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EPIDEMIOLOGY

Global and focal brain volume in long-term breast cancer survivors exposed to adjuvant chemotherapy

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Abstract A limited number of studies have associated adjuvant chemotherapy with structural brain changes. These studies had small sample sizes and were conducted shortly after cessation of chemotherapy. Results of these studies indicate local gray matter volume decrease and an increase in white matter lesions. Up till now, it is unclear if non-CNS chemotherapy is associated with long-term structural brain changes. We compared focal and total brain volume (TBV) of a large set of non-CNS directed chemotherapy-exposed breast cancer survivors, on average 21 years post-treatment, to that of a population-based sample of women without a history of cancer. Structural MRI (1.5T) was performed in 184 chemotherapy-exposed breast cancer patients, mean age 64.0 (SD = 6.5) years, who had been diagnosed with cancer on average 21.1 (SD = 4.4) years before, and 368 age-matched cancer-free reference subjects from a population-based cohort study. Outcome measures were: TBV and total gray and white matter volume, and hippocampal volume. In addition, voxel based morphometry was performed to analyze differences in focal gray matter. The chemotherapy-exposed breast cancer survivors had significantly smaller TBV (−3.5 ml, $P = 0.019$) and gray matter volume (−2.9 ml, $P = 0.003$) than the reference subjects. No significant differences were observed in white matter volume, hippocampal volume, or local gray matter volume. This study shows that adjuvant chemotherapy for breast cancer is associated with long-term reductions in TBV and overall gray matter volume in the absence of focal reductions. The observed smaller gray matter volume in chemotherapy-

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exposed survivors was comparable to the effect of almost 4 years of age on gray matter volume reduction. These volume differences might be associated with the slightly worse cognitive performance that we observed previously in this group of breast cancer survivors.

Keywords Long-term · Survivors · Breast cancer · Adjuvant chemotherapy · Brain volume · MRI

Introduction

Treatment of breast cancer with cytotoxic agents has been associated with structural and functional brain changes (Table 1) [1]. White-matter pathology has been observed within months up to 10 years post-treatment. Compared to healthy controls and breast cancer patients who never received cytotoxic treatment, chemotherapy-exposed patients had more white matter hyperintensities [2, 3] and decreased integrity of major white matter tracts in frontal and temporal regions of the brain [4, 5]. The integrity of the genu of the corpus callosum also was lower in chemotherapy-exposed patients [6].

Few studies have investigated the association between chemotherapy and gray matter volume. One study reported that patients 1 year post-treatment had smaller local gray matter volumes than cancer patients who never received chemotherapy. This was not observed in another group of patients who were 3 years post-treatment [7]. A study that strictly examined hippocampal volume did not find differences between cancer patients who received chemotherapy 3 years before and those who did not [8]. We recently showed that breast cancer survivors who completed high-dose chemotherapy almost 10 years before had less focal gray matter than survivors who never received chemotherapy [4]. A prospective study observed focal gray matter volume decrease 1 month after cessation of chemotherapy, which recovered in some, but not all regions at 1 year post-treatment [9].

The four studies described above performed brain volumetrics from 1 month up to 10 years post-treatment using different imaging protocols and analytic procedures. Their sample sizes were relatively small: the number of chemotherapy-exposed patients ranged from 5 to73 (Table 1) [2–4, 7–10].

To date, it is unclear if standard-dose chemotherapy is associated with long-term effects on brain structure. This issue becomes increasingly important as the number of long-term, hence elderly cancer survivors is steeply increasing [11] and recent literature shows that chemotherapy is associated with cognitive problems in long-term survivors of breast cancer [12]. Because central nervous system (CNS) regeneration is limited [13], it is possible that chemotherapy-induced structural brain changes are persistent rather than transient.

We evaluated whether breast cancer patients who had been exposed to adjuvant chemotherapy on average more than 20 years before, had smaller brain volumes than women from the general population without cancer. Hereto, we compared 1) brain tissue volumes; 2) hippocampal volume; and 3) regional gray matter volume of 184 invasive breast cancer survivors who had been exposed to chemotherapy and radiotherapy to those of 368 age-matched healthy control subjects from a population-based study.

Materials and methods

Participants

The current study is embedded in a study investigating the late effects of adjuvant chemotherapy on brain function and structure in elderly breast cancer survivors. It compares chemotherapy-exposed invasive breast cancer survivors with female subjects without a history of cancer from the Rotterdam Study (RS). Written informed consent was obtained from all participants. The institutional review boards of the two participating institutions (the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital and the Erasmus University Medical Center) approved the study.

