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Geriatric Oncology

Decline in Cognitive Function in Older Adults With Early-Stage Breast Cancer After Adjuvant Treatment

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Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cognition deficits • Breast cancer • Elderly • Chemotherapy • Neuropsychology

Abstract

Background. The impact of chemotherapy on cognition among elderly patients has received little attention, although such patients are more prone to presenting with age-related cognitive deficits and/or cognitive decline during chemotherapy. The present study assessed the cognitive function in older adults treated for early-stage breast cancer (EBC).

Patients and Methods. The participants were newly diagnosed EBC patients aged ≥65 years without previous systemic treatment or neurological or psychiatric disease and matched healthy controls. They underwent two assessments: before starting adjuvant therapy and after the end of chemotherapy (including doxorubicin ± docetaxel [CT+ group], $n = 58$) or radiotherapy for patients who did not receive chemotherapy (CT− group, $n = 61$), and at the same interval for the healthy controls ($n = 62$). Neuropsychological and geriatric assessments were performed. Neuropsychological data were analyzed using the Reliable Change Index.

Results. Forty-nine percent of the patients (mean age, 70 ± 4 years) had objective cognitive decline after adjuvant treatment that mainly concerned working memory. Among these patients, 64% developed a cognitive impairment after adjuvant treatment. Comorbidity was not associated with cognitive decline. No significant difference in objective cognitive decline was found between the two groups of patients; however, the CT+ group had more subjective cognitive complaints after treatment ($p = .008$). The oldest patients (aged 70–81 years) tended to have more objective decline with docetaxel ($p = .05$).

Conclusion. This is the largest published study assessing cognitive function in older adults with EBC that included a group of patients treated with modern chemotherapy regimens. Approximately half the patients had objective cognitive decline after adjuvant treatment. The oldest patients were more likely to have cognitive decline with chemotherapy, particularly with docetaxel. ***The Oncologist*** 2016;21:1337–1348

Implications for Practice: This is the largest published study assessing cognitive function in older adults with early-stage breast cancer that included a group of patients treated with modern chemotherapy regimens. Approximately half the patients had objective cognitive decline after adjuvant treatment. The oldest patients were more likely to have cognitive decline with chemotherapy, particularly with docetaxel. Cognitive deficits could affect patients' quality of life and their compliance to treatment. Assessing cognitive dysfunctions in the elderly cancer population is a challenge in clinical practice, but it could influence the choice of the most appropriate therapy, including the use of oral drugs.

Introduction

The impact of adjuvant chemotherapy on cognition has mainly been studied in middle-age women (age, <60 years) treated with chemotherapy for breast cancer. The findings from longitudinal studies suggest that 15%–25% of patients experience post-treatment cognitive decline [1]. Furthermore, 20%–30% of breast cancer patients will have cognitive impairment before starting adjuvant treatment [2], suggesting a global effect of cancer on cognition.

Although the cancer incidence is greater in older adults, clinical trials usually concern younger participants. Several

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Table 1. Demographic and clinical characteristics of patients and healthy controls

Variable	CT+ group ($n = 58$)	CT− group ($n = 61$)	Healthy group ($n = 62$)	p value
Demographic				
Age (yr)				.13
Mean ± SD	70 ± 3.8	71 ± 4.3	71 ± 5.4	
Range	65–81	65–83	65–88	
Sample size, *n* (%)				
Age 65–69 yr	32 (55)	25 (41)	31 (50)	
Age 70–74 yr	20 (34)	25 (41)	15 (24)	
Age ≥75 yr	6 (11)	11 (18)	16 (26)	
Education level				.63
Low/middle/high (%)	69/17/14	64/13/23	64/13/23	
Mean ± SD	11 ± 2.9	11 ± 2.6	11 ± 2.6	
Time between T1 and T2 (days)				
Median	178	71	156	
Range	93–265	31–294	99–252	
Clinical				
PS (WHO = 0) (%)[a]	84	98	NA	.006
Charlson index (0/1-2)	76/24	82/18	NK	.29
Comorbidities (%)				
Pulmonary	4	7	0	
Peripheral neurological	2	0	1	
Thyroid	5	5	3	
Cardiac	0	0	2	
>3 Comedications (%)	21	32	NK	.13
Medications with potential impact on cognition[b] (%)	15	31	NA	.0502
Cancer stage I–II (%)[a]	74	98	NA	<.0001
Lumpectomy/mastectomy (%)[a]	52/48	90/10	NA	<.0001
Lymph node dissection (%)[a]	95	66	NA	<.0001
HER2-positive (%)[a]	28	3	NA	.0003
Hormone receptor positive (%)	84	94	NA	.11
Protocol of adjuvant CT		NA	NA	NA
FEC + docetaxel (%)	59			
FEC without docetaxel (%)	33			
Other (%)	8			
No. of cycles (mean ± SD; range)	5.5 ± 0.8 (3–6)			
T2 after completion of adjuvant treatment (days)	67 ± 44.9 (CT)	26 ± 51.9 (RT)		<.0001
Adjuvant radiotherapy (%)	89	100	NA	.012
Adjuvant hormonal therapy (% started at T2; aromatase inhibitors for all patients)	26	31	NA	.52

[a]$p < .01$.
[b]Level 3 on WHO analgesic ladder, anxiolytics, antidepressant treatments, and hypnotics.
Abbreviations: CT, chemotherapy; FEC, 5-fluorouracil, epirubicin, cyclophosphamide; NA, not applicable; NK, not known; PS, performance status; RT, radiotherapy; WHO, World Health Organization.

studies have demonstrated that elderly patients are at greater risk of treatment toxicity [3], although cognitive functioning was poorly assessed.

Age is a risk factor for cognitive decline, and older adults are thought to be more vulnerable to the adverse cognitive effects of cancer and its treatments [4–7]. Indeed, 11%–41% of elderly patients had cognitive dysfunctions before adjuvant breast cancer treatment [8, 9]. Chemotherapy could be a risk factor for inducing cognitive decline or increasing dysfunction. Furthermore, treatment-induced accelerated cognitive aging can be expected in vulnerable populations [2]. To date, only one prospective study with a small sample has assessed cognition after adjuvant chemotherapy, particularly in elderly breast cancer patients [8].

