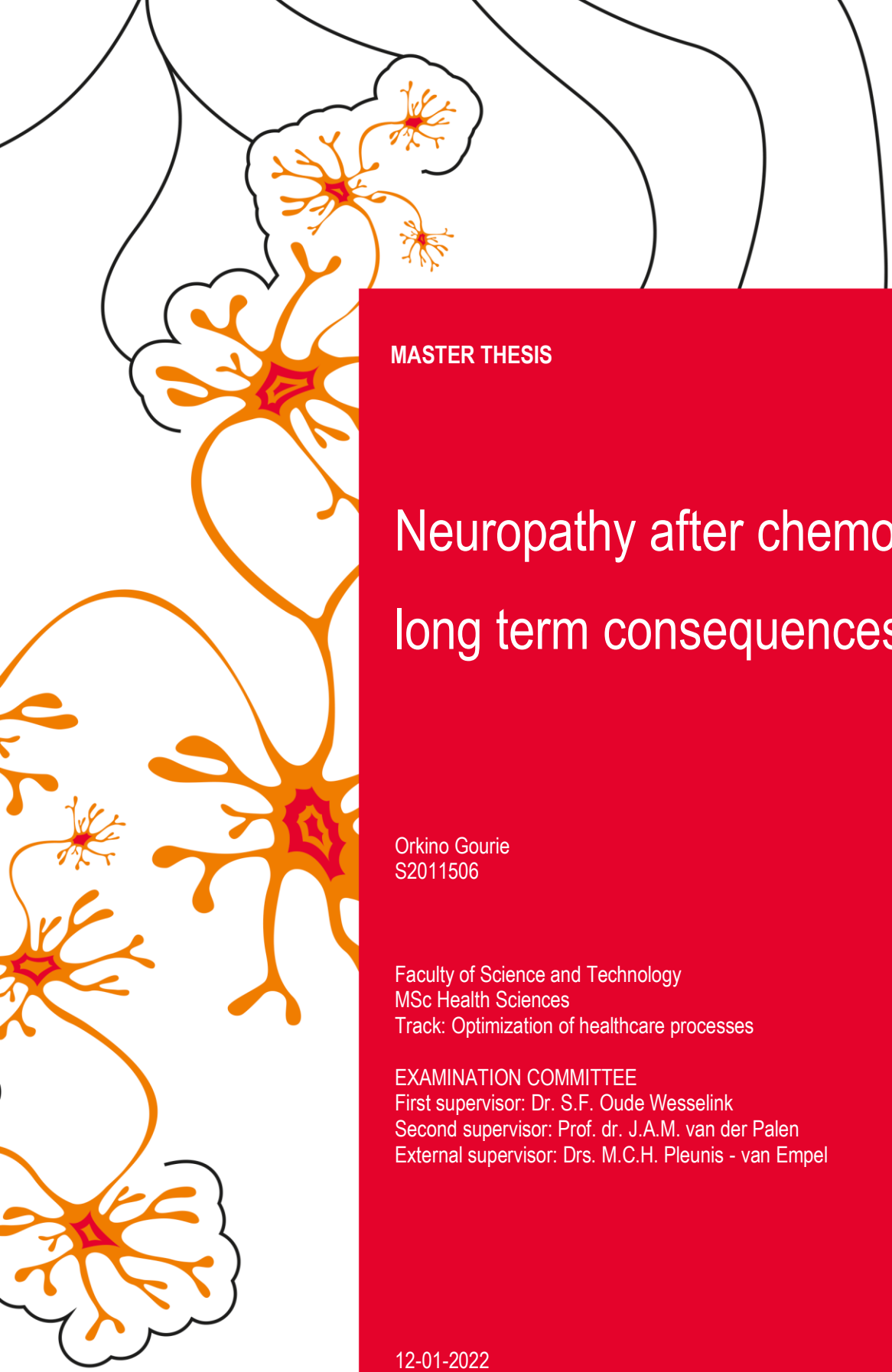

MASTER THESIS

Neuropathy after chemotherapy: long term consequences for patients

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Medisch Spectrum Twente
een santeon ziekenhuis

UNIVERSITY OF TWENTE.

Abstract

Background
Breast cancer is the most common occurring cancer in women in the Netherlands. The incidence and prevalence of breast cancer keep rising. The primary treatment for breast cancer is surgery. Alongside surgery, (neo)adjuvant chemotherapy with taxanes is often given to increase efficacy of tumor regression and survival rate. Chemotherapy often causes many side effects to the patient. The most limiting side effect of taxane chemotherapy is taxane-induced peripheral neuropathy (TIPN). TIPN can impact quality of life by limiting the patient to perform daily activities because of symptoms such as: muscle weakness, numbness and tingling in the hands and/or feet. Limited literature is available about the long-term prevalence of TIPN. Therefore, the aim of this study is to investigate the long-term TIPN prevalence and to analyze relationships between dose reductions, patient-reported neuropathy and treatment regimens and presence of TIPN two years after taxane chemotherapy. The research question of this study is: "What is the prevalence of neuropathy symptoms two years after (neo)adjuvant breast cancer taxane chemotherapy in patients treated in hospital Medisch Spectrum Twente in 2017 – 2019?".