Chemotherapy-exposed subjects

We selected consecutive female patients with unilateral invasive breast cancer from the registries of the Netherlands Cancer Institute/Antoni van Leeuwenhoek Hospital and the Daniel den Hoed Clinic of the Erasmus Medical Center, who had been treated with 6 cycles of CMF chemotherapy (Cyclophosphamide 100 mg/m^2 on days 1–14; Methotrexate 40 mg/m^2 on days 1 and 8; 5-Fluorouracil 600 mg/m^2 on days 1 and 8) between 1976 and 1995.

We included patients who were between 50 and 80 years of age, in whom invasive breast cancer was their first and only malignancy, who had remained disease-free since treatment for breast cancer, and who had sufficient command of the Dutch language. Exclusion criteria were use of adjuvant endocrine therapy and MRI contraindications.

A complete overview of the subject inclusion has been described earlier [14]. In short, of the 291 patients who were eligible, 195 (67.0%) agreed to participate. Of these 195 women, four aborted the scan because of claustrophobia. Three scans were unusable due to motion artifacts. Another four were excluded on the basis of cortical infarctions, leaving 184 scans to be analyzed.

Table 1 Overview of MRI studies that investigated the association between chemotherapy for breast cancer and brain volume

Study	Numer of subjects			Time since end of CT Years (SD)	White matter		Gray matter		Outcome
	CT^+	CT^-	HC		Measure	ROI	Measure	ROI	
Brown et al. [2]	13	–	13	1.0 (0.5)	WMH (ml)	Whole brain	–	–	High dose CT is associated with WMH
Brown et al. [10]	8	–	–	1, 3, 6, 9, 12 months	WMH (ml)	Whole brain	–	–	White matter changes occur as soon as 2 months after chemo and stabilize after 6 months to 1 year. WMH still present at 1 year seem to be permanent
Choi et al. [3]	5	1	–	During treatment	Visually checked	Whole brain	Visually checked	Whole brain	All patients leukoencephalopathy, visible as diffuse periventricular WMH
Yoshikawa et al. [8]	44	31	–	3.5 (1.1)	–	–	Volume (ml)	Hippocampus	No differences in hippocampal volume
Inagaki et al. [7]	51	54	55	0.3 (0.1)	VBM	Whole brain	VBM	Whole brain	Smaller right prefrontal and parahippocampal gyrus in CT^+ patients compared to CT^- patients
	73	59	37	3.3 (1.0)	VBM	Whole brain	VBM	Whole brain	No volume differences between groups
Abraham et al. [6]	10	–	9	1.8 (0.8)	DTI	Genu and Spelnium	–	–	Patients had lower FA in the genu but not in the splenium of the corpus callosum
Deprez et al. [5]	17	10	18	0.4 (0.1)	DTI; VBA	Whole brain	–	–	Compared to HC, CT^+ had lower FA in frontal and temporal WM tracts. In frontal WM patients had increased MD compared to HC. RD values for the above reported regions were higher in C^+ than in HC. Compared to CT^-, CT^+ had lower FA, higher MD, and higher RD in the above reported regions
McDonald et al. [9]	17	12	18	0, 1, 12 months	–	–	VBM	Whole brain	Patients had a decline in gray matter from baseline to 1 month compared to HC. At 1 month CT^+ had decreased gray matter in bilateral frontal, temporal and cerebellar regions and in the right thalamus. Recovery was seen at 1 year in some, but not all regions, indicating persistent decrease
de Ruiter et al. [4]	17	15	–	9.5 (0.8)	DTI; visually checked; 1H-MRS	Whole brain; 1H-MRS in left centrum semiovale	VBM	Whole brain	Whole brain MD and AD were higher in CT^+. In several regions FA was lower and MD and RD were higher in CT^+. No differences were observed in visually checked WMH. NAA/Cr was lower in CT^+ indicating axonal injury. VBM showed gray matter reductions in the posterior parts of the brain in CT^+.

CT^+ Breast Cancer patients treated with Chemotherapy, *CT^-* Breast Cancer patients NOT treated with Chemotherapy, *HC* Healthy Control Subjects, *ROI* Region of Interest, *WMH* White Matter Hyperintensities, *VBM* Voxel Based Morphometry, *DTI* Diffusion Tensor Imaging, *VBA* Voxel Based Analysis, *WM* White Matter, *FA* fractional anisotropy, *MD* Mean Diffusivity, *RD* Radial Diffusivity, *AD* Axial Diffusivity, *1H-MRS* Single voxel MR spectroscopy

Decliners were older than subjects who were willing to participate when invitation letters were sent ([F1,289] = 11.13, $P < 0.05$).

