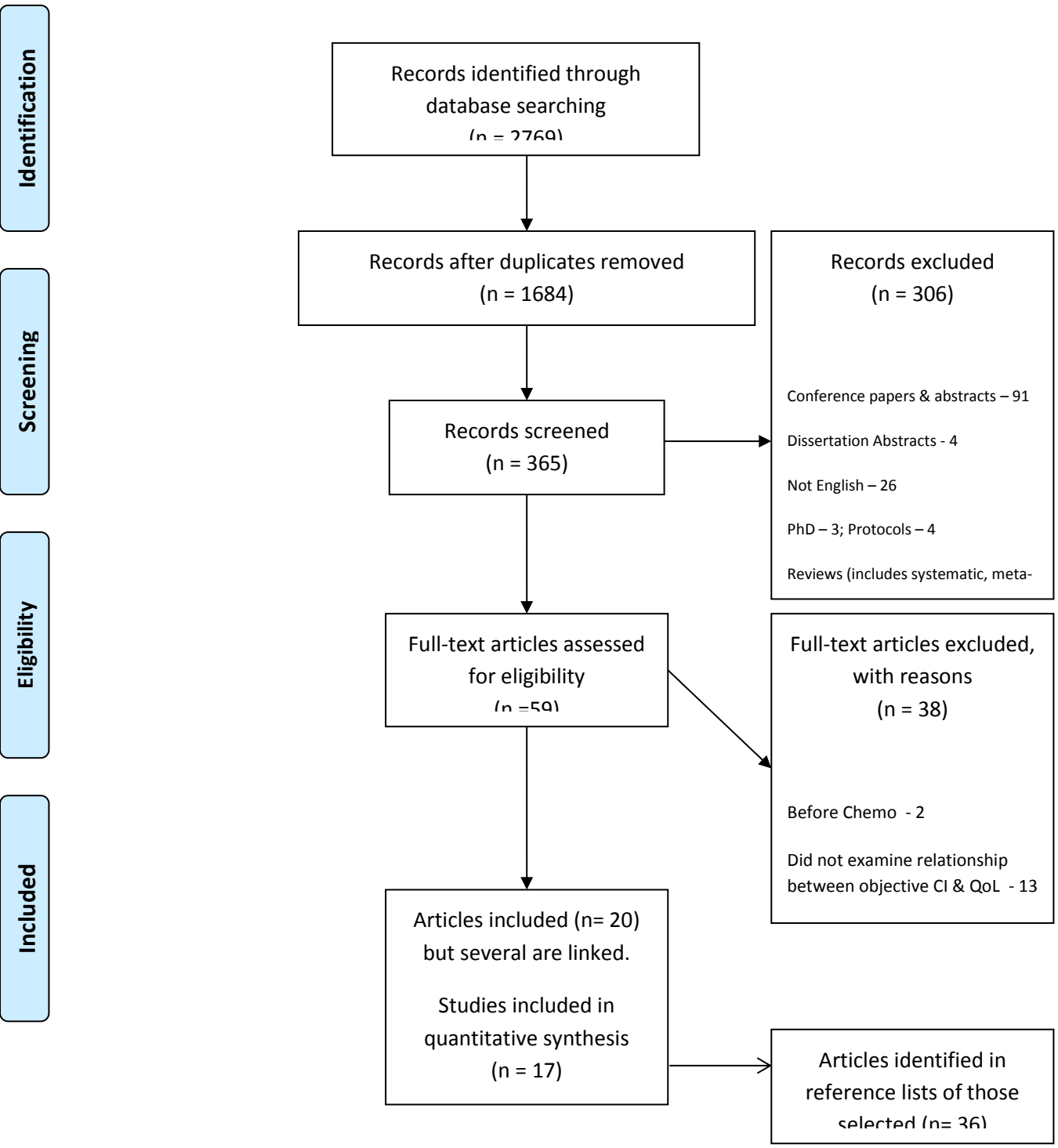
Figure 1: PRISMA Flow Diagram



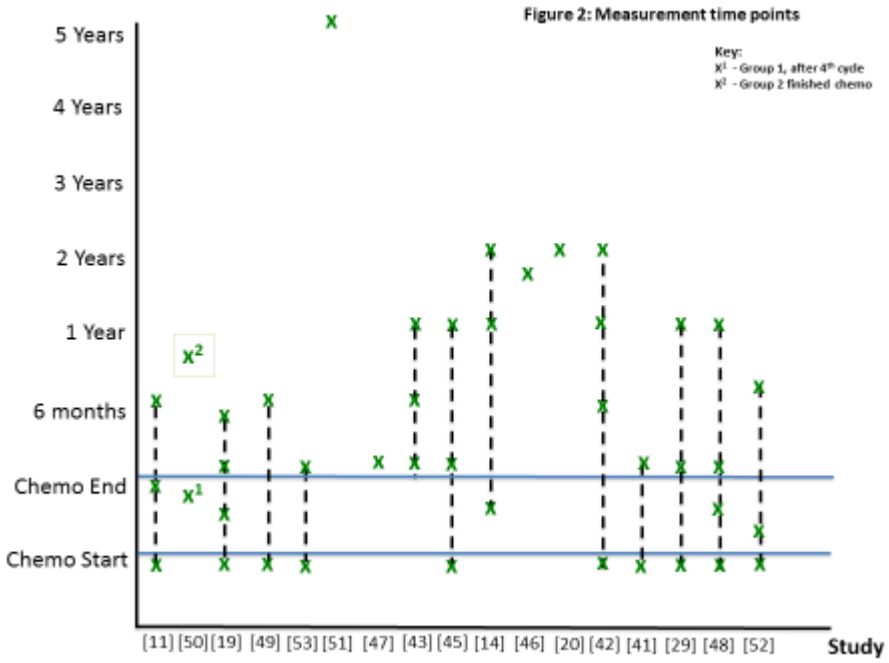


Figure 2: Measurement time points
Key:
X1 - Group 1, after 4th cycle
X2 - Group 2 finished chemo
5 Years
4 Years
3 Years
2 Years
1 Year
6 months
Chemo End
Chemo Start
X2
X1
[11] [50] [19] [49] [53] [51] [47] [43] [45] [14] [46] [20] [42] [41] [29] [48] [52]
Study

Table1: Summary of measures, cognitive domains as defined by the authors, objective cognitive impairment (CI) and the relationship between CI and HRQoL

Article & year	CI?	HRQoL Measure	CI significantly correlated with HRQoL?	Cognitive Domain Measured										
				Processing speed	Memory			Attention		Learning	Executive Function	Self-regulation & planning	Spatial Function	Language/ Verbal Function
					Verbal	Visual	Working	Attention	Visual motor/ psychomotor function	Verbal				
[11] **2014**	✓	EORTC QLQ C30	X		Subtest of Barcelona Test – Imm Mem, Imm Mem-Q, Delayed Mem, Delayed Mem-Q			TMT A*	WAIS-R digit symbol		Stroop C-W, colour & word; TMT B*			
[50] **2002**	X	FACT B	X	TMT A* & B* PASAT Stroop Word, Colour, C-W COWAT	TMT B* Category Test HVLT-R* WMS III- Faces I & II RBANS			TMT A* &B* Category Test HVLT-R* Faces I & II PASAT RBANS Stroop Word, Colour, C-W COWAT	TMT A* &B* Grooved Pegboard RBANS Sensory Perceptual Exam		TMT B* Category Test PASAT Stroop C-W			HVLT-R* RBANS COWAT
