Multimodal MR imaging in breast cancer

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Effects of cancer and cancer treatment on brain and cognition

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‘Ik heb het nog nooit gedaan, dus ik denk wel dat ik het kan’
Pippi Langkous

CONTENT

Chapter 1

General introduction

With an incidence of 15,500 new patients annually, breast cancer is the most common malignancy in women in the Netherlands[1]. Over the last decades, chances of survival for breast cancer patients have improved. The five-year survival rate in 1990 was approximately 77%, which has risen to 87% in 2012[1]. This is probably due to population screening, improved diagnostics and the introduction of systemic treatment. With an increasing number of breast cancer survivors, more research has been directed to studies on quality of life following treatment.

Systemic treatment and cognitive functioning

Systemic treatment, such as chemotherapy and hormonal therapy, is given in addition to loco-regional treatment such as surgery and radiotherapy. It is aimed at reducing the chance of disease recurrence by eliminating occult micro-metastases. The most well-known side effects of chemotherapy, such as vomiting and hair loss, occur during the course of treatment and subside after treatment is ended. Other side effects, such as fatigue, and cognitive impairment may last well into survivorship[2–4] and negatively affect quality of life.

Cognitive impairment has already been found to occur in approximately 40% of breast cancer patients even before the start of treatment[5–12]. Although several biological and psychological factors, such as worry, fatigue, stress, surgery, and disease staging have been associated with pretreatment cognitive impairment, to date no consistent explanatory factor has been identified[7,9,13–2].

Longitudinal studies investigating the effects of cancer treatment on cognitive performance in breast cancer patients have shown cognitive decline during systemic treatment in up to 75% of patients, whereas deterioration after completion of therapies may occur in up to 60% of patients[21]. The most commonly affected cognitive domains seem to be memory and executive function[21]. In addition, MRI studies have shown lower brain volume, lower white matter integrity, and altered brain activation following chemotherapy[22–26].

Mechanisms

During the last decade, preclinical studies have begun to shed light on the mechanisms underlying cancer and cancer treatment-related cognitive impairment. They demonstrated increased apoptosis in healthy proliferating cells as well as damage to neural precursor cells following administration of cytostatic agents[27]. Other neurobiological processes, including oxidative stress, neurotransmitter/ monoamine release, mitrochondial dysfunction and the disruption of blood vessel density and blood supply have likewise been implicated in the etiology of chemotherapy-related cognitive impairment[27,2].

Also, pro-inflammatory cytokines are frequently proposed to play a role in cognitive impairment in cancer patients, but clinical studies have not yet shown a clear picture regarding the relationship

between cytokines and cognitive function[29,3]. Another factor suggested to play a role in the development of cognitive impairment is variance in genetic factors. Although some studies have shown an association between Apolipoprotein E (APOE) or brain-derived neurotrophic factor (BDNF) polymorphisms and cognitive impairment in breast cancer patients[31–33], sample sizes in these studies were small, limiting the generalizability of these findings.

MRI has been employed to further investigate the effects of cancer and cancer treatment on the brain in vivo[22–26]. These studies report differences in brain function and structure before as well as following cancer treatment. To date, only one study used multimodal MRI, showing reduced white matter integrity in areas adjacent to fMRI hypoactivations[34]. In that study, one area of hypoactivation overlapped with a region of lower grey matter volume. Also, reduced levels of N-Acetylaspartate, a marker of neuronal viability, in the semioval center were associated with lower white matter integrity. These findings suggest that the effects of chemotherapy may affect neuronal axons as well as cell bodies, which also has functional implications.

Aims of the thesis

With increasing numbers of cancer survivors, cancer-related cognitive impairment becomes a more important area of research. Although prevalence and severity vary between studies, the existence of cognitive impairment following cancer treatment is widely acknowledged. Preclinical studies have provided evidence for disruption of neurobiological processes, supporting the relation between cancer treatment and cognitive impairment. Cancer-related cognitive impairment has been reported in multiple cancer populations, e.g. testes, ovarian, colon, lymphoma, and lung cancer[35–40]. In the current thesis, I will focus on breast cancer patients.

To further understand the mechanisms underlying cancer-related cognitive impairment, MRI has been employed. To date, no longitudinal multimodal studies investigating the effects of breast cancer on cognitive function and brain function and structure have been published. Combining the results of neuropsychological testing, multimodal MRI, and patient-reported outcomes, will further our understanding of the nature of cancer and cancer treatment-related cognitive impairment. A longitudinal design is necessary to evaluate pretreatment functioning and the role of biological and psychosocial factors therein. It also allows for the accurate assessment of the effects of cancer and cancer treatment, taking into account any prior differences. This information is essential to be able to accurately inform patients and also to identify new targets for possible interventions.

In the current thesis, I describe a longitudinal multimodal study in breast cancer patients, comparing patients receiving systemic treatment to patients not requiring systemic treatment, as well as no-cancer controls. Different MRI modalities, neuropsychological testing and patient-reported outcomes were collected after surgery, but before the start of adjuvant treatment. To assess the effects of systemic treatment, a follow-up evaluation took place at approximately

six months after the last cycle of chemotherapy, or at matched intervals. We compared breast cancer patients receiving adjuvant anthracycline-based chemotherapy with or without endocrine treatment to breast cancer patients who did not require systemic treatment, as well as age-matched no-cancer controls. This allowed us to evaluate the effects of cancer treatment as well as the effects of cancer itself.

Outline of the thesis

In **Chapter 2** we studied cognitive function and brain function and structure prior to systemic treatment. To investigate whether breast cancer patients already show differences depending on the type of treatment they are about to receive, and if patients differ from no-cancer controls, breast cancer patients scheduled to receive systemic treatment were compared to patients not requiring systemic treatment and to no-cancer controls. We evaluated neuropsychological performance, brain function and structure, and the possible relation between these measures and biological and psychosocial factors.

Chapter 3 reports on neuropsychological performance six months after systemic treatment. Cognitive performance was assessed at the group level and by means of a multivariate method to identify individuals demonstrating a deviating pattern of cognitive performance.

In **Chapter 4** we investigated regional brain activation during tasks of executive function and memory encoding and retrieval. By employing two different tasks, covering cognitive domains frequently reported to be affected by cancer treatment, we were able to determine whether the effects of systemic treatment where dependent on the cognitive domain.

Chapter 5 focuses on white matter integrity in the brain after systemic treatment. We also evaluated the relation with cognitive performance, and biological and psychosocial factors.

The general discussion, **Chapter 6**, summarizes and discusses the differences in cognitive performance, brain structure and function prior to as well as after systemic treatment in breast cancer patients. Methodological issues, implications for clinical practice and recommendations for future research are included in this chapter.

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