Healthy reference subjects

Reference subjects were selected from the RS; a population-based prospective cohort study that is ongoing since 1990 [15]. Among other diseases in the elderly, the study targets neurological and psychiatric diseases, and includes an extensive MR brain imaging protocol. As of 2008, the study has included 14,926 subjects. To date, 4,898 participants of the RS have been invited for the Rotterdam Scan Study (RSS). Exclusion of individuals with MRI contraindications ($n = 389$) left 4,509 eligible persons, of whom 4,102 (91%) agreed to participate. Due to physical inabilities, imaging could not be completed in 44 individuals.

Each chemotherapy-exposed breast cancer survivor was matched on age to two randomly selected women without a history of cancer of the 4,058 participants of the RSS who completed MRI examination. This resulted in a total of 368 reference subjects.

Methods

MRI Acquisition

Multi-sequence MRI for both cancer survivors and reference subjects was performed on the same 1.5-T MRI scanner (General Electric Healthcare, Milwaukee, Wisconsin). During the study period, no software or hardware upgrades were performed on the system. Our full scan protocol has been described in detail earlier [16].

For this study we used a high-resolution axial MRI sequence, i.e., a T1-weighted 3-dimensional fast radiofrequency spoiled gradient recalled acquisition in steady state with an inversion recovery prepulse sequence (TR = 13.8 ms, TE = 2.8 ms, inversion time = 400 ms, FOV = 25 × 17.5 cm^2, matrix = 416 × 256 [interpolated to 512 × 512], flip angle = 20°, NEX = 1, bandwidth [BW] = 12.50 kHz, 96 slices with a thickness = 1.6 mm zero-padded in the frequency domain to 0.8 mm, interpolated voxel size = 0.5 × 0.5 × 0.8 = 0.2 mm^3; duration = 6 min.)

Remaining scan sequences such as cerebral blood flow and diffusion weighted imaging will be described separately.

Acquisition of medical and demographic data

Demographic information and medical data that are associated with brain structure were collected for all participants. Sitting blood pressure was measured twice on the right arm with a random-zero sphygmomanometer. We used the average of these two measurements [17]. Data on diabetes, education level, and smoking status were obtained, as they are part of the core interview of the RS [15]. Depressive symptoms were assessed with the Center for Epidemiologic Studies Depression scale (CES-D), which was converted to a sum-score according to the standard scoring rules. [18] Education level was subdivided into three levels: 1) lower vocational education or less; 2) lower secondary education/intermediate vocational education/general secondary education; 3) higher vocational education or better. Smoking status was subdivided into three levels: current-, ever-, and never-smoker.

Pre-processing and segmentation

Non-uniformity correction and automatic reorientation to the anterior commissure was applied to all scans [17]. Reorientation was visually inspected and manually corrected if necessary. Images were segmented into gray matter, white matter, and cerebrospinal fluid (CSF) using the "new segment" module in the Statistical Parametric Mapping software version 8 (SPM8).

Regional gray-matter differences

Regional brain differences were analyzed using voxel-based morphometry (VBM), following diffeomorphic anatomical registration through exponentiated lie algebra (DARTEL) under SPM8 implemented in Matlab R2010b (MathWorks, Natick, Massachusetts). DARTEL is a fully deformable registration method that is effectively unconstrained by number of degrees of freedom. It has proven good segmentation and registration accuracy in comparison with other algorithms [19, 20].

First, an initial template was created by averaging all segmentations per tissue class. Subsequently, a study-specific template was created on the basis of the individual deformation from the initial template of all 184 chemotherapy-exposed survivors and 184 randomly assigned age-matched subjects from the total group of 368 reference subjects. This selection was made to ascertain equal contributions of both groups to the template. Subsequently, the deformation fields of all 552 subjects were warped to the template. Through Jacobian modulation preservation of the initial volumes was achieved. The modulated-warped images were smoothed with an 8 mm full-width at half-maximum Gaussian kernel to increase signal to noise ratio.

Total brain tissue volume

A study-specific brain mask was computed by summing the DARTEL gray matter, white matter, and CSF templates and thresholding this image at a probability of 0.5. Tissue

volumes in milliliters were calculated from masked tissue segmentations in DARTEL space by summing all voxels (0.2 mm^3 each) of the corresponding tissue class across the whole brain.

Hippocampal volume

Left and right hippocampal volumes were segmented separately using an automated segmentation method [21]. In brief, this method was developed in-house and uses both a statistical intensity model and a spatial probability map. The intensity model describes the typical intensities of the hippocampus and the background. The spatial probability map contains for every voxel the probability that it is part of the hippocampus. Both the intensity model and spatial probability map were learned from a set of 18 manually labeled hippocampi. Included in the region of interest were the dentate gyrus, CA1-4, and the alveus [21].