The effect of modern chemotherapy regimens on cognition, including anthracyclines and taxanes, has not been specifically assessed in elderly patients. Nevertheless, these drugs induce cognitive impairment in young breast cancer

Table 2. Neuropsychological tests grouped by main cognitive domains

Cognitive domain	Test	Outcome measure	Range
Episodic memory			
Verbal modality			
Learning abilities	G&B test [24]	Three immediate free recall	(3×) 0–16
Storage capacities	G&B test	Rate of forgetting[a]	%
Retrieval capacities	G&B test	Benefit of cueing[b]	%
Visual modality	Rey Complex Figure [23]	Recall score	0–36
Working memory	WAIS-III [25]: Arithmetic	Number of resolved problems	0–22
	WAIS-III: Digit-span	Correct trials, forward	0–16
		Correct trials, backward	0–14
	WAIS-III: Letter-number sequencing	Total correct trials	0–21
Processing speed	TMT A [22]	Time to complete and errors	≥0
Executive function			
Flexibility	TMT B [22]	Time to complete and number of perseverative errors	≥0
Information generation	Verbal fluency [21]: Category (animal) and letter P	Total score over 2 min	≥0

[a]Rate of forgetting: [(third free recall − delayed free recall)/third free recall] × 100.
[b]Benefit of cueing: (3 total recall − 3 free recall)/(48 − 3 free recall) × 100.
Abbreviations: G&B test, Grober and Buschke test; TMT, Trail Making Test; WAIS, Wechsler Adult Intelligence Scale.

patients [10–12], and preclinical studies have shown that docetaxel can induce cognitive impairment [13, 14]. The present multicenter prospective study assessed the impact of adjuvant treatment on cognition among older adults with early-stage breast cancer (EBC) compared with healthy controls.

Patients and Methods

Participants

Newly diagnosed older women with EBC were recruited from three French comprehensive cancer centers. The recruitment details have been published previously [9].

A sample of healthy controls who met the same inclusion (except for the cancer diagnosis) and exclusion criteria were recruited by community advertisements. The healthy controls were age-, sex-, and education-matched to patients.

The pretreatment assessment (T1) occurred after surgery but before the start of adjuvant therapy. The follow-up assessment (T2) was conducted in patients after the end of the first adjuvant treatment: adjuvant chemotherapy (CT+ group; within a mean of 67 ± 44.9 days after chemotherapy), and after radiotherapy in patients who did not receive chemotherapy (CT− group; within a mean of 26 ± 51.9 days after radiotherapy). The median time between T1 and T2 was 178 days (range, 93–265) for the CT+ group and 71 days (range, 31–294) for the CT− group. The interval for healthy controls was approximately the mean of that of the two patient groups (Table 1). All participants provided written informed consent for the study, which was approved by the local ethics committee and is registered at ClinicalTrials.gov (ClinicalTrials.gov identifier, NCT01333735).

Measures

Neuropsychological testing included the domains most likely to be affected by cancer treatment [15–20], including episodic memory (verbal and visual modalities), working memory, processing speed, and executive functions (Table 2) [21–25]. We used a comprehensive battery of assessments with standard and recommended instruments.

The subjective assessment consisted of self-report measures of cognitive complaints (Functional Assessment of Cancer Therapy, Cognitive Scale [FACT-Cog], version 3 [26, 27], with four subscales [Perceived Cognitive Impairments [PCI], Impact on Quality of Life [QoL], Comments from Others, and Perceived Cognitive Abilities [PCA]), depression (Beck Depression Inventory [BDI] [28]), anxiety (Spielberger State-Trait Anxiety Inventory [STAI] [29]), and fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue [FACIT-Fatigue], version 4 [30]). The geriatric assessment included the Geriatric Depression Scale (GDS) [31], the Instrumental Activities of Daily Living (IADL) [32], the Activities of Daily Living (ADL) [33], the Charlson comorbidity index [34], the number of medications, and the main medical history.

The sociodemographic measures included age and education level. The clinical variables were the performance status (PS), medications with a potential impact on cognition (level 3 on the World Health Organization analgesic ladder, anxiolytics, antidepressant treatments, and hypnotics), cancer stage, type of surgery, HER2-positive, hormone receptor status, adjuvant treatments, and weight.

Blood samples were obtained for measurement of hematologic parameters, thyroid function (thyroid-stimulating hormone [TSH]), C-reactive protein (CRP), folates, and albumin to assess for anemia, inflammation, and level of nutrition. The relationships between these variables and cognition were studied. The healthy controls completed the battery of neuropsychological tests, FACT-Cog, BDI, STAI, and FACIT-Fatigue.

Procedure

Details about the study procedure have been published previously [9].

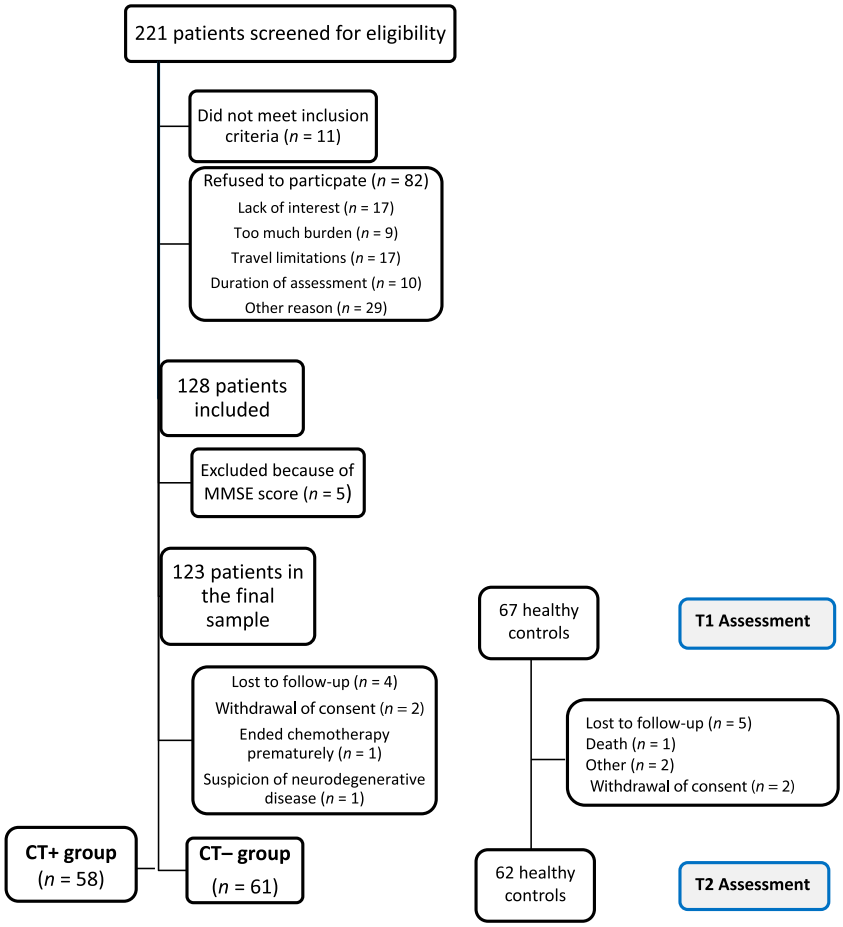

Figure 1. Flow diagram of participant follow-up.
Abbreviation: MMSE, mini-mental state examination.