[19]	✓	FACT O	X	CRT				CRT	CRT					

2015														
[49] **2006**	✓	FACT B	X		HVLT –R*	RCFT		TMT A*	WAIS-III digit symbol, TMT A & B		TMT B*, Stroop colour & word, COWAT*		WAIS-III Block Design, RCFT	WRAT – 3 Reading subtest, Boston naming test, COWAT*
[53] **2004**	X	EORTC QLQ C30	X					MMSE						MMSE
[51] **2007**	✓	EORTC QLQ C30	✓		VLMT – Form A	ROCFT	WMS-R	TMT A & B*, TAP, Test D2			RWT, LPS-3, LPS -4			
[47] **2009**	✓	FACT B	X		WMS-III Logical Memory I & II, Visual Reproduction I & II, Rey AVLT Delayed Recall				WAIS-III digit span, TMT A*		TMT B*, Stroop			COWAT*, Category Fluency
[43] **2010**	✓	FACT B & 1 single item question (‘in general, how satisfied are you with your overall quality of life’)	✓	TMT A & B*	WMS-III Logical Memory I & II, Rey AVLT Delayed Recall & Trials 1-5						Stroop			COWAT*, Category Fluency
[46] **1999**	✓	EORTC QLQ C30	X	FVRT; FBCT; FVST	RAVLT	RCFT WMS-R Visual Reproduction – imm, delayed & recall		D2 WAIS-digit symbol WAIS-digit span	FFTT TMT A*		TMT B*, Stroop			Word fluency subtest from S.A.N test
[44/45] **2006**	✓	FACT B & ES (patients only)	X	Letter cancellation task	WMS logical memory, imm & delayed,	RCFT	WMS III - spatial span, letter/ number sequencing				Stroop			