Method
Firstly, a literature search was conducted to identify literature on breast cancer and TIPN. Furthermore, two methods were used to conduct this research. A retrospective patient record study was conducted to determine inclusion eligibility, including data collection of 200 patients using electronic health records (EHRs). In addition, a prospective quantitative cohort study was conducted, including new data collection using the questionnaires Douleur Neuropathique 4 Questions (DN4) and Common Terminology Criteria for Adverse Events by the National Cancer Institute (CTCAE-NCI) to detect and grade neuropathic pain. 163 patients met the inclusion criteria and were sent a questionnaire. Statistical methods included binary logistic regressions and cross-tabulation analyses to answer the research questions.

Results
In total 73 patients completed and returned the questionnaires. The prevalence of patients with TIPN two years after chemotherapy was 57.5% (N = 42). After logistic regression analysis, age showed to be a significant predictor of TIPN two years after chemotherapy. Older age was associated with a higher risk of long-term TIPN. Furthermore, 46 reported neuropathy symptoms during treatment, of which 37 patients received a dose reduction. Of these 37 patients, 29.7% (N = 11) completely recovered from neuropathy two years after treatment. Out of the 42 patients who suffer from neuropathy two years after treatment, 26.2% (N = 11) did not report neuropathy symptoms during treatment and consequently did not receive a dose reduction. Finally, patients who receive treatment regimens including paclitaxel are almost 3 times more likely to suffer from long-term TIPN compared to patients who receive a treatment regimen including docetaxel.

Conclusion
The prevalence of TIPN two years after completing taxane chemotherapy was 57.5% (N = 42) in breast cancer patients treated in the MST in the period 2017-2019. Dose reductions were not effective to all patients in reducing neuropathy, probably because of late dose reductions. Clinicians should learn to predict on neuropathy symptoms, by explaining the importance of timely dose reductions to the patient, so that the patient also reports TIPN symptoms in time. Recommendations for future research are as following: a better understanding of the pathophysiology of TIPN to develop and evaluate prevention and treatment strategies and use of the same assessment methods to detect and grade TIPN.

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Introduction

Quality of life

For a long time, the sole priority of oncology was keeping patients alive for as long as possible (1). By only focusing on keeping patients alive, the way in which patients survived was of minor importance. People's perception towards treatments has been changed now. An increase in life expectancy has the risk of a decrease in quality of life. Therefore, it is important to weigh the expected increase of life expectancy against the effects on the quality of life.

Quality of life is a broad concept. The World Health Organization (WHO) defines it as: "the individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards, and concerns" (2). Quality of life is a subjective and multidimensional concept which is not only determined by physical consequences, but also by psychological, social and societal aspects, such as social functioning and overall satisfaction with life (3). This concept is of great importance especially in oncology, because of rising incidence rates of cancer and increasing use of chemotherapy, which has a great impact on the life of patients because of the many side effects (4).

Breast cancer and chemotherapy

Breast cancer is the most common occurring cancer in women in the Netherlands. In the last few decades, the incidence of breast cancer keeps increasing. In 2018, around 118.000 patients got diagnosed with breast cancer (4). The 5-year prevalence of patients with breast cancer is around 80.000 (4). The prevalence and incidence of breast cancer patients are shown below in figures 1 and 2.