Statistical Analysis

Descriptive statistics were generated for the sociodemographic and clinical variables. Data from the two neuropsychological assessments were analyzed using a practice effect-adjusted Reliable Change Index (RCI) [35, 36]. The RCI was used to determine the standardized change scores for each patient on every neuropsychological score to compare the T2 and T1 scores. The calculation included the practice effect (i.e., the change from T1 to T2 on the same measure in the healthy group). The Iverson formula includes an adapted standard error of the difference that incorporates T2's variability. A significant change was found at ±1.645 [35] (−1.645 indicated decline; and +1.645 indicated improvement). The RCI scores were grouped together in the cognitive domains. A change in a domain was considered significant when at least one of the domain scores changed significantly (decline or improvement). For the self-report questionnaires, a difference of more than 10% between T1 and T2 was considered clinically significant [37]. Pairwise comparisons by group between the two assessments were performed for the other measures.

We used the *t* test, Wilcoxon test, analysis of variance, or Fisher's exact test to compare the means and proportions, as appropriate, and the paired *t* test to compare changes over time within each group. Subgroups were compared according to the treatment received and age (≥75 or ≥70 years vs. younger) regarding the cognitive and biological scores. Differences in the CT+ group in the cognitive domains were examined within subgroups according to age, docetaxel administration, and 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) dose intensity.

We estimated the mean scores and their differences between groups (CT+ group, CT− group, healthy controls) over time for all neuropsychological data, cognitive complaints, and anxiety and depression scores by a repeated measures linear mixed model with an unrestricted covariance structure, including age at baseline, delay between T1 and T2, groups, assessment time, and groups × assessment time interaction. Given the large number of analyses performed with this model, $p < .01$ was applied to minimize type I error.

Correlations between the cognitive complaints and other measures were assessed with Spearman's rank or Pearson's correlation coefficient, as appropriate. Cognitive domains were considered as categorical variables (decline: yes vs. no) and associated with other measures. Given the large number of correlations, we considered $p < .01$ to minimize type I error. Analyses were conducted using SAS, version 9.3 (SAS Institute, Cary, NC, http://www.sas.com).

Results

Sample Characteristics

At the baseline assessment, of 221 older women with EBC screened, 11 were ineligible, and 82 were not enrolled in the

Table 3. Change in neuropsychological test scores (RCI scores) between baseline (T1) and after adjuvant treatment (T2) compared with healthy women

	CT+ group (%)			CT− group (%)		
Neuropsychological test	**Declined**	**Stable**	**Improved**	**Declined**	**Stable**	**Improved**
Episodic memory						
Immediate recall	5	91	4	2	93	5
Rate of forgetting	9	89	2	3	92	5
Benefit of cueing	9	86	5	8	89	3
Rey recall score	7	91	2	8	82	10
Working memory						
Arithmetic	9	84	7	0	90	10
Digit-span forward	12	83	5	18	71	11
Digit-span backward	9	91	0	0	95	5
Letter-number sequencing	9	84	7	5	95	0
Processing speed						
TMT A time	7	91	2	8	89	3
TMT A errors	5	84	11	16	72	12
Executive function						
TMT B time	0	96	4	5	95	0
TMT B perseverative errors	0	98	2	2	98	0
Verbal fluency category	4	92	4	5	90	5
Verbal fluency letter	7	88	5	7	85	8

Abbreviations: CT, chemotherapy; RCI, Reliable Change Index; TMT, Trail Making Test.

trial for the following reasons: lack of interest ($n = 17$), too much burden ($n = 9$), travel limitations ($n = 17$), duration of the assessment ($n = 10$), or other reasons ($n = 29$). This yielded a 61% participation rate. Moreover, five patients were excluded from the analysis because of a score below the threshold of dementia [38]. Hence, the final sample consisted of 123 patients (stage I, 60%; stage II, 27%; stage III, 13%). However, 4 patients completed only the T1 (Fig. 1). Therefore, the final sample for the T1-T2 analysis was 58 CT+ patients, 61 CT− patients, and 62 healthy controls. Among the patients, 57 were <70 years (48%), 45 were 70–74 years (38%), and 17 were ≥75 years (14%). The participants' demographic and medical information is summarized in Table 1. The breast cancer stage, surgery type, lymph node dissection, and HER2 status were significantly different between the patient groups ($p < .01$). No significant difference was found for the Charlson index, main medical history, comedications, medications with a potential impact on cognition, hormone receptor status, or initiation of hormonal therapy. A significant difference was found in the performance status between the patient groups (CT− group had better PS; $p < .01$).

In the CT+ group, 91% of patients ($n = 53$) received an anthracycline-based regimen. For 59% ($n = 34$) of these patients, the regimen included docetaxel. Also, 21% of patients received FEC 75 ($n = 12$) and 67% FEC 100 ($n = 39$). No significant difference in age and education was observed among the three groups at baseline.

Baseline (T1)

According to the baseline results, 41% of patients had objective cognitive impairment (46% in the CT+ group [26 of 57]; 38% in the CT− group [23 of 61]). No significant difference between the patient groups was observed at baseline regarding the objective cognitive scores, subjective cognitive complaints, anxiety, depression, fatigue, or geriatric and biological measures. Only digit span forward was better in the CT− group ($p < .01$), and the PCA (FACT-Cog) was higher in the CT+ group ($p = .018$).

Compared with the EBC patients, the healthy group was less anxious than the CT+ group ($p < .001$). The healthy group also had more subjective cognitive complaints than the CT+ group (PCI and PCA subscales; $p = .01$), but this had less impact on quality of life (FACT-Cog, QoL subscale; $p = .02$).