					RAVLT recall 1-7		& digit span							
[10/14] **2005**	✓	FACT-G Version 4 FACT ES	X	HSCS				HSCS, CPT	HSCS, TMT A &B*			HSCS	HSCS	HSCS
[20] **1998**	✓	EORTC QLQ C30	X	FVRT; FBCT; FVST	REY15 words	Complex figure		D2 test WAIS-digit symbol WAIS-digit span	TMT A* FFTT		Stroop TMT B*		RCFT (copy)	Word Fluency subtest from the DAST
[54/42] **2015**	✓	FACT G	X	WAIS III Digit Symbol TMT A & B*	HVLT-R* CANTAB - VRM	BVMT-R	CANTAB - SWM	CANTAB - RVP	CANTAB – MOT & RVP & RTI	CANTAB - VRM				
[41] **2009**	✓	FACT G	✓	SDMT	AVLT	WMS-III Visual Reproduction – imm, delayed & recognition	WAIS-III Backward digit span	TEA Visual Elevator & Telephone search	Purdue Pegboard		WAIS-III Matrix Reasoning Stroop, DKEFS Card sorting, COWAT*			
[29] **2004**	✓	FACT B	X	WAIS-R Digit Symbol, TMT A*	VSRT delayed recall, NVSRT delayed recall			WAIS-R Digit Span & Arithmetic	Grooved Pegboard	VSRT Long term storage, NVSRT Long term storage	TMT B*, Booklet Category Test, WAIS-R Similarities		WAIS-R Block Design	
[48] **2010**	✓	FACT B	X	WAIS-R Digit Symbol, TMT A*	HVLT*			WAIS-R Digit Span		HVLT*	TMT B*, MAE COWA*			
[52] **2008**	✓	FACT L	X		HVLT—R*, RCFT			Gordon CPT	WAIS-block design		COWA* WCST-64			

Key: * = this is one of the ICCTF's recommended core neurological assessments.

EORTC QLQ C30: European Organization for Research and Treatment of Cancer Quality of Life questionnaire;
FACT O: For patients with Ovarian cancer
FACT G: Functional Assessment of Cancer Therapy – General; FACT B: For patients with Breast cancer; FACT ES: For patients with Endocrine Symptoms; FACT L: For patients with Lung cancer;
Imm-Mem: Immediate memory; Imm-Mem-Q: Immediate memory-questions; Delayed-Mem: Delayed memory; Delayed-Mem-Q: Delayed memory-questions;
TMT A & B: Trial Making Test Part A & Part B; WAIS-R Digit Symbol: Wechsler Adult Intelligence Scale Revised Digit Symbol; MMSE: Mini- Mental State Examination;
CRT: Headminder Clinical Research Tool;
WAIS-R Digit Span: Wechsler Adult Intelligence Scale Revised Digit Span; Stroop C-W: Stroop interference trial;
HVLT-R: Hopkins Verbal Learning Test – Revised;
RBANS: Repeatable Battery for the Assessment of Neurospcyhological Status;
Category Test;
PASAT: Paced Auditory Serial-Addition Task; COWAT/COWA: Controlled Oral Word Association Test
Grooved Pegboard;
Sensory Perceptual Exam;
RCFT: Rey-Osterrieth Complex Figure test; WAIS-III: Wechsler Adult Intelligence Scale –III; WRAT-3: The Wide Range Achievement Test, Third Edition;
MMSE: Mini- Mental State Examination;
VLMT: Auditory Verbal Learning Test – German modified version;ROCFT: Rey-Osterrieth complex figure test; TAP: Test battery for attentional performance; Test D2: D2 cancellation test;RWT: Regensburg Word Fluency Test;
LPS: achievement measure test;
WMS-III Logical Memory: Wechsler Memory Scale – third edition Logical Memory; WMS-III Visual Reproduction: Wechsler Memory Scale – third edition Visual Reproduction; Faces I & II: Facial Recognition Tests;
RAVLT/Rey AVLT: Rey Auditory Verbal Learning Test; FFTT: Fepsy finger-tapping task; FVRT: Fepsy visual reaction test; FBCT: Fey binary choice test; FVST: Fepsy visual searching test;
S.A.N Test: Please see full reference in Supplementary File 4
Letter cancellation test;
HSCS: High Sensitivity Cognitive Screen; CPT: Continuous Performance Test; DAST: Dutch Aphasia Society Test;
CANTAB Battery: RVP: Rapid Visual Information Processing; RTI: Reaction Time; VRM: Verbal Recognition Memory; SWM: Spatial Working Memory; MOT: Motor Screening;
BVMT-R: Brief Visuospatial Memory Test Revised; SDMT: Symbol Digit Modalities Test; TEA: Test of Everyday Attention;
Elevator & Telephone search;
Perdue Pegboard;
DKEFS: Delis-Kaplan Executive Function Scale; NVSRT: Nonverbal Selective Reminding Test; VSRT: Verbal Selective Reminding Test; Grooved Pegboard
MAE COWA: Multilingual Aphasia Examination controlled oral word association; WCST-64: Wisonsin Card Sorting Test Conceptual Level Responses; Gordon CPT: Gordon Continuous Performance Test.
See Supplementary File 4 for all of the measurement references