Analysis

Intracranial volume (ICV) was defined as the sum of gray matter, white matter, and CSF. Total brain volume (TBV) was defined as the sum of gray matter and white matter. Analysis of (Co)variance (AN(C)OVA) and χ^2 tests were used to compare medical and demographic characteristics between chemotherapy-exposed and reference subjects. We used general linear models to compare groups on gray and white matter volume, CSF, and TBV.

Whole brain voxel-wise comparison in the context of the general linear model with Family Wise Error (FWE) correction was performed in SPM to identify regional gray matter volume differences between groups. All primary analyses were adjusted for ICV, height, age, age-squared, mean systolic and diastolic blood pressure, self-reported prevalence of diabetes, education level, smoking status and symptoms of depression, as these have been associated with brain volume [17, 22, 23]. To be able to compare the association between chemotherapy and brain tissue volume with the effect size of age we additionally ran the same general linear model but without including age-square.

Results

Population characteristics are presented in Table 2. Chemotherapy-exposed patients had been diagnosed with breast cancer on average 21.1 years before participation in this study at a mean age of 42.9 years. They were taller, better educated and had higher diastolic blood pressure than women from the reference group. No significant differences were observed between the groups regarding age, systolic blood pressure, CES-D score, smoker status, and prevalence of diabetes.

Total tissue volumes are presented in Table 3.

Segmentation of the hippocampi failed in seven chemotherapy-exposed patients, leaving 177 subjects to be analyzed. The chemotherapy-exposed survivors had significantly smaller TBV (−3.5 ml, $P = 0.019$) and smaller gray matter volume (−2.9 ml, $P = 0.003$) than the reference group. No significant differences were observed in total ICV, white matter volume, CSF volume, or right or left hippocampal volume between chemotherapy-exposed breast cancer patients and the reference group. In the model without age-square the effect of chemotherapy on TBV remained −3.5 ml ($P = 0.018$) and on gray matter volume remained −2.9 ml ($P = 0.003$), whereas the effect of age on TBV was −0.99 ml ($P < 0.001$) per year and on gray matter was −0.75 ml ($P < 0.001$) per year.

Subsequently, DARTEL revealed no significant regional gray matter volume differences between groups.

Discussion

Here, we report the first study on the late effects of standard-dose adjuvant chemotherapy on brain volume in a large sample of breast cancer survivors on average more than two decades after cessation of treatment. Chemotherapy-exposed breast cancer survivors had significantly smaller TBV and gray matter volume than reference subjects without a history of cancer. No differences were observed in white matter volume, CSF volume, hippocampal volume or focal gray matter volume.

Strengths of our study are the large sample size, the long time since chemotherapy, the homogeneous study population regarding cytotoxic agents (regimen, number of cycles), and the large population sample of age-matched women without a history of cancer.

We are aware that our study has some drawbacks that need to be addressed. Because we did not include a non-chemotherapy-exposed breast cancer control group we cannot separate the effect of chemotherapy and cancer itself. However, the only two studies investigating brain structure in breast cancer patients that included both healthy controls and breast cancer patients not exposed to chemotherapy did not report a difference between these two groups, suggesting no effect of cancer itself on brain structure [7, 9].

Another point of discussion is whether the findings of this study could also translate to breast cancer patients treated with contemporary regimens. Since both cyclophosphamide and 5-fluorouracil continue to be implemented in current regimens, and these agents, as well as many other commonly used agents are independently associated with structural brain changes in animals [24, 25], our study results might also apply to contemporary regimens.

Table 2 Population characteristics

	Chemotherapy-exposed breast cancer survivors ($n = 184$)	Reference group ($n = 368$)	*P*
Age in years (mean (SD))	64.0 (6.5)	64.0 (6.5)	0.995
Height in cm (mean (SD))	164.9 (6.4)	162.2 (6.0)	<0.001
Systolic bloodpressure in mm Hg[a] (mean (SD))	140.5 (20.1)	137.7 (20.2)	0.13
Diastolic bloodpressure in mm Hg[a] (mean (SD))	84.3 (10.5)	80.7 (9.6)	<0.001
Depression score (CESD) (mean (SD))	4.8 (5.7)	5.9 (7.8)	0.11
Diabetes (n (%))	14 (7.6)	16 (4.3)	0.12
Education level (n (%)):			<0.001
Low[b]	84 (47.5)	242 (65.8)	
Intermediate[c]	41 (22.3)	83 (22.6)	
High[d]	59 (32.1)	43 (11.7)	
Smoker status (n (%)):			0.28
Current	22 (12.0)	67 (18.2)	
Ever	97 (52.7)	180 (48.9)	
Never	65 (35.3)	121 (32.9)	
Age at cancer diagnosis in years (mean (SD))	42.9 (5.4)	–	–
Time since chemotherapy in years (mean (SD)	21.1 (4.4)	–	–