Neuropsychological Outcomes

RCI Analysis (Objective Cognitive Results)

Tables 3 and 4 and Figure 2 show the change in neuropsychological scores and objective cognitive domains between T1 and T2 compared with healthy women. Forty-nine percent of patients had an objective decline and 25%, objective improvement in at least one domain. The domain with the greatest objective decline was working memory (25% of patients).

Overall, no significant difference was observed between the two patient groups in objective change in at least one domain or any cognitive domain. Among the patients who had objective cognitive decline (49%; $n = 58$ of 118), 12% ($n = 7$ of 58) already had objective cognitive impairment before adjuvant treatment and 64% ($n = 37$ of 58) developed objective cognitive impairment after adjuvant treatment (according to the T1 data based on normative data [9]). The other 24% of patients ($n = 14$ of 58) had cognitive decline without

Table 4. Change in neuropsychological test scores (RCI scores) between baseline (T1) and after adjuvant treatment (T2) compared with healthy women by patient subgroup

	Declined (%)						
	CT+ group			CT− group			
Cognitive domain	Age 65–69 yr	Age 70–74 yr	Age ≥75 yr	Age 65–69 yr	Age 70-74 yr	Age ≥75 yr	*p* value[a]
At least one domain	14/31 (45%)	10/20 (50%)	4/6 (67%)	14/25 (56%)	14/25 (56%)	2/11 (18%)	.1094
Verbal episodic memory	3/31 (10%)	5/20 (25%)	2/6 (33%)	3/24 (13%)	5/25 (20%)	0/11 (0%)	.1103
Visual episodic memory	2/31 (6%)	0/20 (0%)	2/6 (33%)	2/25 (8%)	2/25 (8%)	1/11 (9%)	.5147
Working memory	10/30 (33%)	4/20 (20%)	2/6 (33%)	7/25 (28%)	6/25 (24%)	1/11 (9%)	.5147
Processing speed	1/31 (3%)	0/20 (0%)	0/6 (0%)	2/25 (8%)	0/25 (0%)	0/11 (0%)	1.0000
Executive function	1/30 (3%)	5/20 (25%)	1/6 (17%)	2/25 (8%)	5/24 (21%)	0/11 (0%)	.3529

	CT+ group				
	Docetaxel		No docetaxel		
	Age 65–69 yr	Age ≥70 yr	Age 65–69 yr	Age ≥70 yr	*p* value[b]
At least one domain	12/25 (48%)	5/9 (56%)	2/6 (33%)	10/21 (48%)	1.0000
Verbal episodic memory	3/25 (12%)	3/9 (33%)	2/6 (33%)	4/19 (21%)	.3060
Visual episodic memory	2/25 (8%)	1/9 (11%)	0/6 (0%)	1/19 (5%)	1.0000
Working memory	8/24 (33%)	2/9 (22%)	2/6 (33%)	4/19 (21%)	.6859
Processing speed	1/25 (4%)	0/9 (0%)	0/6 (0%)	0/19 (0%)	1.0000
Executive function	1/24 (4%)	3/9 (33%)	0/6 (0%)	4/19 (21%)	.0468

	CT+ group		
	FEC 75	FEC 100	*p* value
At least one domain	6/10 (60%)	19/41 (46%)	.4416
Verbal episodic memory	2/10 (20%)	7/41 (17%)	.8278
Visual episodic memory	0/10 (0%)	3/41 (7%)	.9582
Working memory	3/10 (30%)	12/40 (30%)	1.0000
Processing speed	0/10 (0%)	1/41 (2%)	.9639
Executive function	2/10 (20%)	4/40 (10%)	.1199

[a]Comparisons between CT+ group aged ≥75 years and CT− group aged ≥75 years.
[b]Comparisons between two age groups of patients receiving docetaxel.
Abbreviations: CT, chemotherapy; FEC, 5-fluorouracil, epirubicin, cyclophosphamide.

impairment (scores greater than the threshold of impairment based on normative data [9]). No difference was observed between the groups for episodic memory processes (learning, retrieval, storage; Table 3).

However, the oldest patients were more likely to have objective cognitive decline, especially those in the CT+ group (Table 4). The oldest patients (≥75 years) treated with CT tended to have more objective decline in at least one domain compared with those in the CT− group (67% in the CT+ group [$n = 4$ of 6] vs. 18% in the CT− group [$n = 2$ of 11]; $p = .10$).

Among the patients receiving docetaxel, those aged ≥70 years were more likely than those aged <70 years to experience objective decline in executive functions ($p = .047$, Table 4). No chemotherapy dose-dependent effect (FEC 75 vs. FEC 100) was observed for objective cognitive decline. No relationship was found between the duration of chemotherapy and objective cognitive decline.

Changes in Subjective and Biological Scores

Table 5 shows the subjective assessment scores and Table 6 the clinically significant change in subjective scores. The CT+ group had a significantly greater increase in subjective cognitive complaints after treatment than the CT− and healthy groups (PCI subscale; $p = .008$; Table 6). A clinically significant subjective decline in the PCA subscale score was observed mainly in the CT+ group ($p = .03$) and mainly concerned CT+ patients older than 75 years compared with CT− patients ($p = .067$).

The CT+ group also expressed significantly more fatigue after treatment ($p < .001$). However, the CT+ group experienced significantly less anxiety ($p = .001$) after treatment compared with the other groups. The intragroup depression score did not change significantly between the assessments.

Treatment did not significantly affect the geriatric scores (ADL, IADL, GDS, number of medications), or folate, CRP, or TSH levels. However, the CT+ group decreased more in weight, hemoglobin, and albumin level after treatment than the CT− group ($p = .001$, $p < .001$, and $p = .022$, respectively; Table 7). No effect of the CT regimen or dose intensity was found on subjective cognitive complaints or fatigue.