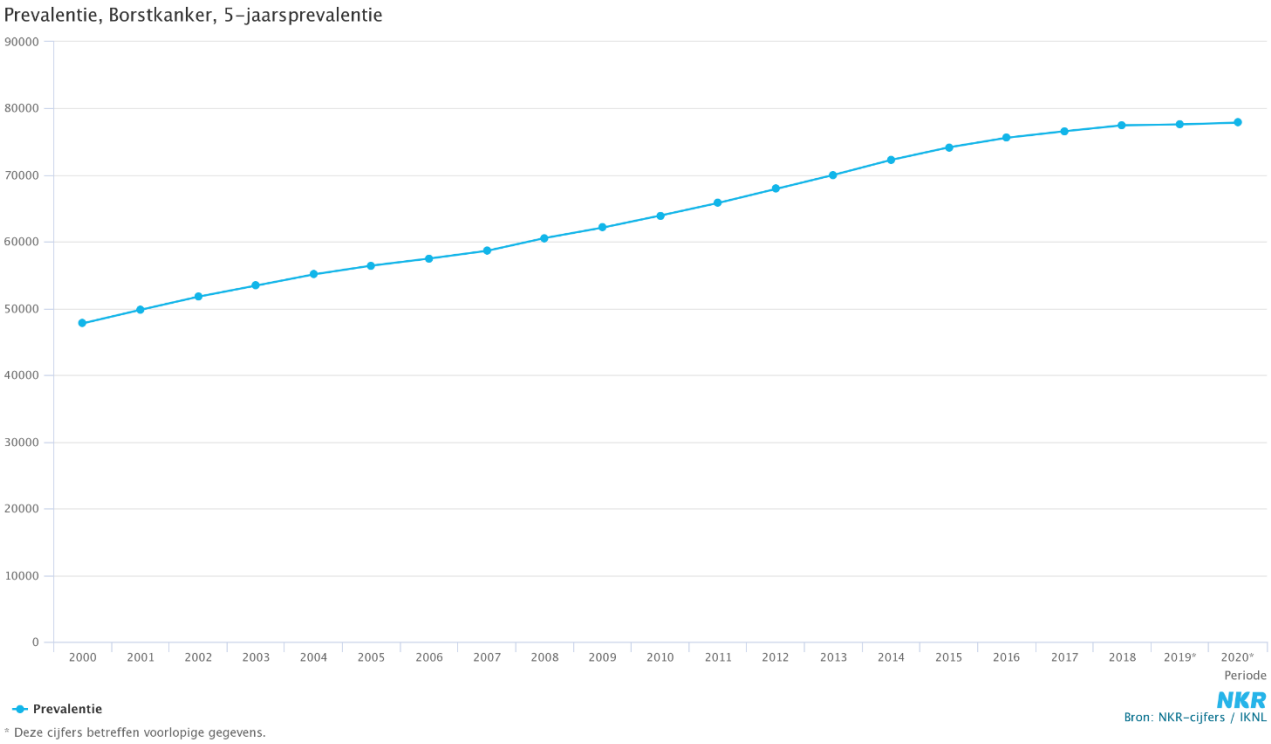

Figure 1. 5-years prevalence of patients with breast cancer in the Netherlands (4).

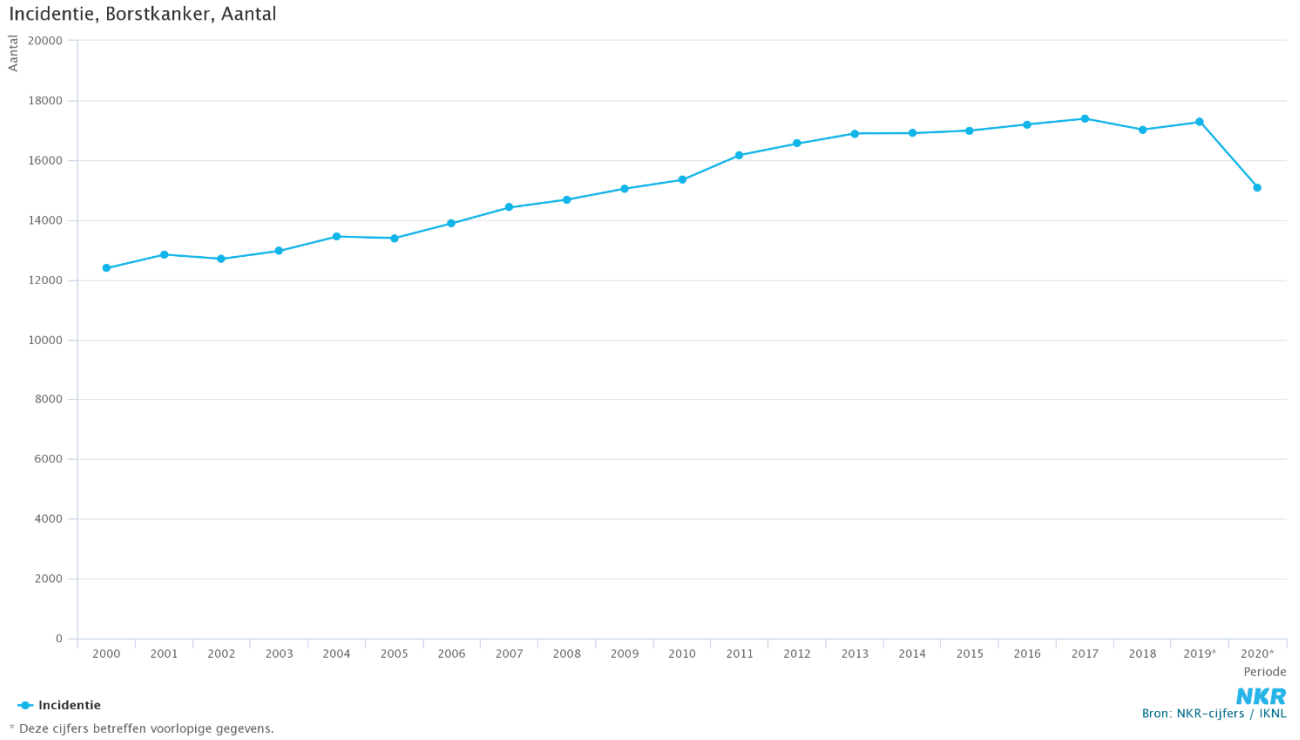

Figure 2. Incidence of patients with breast cancer in the Netherlands (4).