SD standard deviation, *CESD* center for epidemiologic studies depression Scale

[a] In sitting position

[b] Lower vocational education or less

[c] Lower secondary education, intermediate vocational education and general secondary education

[d] Higher vocational education or better

Table 3 Total brain tissue volumes (in milliliter)

Tissue/ROI	Chemotherapy-exposed breast cancer survivors ($n = 184$)		Reference group ($n = 368$)		β	95% CI for β	*P*
	Mean	SD	Mean	SD			
Intracranial volume	1318.7	136.5	1315.7	185.3	3.0	−13.9; 19.8	0.73
Brain volume	1087.0	23.5	1090.7	23.9	−3.5	−6.4; −0.6	0.019
Gray matter	617.0	15.6	620.0	21.1	−2.9	−4.8; −1.0	0.003
White matter	470.0	17.4	470.6	23.7	−0.6	−2.8; 1.6	0.59
Cerebrospinal fluid	235.5	15.5	233.8	21.1	1.6	−0.3; 3.5	0.10
Left hippocampus[a]	2.9	0.4	2.9	0.6	−0.05	−0.10; 0.01	0.07
Right hippocampus[a]	2.9	0.4	2.9	0.6	−0.01	−0.06; 0.04	0.81

ROI Region of Interest, *SD* standard deviation, *CI* Confidence Interval

[a] *n* chemotherapy-exposed breast cancer patients = 177

Previously two studies applied VBM to investigate the effects of chemotherapy on focal gray matter volume. Inagaki et al [7]. reported smaller right prefrontal and parahippocampal gyrus in chemotherapy-exposed patients than non-exposed patients at 3 months post-treatment. However, no volumetric difference was observed between another sample of chemotherapy-exposed and non-exposed patients who were more than 3 years post-treatment [7]. Likewise, McDonald et al. [9] reported that chemotherapy-exposed patients had decreased gray matter in bilateral frontal, temporal, and cerebellar regions and in the right thalamus at 1 month post-treatment, but that recovery was seen at 1 year in several, although not all regions [9]. These studies suggest that chemotherapy may induce transient local gray matter volume reductions that may (partly) recover over time. This is in line with the absence of large differences between chemotherapy-exposed survivors and the general population more than 20 years post-treatment that we observed. The only other study that investigated the association between hippocampal volume and chemotherapy did also not observe a relationship between the two [8].

Of all studies that investigated the effect of chemotherapy on brain structure, none examined total tissue volumes after cytotoxic treatment [2–4, 7–10]. We found significant effects of chemotherapy on TBV and gray matter volume. In our analysis the lower amount of gray matter in chemotherapy-exposed survivors was comparable to the effect of almost 4 years of age on gray matter volume. The clinical relevance of this volume difference is not straightforward, but considering the effect size, chemotherapy might be associated with cognitive problems that we observed previously in this group of patients [26]. Two other recent studies also reported a negative association between chemotherapy and long-term cognitive functioning [12, 27].

Up till now three studies have reported adverse effects of chemotherapy on white matter as measured with diffusion tensor imaging (DTI) [4–6]. Therefore, it might be that the small effects of chemotherapy on total gray matter volume may be accompanied by microstructural white-matter changes.

The exact mechanisms for chemotherapy-associated gray matter volume reductions are largely unknown. Postulated explanations are enhanced neural cell death and decreased cell division [28], due to crossing of the blood–brain barrier by certain chemotherapeutic agents and increased levels of oxidative stress [29]. Cell death however is less likely to explain the smaller volume, since it is considered irreversible and therefore contradictive to the partial recovery of local gray matter reductions that were reported in a longitudinal study after the effects of chemotherapy. In addition, another study reported smaller gray matter volumes in a group of patients 1 year post-treatment, but not in a group of patients 3 years post-treatment [7, 9].

Conclusion

In this study, we investigated the very late effects of chemotherapy on the macrostructure of the brain. We observed on average smaller total gray matter volume and TBV in chemotherapy-exposed breast cancer survivors than in a population-based reference sample of age-matched women. This volume difference was comparable to the effect of almost 4 years of age on gray matter volume loss. No focal gray matter volume reductions between groups were observed.

Ethical standards

The current study has been conducted in compliance with the current laws of the Netherlands.

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Conflict of interest None.

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