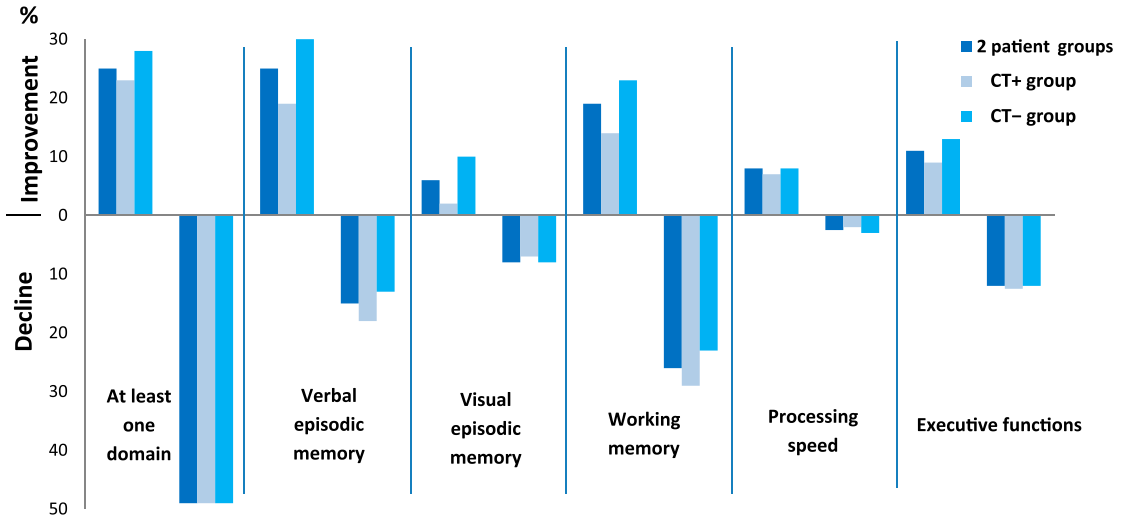

Figure 2. Frequency of patients with improvement or decline in cognitive domains (Reliable Change Index based on healthy control scores). Forty-nine percent of patients had a decline in at least one domain. The domain with the greatest decline was working memory (25% of patients). No significant difference was observed between the two patient groups.

Mixed Model Analysis

Table 8 shows the results of the mixed model analysis. According to the groups × time analysis, no significant effect was found for any of the objective and subjective cognitive scores. Age had a significant effect on 4 of 14 objective cognitive scores and a delay between T1 and T2 had a significant effect on 3 of 14 objective cognitive scores (less delay resulted in a better score).

Relationships Between Objective Cognitive Decline and Subjective and Biological Scores

Objective Cognitive Decline and Other Measures

Overall, no relationship was found between objective decline in any cognitive domain and subjective cognitive complaints. However, an objective decline in at least one domain was related to the QoL subscale (FACT-Cog; $p = .006$). Objective cognitive decline was not associated with education level, fatigue, anxiety, depression, medications with a potential effect on cognition, type of surgery, Charlson index, comedications, performance status, cancer stage, weight, initiation of aromatase inhibitors, or geriatric or biological scores. Medications potentially affecting cognition were related only to an objective decline in visual episodic memory ($p = .0314$). Among the objective cognitive domains, age was related to executive function decline ($p = .0493$), with patients aged >70 years having greater decline.

Subjective Cognitive Complaints and Other Cognitive Measures

Patients with more subjective cognitive complaints at T1 (PCI subscale) were those with more objective cognitive decline in verbal episodic memory (odds ratio, 0.956; 95% confidence interval, 0.920–0.994; $p = .029$). Also, patients with more subjective cognitive complaints at T1 were those who increased more in subjective cognitive complaints at T2 (PCI subscale; $p = .013$). Nevertheless, this increase in cognitive complaints was not clinically significant using the definition of less than 10%.

Discussion

The present study is the largest published prospective study assessing cognitive function in older adults with EBC that included a group treated with modern chemotherapy regimens (including anthracycline ± docetaxel) and a group of healthy controls. Regardless of the adjuvant treatment, approximately half the patients had objective cognitive decline after adjuvant treatment. However, the oldest patients treated with chemotherapy were more likely to experience objective cognitive decline than those treated without chemotherapy, especially when the regimen included docetaxel.

All Patients

Before adjuvant treatment, 41% of patients had objective cognitive impairment. The percentage of patients exhibiting pretreatment impairment was higher than that reported in studies of younger breast cancer patients (20%–30%) [2]. This finding supports the hypothesis that elderly patients might be more sensitive to the impact of cancer on cognition [1].

Forty-nine percent of patients had objective cognitive decline after adjuvant treatment that mainly concerned working memory. Our results are higher than those observed in a previous study using the same method of RCI analysis [39]. In that study, cognitive decline after adjuvant treatment was observed in 20% of the chemotherapy group and 26% of the group without chemotherapy. However, they did not include elderly patients (mean age, 51 and 59 years). Therefore, our results suggest that age might affect post-treatment cognitive functioning. Overall, regardless of the statistical method used, longitudinal studies of middle-age breast cancer women (age <60 years) have suggested that 15%–25% of patients will experience post-treatment cognitive decline [1]. Therefore, age seems to be a risk factor for cognitive decline, and older adults could be more vulnerable to the adverse cognitive effects of cancer and its treatments.

The domain mostly affected in our study was working memory, similar to the reports of younger breast cancer patients [12, 40, 41]. Daily, this alteration induces difficulties

Table 5. Neuropsychological, cognitive complaints, quality of life, anxiety, and depression scores