The primary treatment for breast cancer is surgery, this can be either breast-conserving surgery (removal of part of the breast) or mastectomy (removal of the entire breast). After surgery, adjuvant therapy can be given to fight undetectable metastases and increase the chance of survival (5). Adjuvant therapy can consist of chemotherapy, radiotherapy, immunotherapy, anti-hormonal therapy or a combination of these therapies (5).

In this study, the focus will be on chemotherapy and the side-effects of it. Chemotherapy is the treatment of cancer with cytotoxic chemicals, which are chemicals that kill cancer cells or inhibit the cell division (6). The aim of this treatment is to completely eliminate the tumor or to ease the tumor-related symptoms and extend life expectancy (6). Chemotherapy can be given in different ways, it can be given preoperatively (neoadjuvant) and postoperatively (adjuvant), before or after radiation treatment (5). Chemotherapy is often given neoadjuvantly, to shrink the tumor and increase the chance of breast-conserving surgery (6). Several schedules exist for intravenous administration, such as FEC-Docetaxel (fluorouracil, epirubicin and cyclophosphamide followed by docetaxel), TAC (docetaxel, adriamycin and cyclophosphamide), AC-Paclitaxel, treatment combinations with trastuzumab/pertuzumab. and other schedules including the taxanes docetaxel or paclitaxel (5). Deciding which chemotherapy must be given is based on the following clinical features (5):

- the TNM classification (tumor size, the presence of axillary lymph node metastases, the presence of distant metastases)
- the tumor type
- the age of the patient
- any comorbidity
- tumor characteristics, such as hormone receptors and increased expression of HER2/neu (human epidermal growth factor receptor type 2)

In addition, another clinical feature that is important is the body surface area (BSA) of the patient. Taxane dosing is based on the BSA of the patient. The relative dose intensity (RDI) is a tool that measures the effectiveness of this dosing. This is done by calculating the ratio between the administered dose per m^2 of BSA per week and the optimal dose per m^2 of BSA per week (30).

Neuropathy

As stated before, chemotherapy can cause many side effects to the patient. One of the most limiting side effects is chemotherapy-induced peripheral neuropathy (CIPN) (7). This is a side effect of many chemotherapeutic agents that target microtubules. Most of the times, neuropathy begins during treatment and can continue for many years, sometimes it can be temporary and disappear, but it is often chronic (8). It causes dysfunction and disturbance of the somatic and/or nervous systems (9). Taxanes belong to the most important drugs in treating breast cancer (7). Neuropathy is also one of the most frequently occurring side effect of taxane therapy with early-stage breast cancer, which is called taxane-induced peripheral neuropathy (TIPN) (7) (8) (9) (10) (11). The prevalence of TIPN is not well studied, however a systematic review showed that TIPN prevalence among patients with breast cancer was 70.8% (12). Some more recent studies suggest that the prevalence after completion of chemotherapy varies between 23% to 80% (9) (11). There is a lot of variation in prevalence rates, this variation can be explained by differences in patient population, outcome measures, chemotherapy regimens, collected variables, follow-up time and drug dosing (9) (13).

TIPN is an important challenge for both the patient and clinician. It is a challenge for clinicians because it has a big impact on treatment outcomes resulting from compromised dose delivery, dose delays/reductions and discontinuation of treatment. At the same time it is also a challenge for the patient, because the patient does not always want to reduce the dose due to fear for recurrence of cancer (7) (8) (10). Besides the effects on the treatment, it can also greatly impact the life of the patient, because of symptoms such as: paresthesia (numbness, tingling), muscle weakness and pain (11). Such effects may limit the ability of the patient to perform daily activities, which ultimately leads to a decreased quality of life.

Aim of the study

Much literature is available and has been found on neuropathy as side-effect after chemotherapy. However, limited literature is available about the long-term prevalence of neuropathy.

Therefore, the aim of the study is to investigate to which extent patients that have been treated for breast cancer in Medisch Spectrum Twente (MST) in 2017 – 2019 suffer from neuropathy symptoms on the long term. By mapping this, it contributes to better inform future patients about neuropathy to prevent it from getting worse.

Hereby, the following research question is formulated:

- What is the prevalence of neuropathy symptoms two years after (neo)adjuvant breast cancer taxane chemotherapy in patients treated in hospital Medisch Spectrum Twente in 2017 – 2019?

To answer the research question the following research sub-questions are formulated:

- To what extent is neuropathy present two years after taxane chemotherapy?
- What is the relationship between a dose reduction during treatment and the presence of neuropathy two years after taxane chemotherapy?
- What is the relationship between the relative dose intensity (RDI) during treatment as result of the patient reporting neuropathic symptoms during treatment and the presence of neuropathy two years after taxane chemotherapy?
- What is the relationship between the treatment regimens and the presence of neuropathy two years after taxane chemotherapy?

Method

Study design and population

This research was conducted using two methods. Firstly, this is a retrospective patient record study, which included the clinical and personal data collection of the patients using electronic health records (EHRs). Secondly, it is a prospective quantitative cohort study with an exploratory nature. This included the data collection, using questionnaires, and data analysis based on patients with breast cancer, which were treated with adjuvant and neoadjuvant chemotherapy with taxanes in the MST in the period 2017 – 2019.

The study population in this study included patients with breast cancer who have been treated (neo)adjuvantly with taxanes in MST in the period 2017 – 2019. The following inclusion and exclusion criteria from table 1 were used.

Table 1
Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
1) Patients with breast cancer 2) Treated in hospital MST 3) (Neo)adjuvant chemotherapy started between 01-01-2017 until 01-04-2019 4) Chemotherapy included taxanes (docetaxel or paclitaxel)	1) Metastatic disease

Data collection

Firstly, the patient data was obtained from "XCare" and "Digitale Status Voering (DSV)". These two systems are both EHRs used by the MST. With the data obtained from these two EHRs, a dataset was made. Finally, a selection was made in the dataset based on the inclusion and exclusion criteria to determine which patients must be included in the research and should receive the questionnaires.

To answer the research questions, new data was collected by sending out questionnaires to the selected study population via postal mail. This mail included a patient information folder (Appendix II), two questionnaires (Appendix III and IV) and a pre-paid return envelope for the responses. The first questionnaire is a DN4 questionnaire which stands for "Douleur Neuropathique 4 Questions" and translates to "neuropathic pain four questions" (14). This validated questionnaire consists of four questions and is developed to screen for symptoms and signs of neuropathic pain. (14). The first two questions (I and II) were based on the description of neuropathic symptoms and the last two questions (III and IV) were based on a standardized clinical examination. Since this is a self-administered questionnaire that is filled in by patients at home, the last two questions (III and IV) have been excluded from the questionnaire.

The second questionnaire is a NCI-CTCAE (version 5.0) questionnaire, which stands for Common Terminology Criteria for Adverse Events by the National Cancer Institute (15). This questionnaire contains descriptive terminology that is used for adverse event reporting (15). The CTCAE categorizes adverse reactions from grade 1 to 5 with grade 1 being mild symptoms and grade 5 being death (15). In this research, grade 5 has been excluded, since death is a very unlikely outcome of neuropathy. Table 2 illustrates the used questionnaires. With these two questionnaires the presence of neuropathy is determined two years or longer after chemotherapy and if present, the severity is also determined by asking about the impact on daily activities.

Table 2
Description of questionnaires.

Questionnaire	**Scale**	**No of items**	**Response scale**	**Range of score**	**Outcome**
DN4	Neuropathic pain	7	0/1 (yes/no)	0-7	Score ≥1 = Neuropathic pain
CTCAE	Severity of neuropathy	4	0/1 (yes/no)	0-4	Score 1 = Mild symptoms Score 2 = Moderate symptoms Score 3 = Severe symptoms Score 4 - Very severe symptoms

One week after sending out the questionnaires, all non-respondents were contacted by phone. During the phone call, participants had the opportunity to ask questions and get additional information about the research. This was done to increase the response rate of the questionnaire.

Study variables

The variables that have been used in the analyses, include:

- Treatment regimen
- Patient-reported neuropathy during treatment
- RDI
- Dose reduction
- Presence of neuropathy after two years
- Severity of neuropathy after two years

To describe possible relationships, the following patient characteristic was used:

- Age

Setting

Due to the coronavirus outbreak, the research was mainly carried out from home and had several phases. Firstly, a literature search has been conducted to identify available literature on breast cancer and neuropathy after chemotherapy. Subsequently, questionnaires were sent out to a selection of patients with breast cancer who were treated in MST in the period 2017 – 2019. This was done in the MST, by preparing an envelope for every selected patient and sending the envelopes out.

Study size

The study size consisted of 200 patients who underwent (neo)adjuvant chemotherapy with taxanes in MST in the period 2017 – 2019. To determine inclusion eligibility, a manual selection had been done based on the inclusion criteria, by looking in the EHRs XCare and DSV. 37 patients were excluded because they did not meet the inclusion criteria. Therefore, the second version of the dataset consisted of 163 patients who were eligible for the questionnaire. The third and final version of the dataset consisted of the patients who completed and returned the questionnaire. No sample size calculation was performed, because all patients in this cohort were approached beforehand.