Variable	CT+ group T1	CT+ group T2	Paired *t* test *p* value	CT− group T1	CT− group T2	Paired *t* test *p* value	Healthy controls T1	Healthy controls T2	Paired *t* test *p* value	ANOVA *p* value[a]
Neuropsychological										
Episodic memory										
Immediate recall	31.3 ± 5.0	32.0 ± 5.7	.249	31.0 ± 4.4	32.1 ± 5.5	.024	31.8 ± 5.4	32.2 ± 5.7	.465	.758
Rate of forgetting	−1.3 ± 18.7	−2.52 ± 18.4	<.001	−4.8 ± 16.3	−5.2 ± 15.1	<.001	−4.6 ± 15.5	−5.3 ± 18.1	<.001	<.001
Benefit of cueing	95.1 ± 7.1	93.0 ± 10.6	<.001	94.6 ± 6.8	90.0 ± 10.8	<.001	92.5 ± 10.5	90.7 ± 11.3	<.001	<.001
Rey recall	15.6 ± 6.3	16.8 ± 6.5	.046	15.0 ± 6.3	17.6 ± 6.8	.001	16.9 ± 5.0	18.7 ± 5.5	.004	.068
Working memory										
Arithmetic	10.3 ± 4.3	9.7 ± 4.2	.068	10.0 ± 4.5	10.3 ± 7.9	.205	10.5 ± 4.7	10.3 ± 4.5	.555	.801
Digit-span forward	7.2 ± 1.8	7.5 ± 1.9	.123	8.7 ± 2.3	9.0 ± 2.8	.345	7.8 ± 1.9	8.1 ± 2.0	.077	<.001
Digit-span backward	5.0 ± 1.7	4.7 ± 1.5	.226	4.9 ± 1.5	5.1 ± 1.8	.304	5.2 ± 1.6	5.4 ± 1.7	.204	.147
Letter-number sequencing	7.6 ± 2.3	7.6 ± 2.3	.646	7.7 ± 2.5	8.1 ± 2.6	.060	8.3 ± 2.6	8.8 ± 2.5	.062	.015
Processing speed										
TMT A time	46.6 ± 16.0	42.7 ± 15.3	.049	44.2 ± 18.6	40.3 ± 15.6	.044	49.6 ± 20.0	50.4 ± 20.1	.660	.002
TMT A errors	0.1 ± 0.3	0.2 ± 0.5	.252	0.2 ± 0.6	0.2 ± 0.4	.454	0.2 ± 0.5	0.2 ± 0.4	1.0	.362
Executive function										
Fluency category	27.3 ± 6.6	27.1 ± 8.4	.711	28.5 ± 7.4	28.7 ± 7.2	.891	26.5 ± 6.9	27.2 ± 6.3	.341	.133
Fluency letter	18.9 ± 6.9	19.9 ± 7.4	.076	19.7 ± 6.2	21.2 ± 6.3	.023	20.7 ± 6.0	21.5 ± 5.6	.179	.135
TMT B time	110.2 ± 43.5	110.5 ± 51.8	.882	112.1 ± 48.1	101.7 ± 43.3	.024	122.3 ± 53.7	116.3 ± 61.3	.365	.142
TMT B pers. errors	0.5 ± 0.8	0.3 ± 0.7	.115	0.6 ± 0.9	0.5 ± 0.9	.201	0.7 ± 0.9	0.7 ± 1.0	1.0	.020
Cognitive complaints (FACT-Cog)										
PCI	61.7 ± 10.2	56.4 ± 13.3	.002	58.9 ± 9.6	57.9 ± 12.0	.382	55.4 ± 9.4	54.8 ± 11.0	.481	.008
QoL	11.5 ± 4.3	10.5 ± 4.6	.240	11.8 ± 3.9	11.7 ± 4.0	.682	13.2 ± 2.7	12.9 ± 3.3	.540	.106
Oth	15.7 ± 0.8	15.3 ± 1.7	.084	15.4 ± 1.3	15.3 ± 1.4	.530	15.2 ± 1.6	15.3 ± 1.3	.450	.685
PCA	20.6 ± 4.0	18.4 ± 5.5	.002	18.4 ± 5.6	18.9 ± 5.1	.467	17.6 ± 4.5	17.1 ± 5.2	.465	.031
Anxiety, depression										
Beck	3.0 (3.4)	3.5 ± 3.3	.219	3.7 ± 3.3	3.6 ± 3.7	.846	3.7 ± 2.4	3.6 ± 2.3	.507	.063
STAI State	39.05 (10.5)	36.37 ± 11.1	.056	36.35 ± 11.0	36.10 ± 11.0	.887	32.16 ± 7.9	33.79 ± 8.4	.143	.001

Data presented as mean ± SD.

For cognitive complaint measures, higher scores represent fewer complaints (i.e., better functioning); for anxiety and depression measures, higher scores represent more anxiety and a higher of level depression.

[a]Comparison of changes between groups.

Abbreviations: ANOVA, analysis of variance; Beck, Beck Depression Inventory; CT, chemotherapy; FACT-Cog, Functional Assessment of Cancer Therapy, Cognitive Scale; Oth, comments from others; PCA, perceived cognitive abilities; PCI, perceived cognitive impairment; pers. errors, perseverative errors; QoL, impact on quality of life; STAI State, Spielberger State-Trait Anxiety Inventory; T1, baseline assessment; T2, assessment after adjuvant therapy; TMT, Trail Making Test.

in the temporary maintenance of memory and manipulation of information during short periods and when performing activities.

In our study, we did not find an association between cognitive impairment and breast cancer stage and comorbidity, in contrast to the results of another study of elderly patients [42]. One explanation might be that our population had few comorbidities. Treatment-related objective cognitive decline was not associated with other measures (clinical, mood, or biological), and aromatase inhibitors do not seem to affect cognition [43]. Nevertheless, this lack of association between these factors/variables and objective cognitive decline might have resulted from the limited sample size. Only age had an effect on executive function.

Overall, although cognitive complaints were not related to the objective scores, just as was frequently the case in other studies [44], a decline in at least one cognitive domain was related to the cognitive complaint subscale: impact [of cognitive disorders] on quality of life. We also found that cognitive complaints could be predictive of cognitive decline. Cognitive complaints in subjects with normal neuropsychological scores could be a harbinger of further decline [45]. This phenomenon has been studied, in particular, in subjects who developed mild cognitive impairment or Alzheimer disease [46]. Therefore, it is important to assess cognitive complaints, including the impact on quality of life. This could make it possible to detect patients at risk of decline and to anticipate cognitive alterations by proposing adapted interventions such as cognitive training [47].

Comparison Between CT+ and CT− Groups

Overall, no significant difference was found in objective cognitive decline between our patient groups receiving or not receiving chemotherapy (RCI and mixed model analysis results). These

Table 6. Clinically significant[a] change in subjective scores between T1 and T2

Variable	CT+ group (%)	CT− group (%)	Healthy controls (%)	*p* value[b]
Cognitive complaints				
PCI (FACT-Cog)	34	24	10	.008
PCA (FACT-Cog)	49	25	29	.03
PCA (FACT-Cog) for patients aged >75 yr	80	30	NA	.067
QoL (FACT-Cog)	40	26	21	.11
Fatigue				
FACIT-Fatigue	53	30	13	.001

[a]A difference of more than 10% between T1 and T2 was considered clinically significant [37].
[b]Comparison of proportions of clinically significant change.
Abbreviations: CT, chemotherapy; FACIT-Fatigue, Functional Assessment of Chronic Illness Therapy-Fatigue; FACT-Cog, Functional Assessment of Cancer Therapy, Cognitive Scale; PCA, perceived cognitive abilities; PCI, perceived cognitive impairment; QoL, impact on quality of life; T1, baseline assessment; T2, assessment after adjuvant therapy.