Statistical methods

The dataset was analyzed with IBM SPSS Statistics version 27. The patient characteristics from the dataset were used to describe the study population. Means, standard deviation, median, interquartile range and frequencies were calculated. These descriptive variables are written as means (standard deviation) if the variable is normally distributed. The number of patients and percentages are shown in tables as % (N).

The dataset was modified by recoding certain variables to dummy variables and creating new variables. First of all, the variables “patient-reported neuropathy” and “dose reduction because of neuropathy” were recoded into dummy variables with “1” indicating “yes” and “0” indicating “no”. After that, the variable “total score” was created, which is the sum of the scores of both the DN4 and CTCAE questionnaires, with the requirement that the questionnaires were filled in correctly. For example, when a patient answered “No” for all symptoms in the DN4 questionnaire, the CTCAE questionnaire should not be filled in then. However, if the patient filled in the CTCAE questionnaire, the total score would still be 0. Missing values were encoded as “999”. The variable “CTCAE score” was recoded into a new variable “severity of neuropathy”. The variable “total score” was recoded into the dummy variable “presence of neuropathy”. The variable “treatment regimen” was recoded into 7 dummy variables for each treatment regimen. Besides that, this variable was also recoded into the dummy variables “paclitaxel” and “docetaxel”.

Finally, the research questions were answered by carrying out binary logistic regressions and cross-tabulation analyses with “presence of neuropathy” as dependent variable.

The full SPSS syntax can be found in appendix IX.

Ethical considerations

This study concerns medical and privacy-sensitive data. A lot of this data has been collected and analyzed in this research, which makes it necessary to deal with it in an ethically responsible manner. This study has been applied for ethical review by the BMS Ethics Committee and the Board of Directors of the MST. They have both approved this study, under number K21-27. Accordingly, this research is

conducted in an ethically responsible manner. The ethical reviews and application files can be found in Appendices V – VIII.

The participants were informed in advance about the nature and purpose of the study. Hereby, written informed consent was obtained. Participating in this research was completely voluntary and participants could withdraw from the study at any time. There was some discussion about whether calling back patients was somewhat pushy. However, it was agreed on to call back the non-responders. The dataset file is stored securely on an MST network drive with a key. The research data used during the research is protected with a code number. Only the researcher knows which person belongs to this code number. The researcher may share the coded research data with other researchers and institutions that are involved in the research or have an interest in the research results. The research may also be published. Research data is coded, so that this data cannot be traced back to a specific patient without key.

Results

Baseline characteristics

Of the 163 patients, 73 patients completed and returned the questionnaire. The baseline characteristics of the study population are summarized in table 3 below. The mean age of the patients was 58 years (range 34-77). A total of 24 patients received ACdd-Paclitaxel, which was the most common treatment regimen. Furthermore, 11 patients received AC-Paclitaxel and 11 patients received AC-Paclitaxel/Trastuzumab, which were the second most common treatments. The results of all treatment regimens are presented in table 3. A total of 46 patients reported neuropathy symptoms during treatment. Of these 46 patients, 43 patients received a dose reduction. Of the 43 patients who received a dose reduction, 37 patients received a dose reduction because of neuropathy. Other reasons for dose reductions were neutropenia, mucositis, dose delay and epistaxis. The results showed that 42 patients suffer from neuropathy two years after chemotherapy. Of these 42 patients, 29 patients reported grade 1 neuropathy, 9 patients reported grade 2 neuropathy, 1 patient reported grade 3 neuropathy, 1 patient reported grade 4 neuropathy and 2 patients did not fill in the CTCAE questionnaire, which were marked as missing in the dataset.

Table 3

Baseline characteristics.

Variables	Total (N = 73)
Patient characteristics	
Age, years	
Mean (SD)	58 (8.9)
Range	34 – 77
Outcomes of the study	
Treatment regimen, % (N)	
Docetaxel	*32.9% (24)*
TAC	17.8% (13)
AC-PDTq	4.1% (3)
ACdd-PDT	11.0% (8)
Paclitaxel	*67.1% (49)*
AC-Paclitaxel	15.1% (11)
ACdd-Paclitaxel	32.9% (24)
AC-Paclitaxel/Trastuzumab	15.1% (11)
ACdd-Paclitaxel/Trastuzumab	4.1% (3)
Patient-reported neuropathy during treatment, % (N)	63.0% (46)
RDI, % (N)	-
Dose reduction, % (N)	
No	41.1% (30)
Yes, because of neuropathy	50.7% (37)
Yes, because of neutropenia	2.7% (2)
Yes, because of mucositis	2.7% (2)
Yes, because of dose delay	1.4% (1)
Yes, because of epistaxis	1.4% (1)
Presence of neuropathy after two years, % (N)	57.5% (42)
Severity of neuropathy after two years, % (N)	
Grade 1	39.7% (29)
Grade 2	12.3% (9)
Grade 3	1.4% (1)
Grade 4	1.4% (1)
Missing	2.7% (2)

To determine if the patient characteristic age has a significant predictive value on the presence of neuropathy two years after taxane chemotherapy, a logistic regression was performed. The results of this regression are shown in table 4 below. These results showed that age is statistically significant and positively correlated to the presence of neuropathy two years after taxane chemotherapy. This means the higher the age of the patient, the greater the risk that neuropathy is present two years after treatment. To give an example, a 70-year-old patient was compared to a 54-year-old patient. The odds ratios were 5.76 and 0.98, respectively. This means that a 70-year old patient has almost 6 times more risk to suffer from neuropathy two years after treatment compared to a 54-year old patient.

Table 4
Logistic regression of age associated with presence of neuropathy two years after taxane chemotherapy.

N=73	**B**	**OR (CI 95%)**	**P value**
Age*	0.111	1.12 (1.05-1.19)	0.001

**p < 0.05*
B = Regression beta coefficient, estimation of the increase in the dependent variable with an increase of 1 in the independent variable.
OR = Odds Ratio, ratio between the probability that an event will occur and the probability that it will not occur.
P value = Significance, p-value < 0.05 is significant.
CI = 95% confidence interval, if CI goes through 1 it is not significant.

Research questions

1st research question: "To what extent is neuropathy present two years after taxane chemotherapy?"

To determine the prevalence of neuropathy two years after taxane chemotherapy, the frequencies were analyzed. These results showed that 42 patients reported to suffer from neuropathy, two years after taxane chemotherapy, which is 57.5% of the study population. This means that more than half of the patients in this study, suffered from neuropathy. The results are illustrated in the form of a bar chart, in figure 3 below.

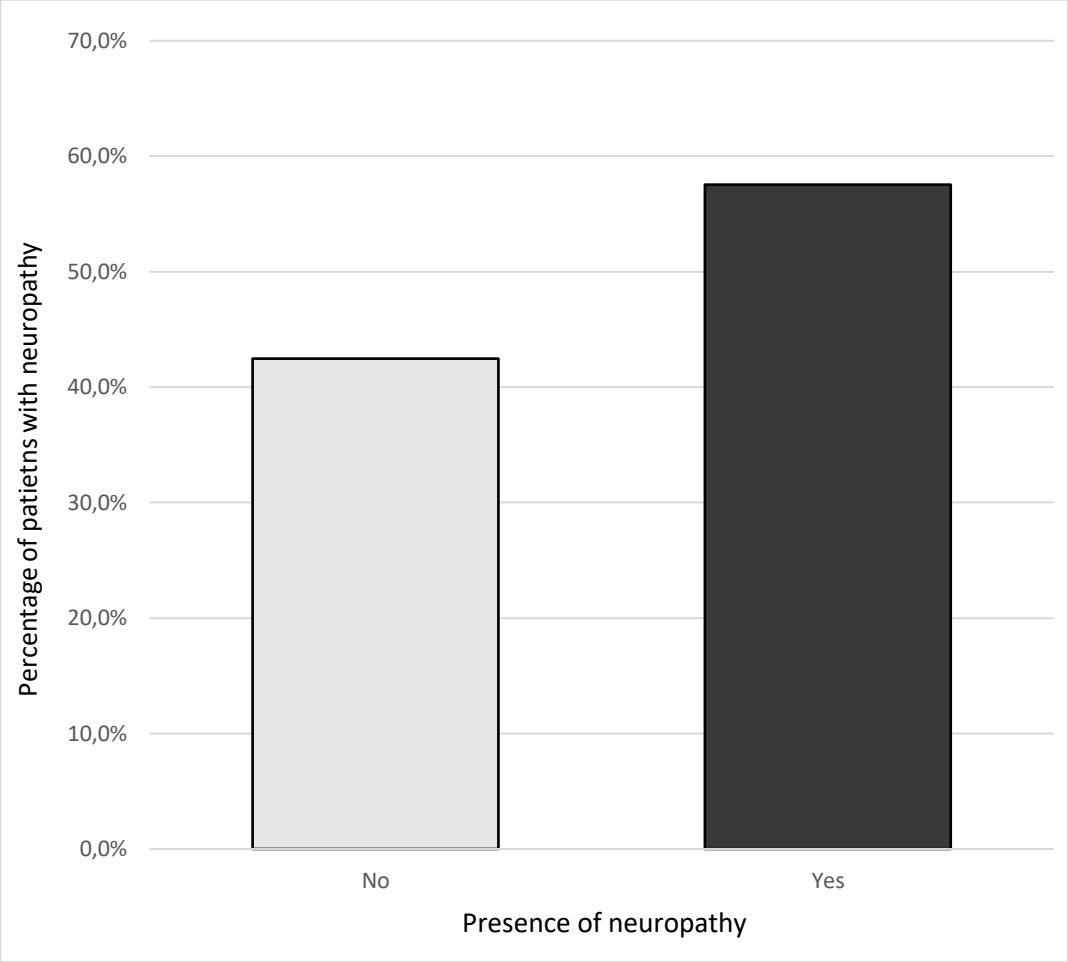

Figure 3. Percentage of patients with neuropathy two years after taxane chemotherapy.