Table 7. Geriatric and biological scores

	CT+ group			CT− group			
Variable	T1	T2	Paired *t* test *p* value	T1	T2	Paired *t* test *p* value	Paired *t* test *p* value[a]
ADL	5.98 ± 0.1	5.93 ± 0.3	.261	6.0 ± 0.0	6.0 ± 0.0	1.00	.261
IADL	0.23 ± 0.7	0.40 ± 0.8	.058	0.27 ± 0.9	0.23 ± 0.8	.532	.057
GDS	0.23 ± 0.7	0.19 ± 0.6	.735	0.17 ± 0.6	0.23 ± 0.6	.659	.592
Medications (*n*)	1.0 ± 0.8	0.6 ± 0.6	.004	1.3 ± 0.8	1.1 ± 0.8	.073	.093
Weight (kg)	71.3 ± 12.9	69.5 ± 13.1	<.001	67.7 ± 13.3	68.0 ± 13.1	.912	.001
Hg (g/100 mL)	13.5 ± 0.9	12.3 ± 1.3	<.001	13.3 ± 0.9	13.3 ± 1.0	.547	<.001
TSH (mUI/L)	1.9 ± 1.4	1.7 ± 0.8	.593	1.5 ± 0.9	1.8 ± 1.3	.035	.102
Albumin (g/L)	43.5 ± 2.9	41.9 ± 2.5	<.001	43.9 ± 2.1	43.2 ± 2.0	.079	.022
Folate (nmol/L)	21.3 ± 31.9	17.1 ± 19.0	.305	15.6 ± 6.2	20.2 ± 37.4	.318	.153
CRP (mg/L)	3.8 ± 4.9	5.7 ± 8.8	.171	5.4 ± 5.2	5.3 ± 9.3	.819	.212

Data presented as mean ± SD.
[a]Comparison of changes between groups.
Abbreviations: ADL, activities of daily living; CRP, C-reactive protein; CT, chemotherapy; GDS, Geriatric Depression Scale; Hg, hemoglobin; IADL, instrumental activities of daily living; T1, baseline assessment; T2, assessment after adjuvant therapy; TSH, thyroid-stimulating hormone.

results are consistent with others [48] of younger breast cancer patients, which showed that cognitive deficits were likely due to the general effects of the cancer diagnosis and treatments rather than to systemic treatment. Other studies have failed to confirm previous reports suggesting that adjuvant chemotherapy is associated with cognitive dysfunction among younger breast cancer patients [39, 49–52]. In our study, we probably overestimated the effect of radiotherapy on cognition by making the cognitive assessment of this group just after the end of radiotherapy; thus, the subjects probably had had insufficient time to recover from the fatigue induced by treatment. Although most young patients will recover within 1 year after chemotherapy [15, 53], this might not be the case for elderly patients, with chemotherapy inducing some direct damage to the brain [54]. Therefore, long-term follow-up of patients is important to demonstrate the real effect of the adjuvant treatment modalities administered and how they affect the recovery of cognitive functioning in elderly patients.

However, when we focused on the CT+ group, who were mainly treated with anthracycline ± docetaxel, 49% of the patients had an objective cognitive decline. In published cognitive studies of the elderly, very few patients received a CT regimen that included docetaxel. In a previous pilot study exploring postchemotherapy (mainly CMF [cyclophosphamide, methotrexate, and 5-fluorouracil]), cognitive functioning in elderly EBC patients ($n = 28$), Hurria et al. showed that 25% of patients experienced cognitive decline [8]. In other studies of elderly patients using the RCI, 52% of colon cancer patients and 33% of cancer patients (mainly breast and colon cancer, principally treated with FU-FA [5-fluorouracil, folinic acid] and CMF) experienced cognitive declines after chemotherapy [55, 56]. These rates are comparable to those for our patients, but those studies did not include a group of healthy controls to accurately assess the decline.

In terms of age group, the CT+ group aged ≥75 years tended to have a greater incidence of objective decline in at least one domain than did patients of the same age group treated without chemotherapy (67% vs. 18%). Nevertheless, this result needs to be confirmed owing to the low number of patients aged ≥75 years.

Furthermore, the oldest patients were more likely to experience objective cognitive decline when the regimen included docetaxel. The deleterious effect of docetaxel on

Table 8. Estimated neuropsychological, cognitive complaints, quality of life, anxiety, and depression scores by group (linear mixed model)

							p value				
	CT+ group		CT− group		Healthy controls						
Variable	T1	T2	T1	T2	T1	T2	Age[a]	Delay between T1 and T2	Groups	Time	Groups × time
Neuropsychological											
Episodic memory											
Immediate recall	31.3 ± 0.6[b]	32.0 ± 0.7	31.0 ± 0.6	32.1 ± 0.7	31.8 ± 0.6	32.2 ± 0.7	.0011	.0015	.3577	.1295	.7108
Rate of forgetting	−1.3 ± 2.2	−2.5 ± 2.3	−4.8 ± 2.2	−5.2 ± 2.2	−4.6 ± 2.1	−5.3 ± 2.2	.5102	.5020	.4015	.5828	.7113
Benefit of cueing	95.1 ± 1.1	93.0 ± 1.4	94.6 ± 1.1	90.0 ± 1.4	92.5 ± 1.1	90.7 ± 1.4	.2917	.3230	.3473	.0054	.4700
Rey recall	15.6 ± 0.8	16.8 ± 0.8	15.0 ± 0.7	17.6 ± 0.8	16.9 ± 0.7	18.7 ± 0.8	.0025	.0664	.8248	.0216	.3749
Working memory											
Arithmetic	10.3 ± 0.6	9.7 ± 0.6	10.0 ± 0.6	10.3 ± 0.6	10.5 ± 0.6	10.3 ± 0.6	.0329	.9749	.5285	.7064	.5191
Digit-span forward	7.2 ± 0.3	7.5 ± 0.3	8.7 ± 0.3	9.0 ± 0.3	7.8 ± 0.3	8.1 ± 0.3	.7815	.6952	<.0001	.3567	.9758
Digit-span backward	5.0 ± 0.2	4.7 ± 0.2	4.9 ± 0.2	5.1 ± 0.2	5.1 ± 0.2	5.4 ± 0.2	.9669	.7375	.6895	.9639	.2237
Letter-number sequencing	7.6 ± 0.3	7.6 ± 0.3	7.7 ± 0.3	8.1 ± 0.3	8.3 ± 0.3	8.8 ± 0.3	.0020	.5545	.3638	.3709	.8510
Processing speed											
TMT A time	46.6 ± 2.4	42.7 ± 2.3	44.2 ± 2.3	40.3 ± 2.2	49.6 ± 2.3	50.4 ± 2.2	.2837	<.0001	.5253	.1076	.9451
TMT A errors	0.1 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	.0186	.6697	.0854	.6443	.1161
Executive function											
Fluency category	27.3 ± 0.9	27.1 ± 1.0	28.5 ± 0.9	28.7 ± 0.9	26.5 ± 0.9	27.2 ± 0.9	.0101	.0005	.7127	.9253	.9446
Fluency letter	18.9 ± 0.8	19.9 ± 0.9	19.7 ± 0.8	21.2 ± 0.8	20.7 ± 0.8	21.5 ± 0.8	.0279	.1229	.1577	.0966	.7026
TMT B time	110.2 ± 6.4	110.5 ± 7.1	112.1 ± 6.2	101.7 ± 6.8	122.3 ± 6.2	116.3 ± 6.7	<.0001	.7837	.3157	.2790	.3947
TMT B pers. errors	0.4 ± 0.1	0.6 ± 0.1	0.7 ± 0.1	0.6 ± 0.1	0.4 ± 0.1	0.2 ± 0.1	.0753	.3514	.9842	.7484	.3099
Cognitive complaints (FACT-Cog)											
PCI	61.7 ± 1.3	56.4 ± 1.7	58.8 ± 1.3	57.9 ± 1.6	55.4 ± 1.2	54.8 ± 1.5	.2336	.5808	.8311	.0467	.1922
QoL	11.5 ± 0.5	10.5 ± 0.6	11.8 ± 0.5	11.7 ± 0.5	13.1 ± 0.5	12.9 ± 0.5	.2262	.6907	.0899	.3478	.5026
Oth	15.7 ± 0.2	15.3 ± 0.2	15.4 ± 0.2	15.3 ± 0.2	15.2 ± 0.2	15.3 ± 0.2	.1949	.2445	.9869	.1334	.4296
PCA	20.6 ± 0.7	18.4 ± 0.7	18.4 ± 0.6	18.9 ± 0.7	17.6 ± 0.6	17.1 ± 0.7	.8113	.0717	.0957	.1984	.0566
Anxiety, depression											
Beck	3.0 ± 0.4	3.5 ± 0.4	3.7 ± 0.4	3.6 ± 0.4	3.7 ± 0.4	3.6 ± 0.4	.3888	.4698	.6816	.7618	.4158
STAI State	37.5 ± 1.2	36.3 ± 1.1	36.4 ± 1.1	35.0 ± 1.1	35.9 ± 1.1	35.9 ± 1.1	.5698	.0410	.6863	.2509	.9731

Data presented as mean ± SD.

[a]Age at baseline.

[b]Scores estimated using linear mixed model.

Abbreviations: ANOVA, analysis of variance; Beck, Beck Depression Inventory; CT, chemotherapy; FACT-Cog, Functional Assessment of Cancer Therapy, Cognitive Scale; Oth, comments from others; PCA, perceived cognitive abilities; PCI, perceived cognitive impairment; pers. errors, perseverative errors; QoL, impact on quality of life; STAI State, Spielberger State-Trait Anxiety Inventory; T1, baseline assessment; T2, assessment after adjuvant therapy; TMT, Trail Making Test.

cognition has been previously shown in preclinical studies [13, 14]; however, the effect of age was not assessed. No dose-dependent effect of FEC on cognition was found, but only our younger patients received the highest dose.

Cognitive complaints were more frequent after treatment for patients treated with chemotherapy than for those treated without it, particularly among the oldest patients. Although the CT+ group had fewer cognitive complaints before adjuvant treatment, they had a greater increase in complaints after it. Previous studies have not been conclusive on this issue. In one series of breast cancer patients aged ≥65 years, cognitive complaints after chemotherapy were present only in 10% of patients and no significant change occurred from baseline [57]. However, in another sample of breast cancer patients aged ≥65 years who had received adjuvant chemotherapy, 51% reported a decline in subjective cognitive function, which was most pronounced in patients who had reported pre-existing memory problems [58]. We also found that patients with more cognitive complaints before treatment were those with a greater increase in cognitive complaints after it.

Strengths and Limitations of the Study

The strengths of the present study are that it included the largest published sample of elderly EBC patients to date, including a group treated with modern chemotherapy regimens that included anthracyclines and docetaxel and a group of healthy controls. Our study used objective and subjective cognitive measures, a comprehensive battery of assessments using standard and recommended instruments, and geriatric and biological assessments.

Although they are not comparable, two complementary methods of statistical analysis were used: the RCI and a mixed model analysis. In addition, the RCI accounts for the results of

each patient individually and for the test-retest effect. Using a subgroup analysis in which the treatment received and age were considered, the RCI showed different and complementary results to those of the mixed model.

Overall, the present study failed to confirm previous results that showed significant differences in objective cognitive functioning between patients who had received chemotherapy and those who had not. This result could have partly resulted from overestimation of the effect of radiotherapy on cognition by performing the cognitive assessment just after the end of radiotherapy in this group, such that the subjects probably had insufficient time to recover from the fatigue induced by the treatment. The post-treatment assessment differed between the patient groups. For practical reasons and so that the patients did not have to return to the hospital just for the study, the cognitive assessment was conducted with a follow-up consultation or medical examination. However, the delay between the two assessments (controlled in the mixed model) had no major effect on cognition (learning effect only for 3 of 14 objective cognitive scores).

The negative effect of CT on cognition among the group aged more than 75 years requires confirmation by a larger study that includes elderly patients.

Conclusion

The present study is the largest published prospective study assessing cognitive function in older adults with EBC that included a group of patients treated with modern chemotherapy regimens and a group of healthy controls. Regardless of the adjuvant treatment, approximately half the patients experienced objective cognitive decline after such treatment. The oldest patients were more likely to experience an objective cognitive decline with chemotherapy, in particular, when the regimen included docetaxel. Additional research is needed to understand, anticipate, and manage the short- and long-term effects of cancer therapy on cognitive function of elderly patients, especially those receiving chemotherapy.

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Disclosures

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