2nd research question: "What is the relationship between a dose reduction during treatment and the presence of neuropathy two years after taxane chemotherapy?"

To assess the effect of a dose reduction on the presence of neuropathy two years after taxane chemotherapy, a cross-tabulation analysis was conducted. Patient-reported neuropathy was also taken into account, because dose reductions are made dependent on whether patients report neuropathy symptoms. The results are presented in table 5 below. The results have shown that 46 patients reported neuropathy symptoms during treatment. Of these 46 patients, 37 patients received a dose reduction. Of these 37 patients, 29.7% (N = 11) recovered from neuropathy two years after treatment, while 70.3% (N = 26) suffer from neuropathy.

Out of the total 42 patients who suffer from neuropathy two years after treatment, 26.2% (N = 11) did not report neuropathy symptoms during treatment, which also means there was no dose reduction.

Finally, this means that dose reductions have been effective to 29.7% of the patients. However, if there had been no dose reductions, the percentage of patients suffering from neuropathy after reporting neuropathy symptoms might have been higher.

Table 5
Relationship between patient-reported neuropathy and dose reduction and presence of neuropathy two years after taxane chemotherapy.

Patient-reported neuropathy during treatment	**Neuropathy two years after treatment**	**No dose reduction during treatment because of neuropathy**	**Dose reduction during treatment because of neuropathy**	
No	No	16	0	16
	Yes	11	0	11
	Total	***27***	***0***	***27***
Yes	No	4	11	15
	Yes	5	26	31
	Total	***9***	***37***	***46***
Total		***36***	***37***	***73***

3rd research question: "What is the relationship between the relative dose intensity (RDI) during treatment as result of the patient reporting neuropathic symptoms and the presence of neuropathy two years after taxane chemotherapy?"

Unfortunately, there was no sufficient data on the RDI of the patients, therefore this research question could not be answered.

4th research question: "*What is the relationship between the treatment regimens and the presence of neuropathy two years after taxane chemotherapy?"*

To assess the effect of the paclitaxel and docetaxel treatment regimens on the presence of neuropathy two years after taxane chemotherapy, the relationship between the treatment regimens and neuropathy were analyzed. In table 3, all treatment regimens were presented. These treatment regimens consist of four paclitaxel regimens and three docetaxel regimens. The majority of patients (N = 49) received paclitaxel regimens, while others (N = 24) received docetaxel regimens. These regimens were combined into two variables: docetaxel and paclitaxel. To compare these two taxanes, a binary logistic regression was carried out to compare the two taxanes with regard to the effect on the presence of neuropathy two years after treatment. The regression results of this analysis are shown in table 6 below. These results show that patients who receive a regimen including paclitaxel, are almost 3 times (OR: 2.68, 95% CI: 0.88-8.15) more likely to suffer from neuropathy two years after treatment compared to patients who receive a regimen that includes docetaxel. Moreover, this relationship is borderline significant.

Table 6
Logistic regression between age, the paclitaxel and docetaxel regimens and the presence of neuropathy two years after taxane chemotherapy.

N=73	**B**	**OR (95% CI)**	**P value**
Age*	0.110	1.12 (1.04-1.20)	0.001
Docetaxel		1.00	
Paclitaxel	0.987	2.68 (0.88-8.15)	0.081

**p < 0.05*

Discussion

The aim of this study was to gain insight into the prevalence of neuropathy two years after completing taxane chemotherapy. Furthermore, the aim was to examine whether dose reductions, treatment regimens, age and patient-reported neuropathy during treatment relate to the presence of neuropathy two years after treatment.

Strengths and limitations

This study contains both strengths and limitations, which must be acknowledged. To determine the prevalence of neuropathy and whether the patient had reported neuropathy during treatment, questionnaires were sent and analyzed. Of the 163 patients, 73 patients completed and returned the questionnaire, which means there was a response rate of 44.8%, which is a typical response rate for this type of questionnaire (16). Also, possible selective non-response should be taken into account, which means that it is likely that relatively more patients that did not have any symptoms decided not to fill in the questionnaire.

A strong point of this study, was its prospective design with a follow-up time of at least two years. Besides the retrospective nature of this study, which included the data collection of the patients using EHRs, there was also a prospective data collection using questionnaires. Through these questionnaires, long-term neuropathy outcomes were collected. Since there is limited literature available about the long-term neuropathy outcomes, this study contributes to this limited knowledge, which means this study also has an exploratory nature (8) (11) (12).

Another important aspect of this study, was the use of a validated tool to identify presence of neuropathic pain, which is the DN4 questionnaire (14). This tool reliably detects presence of neuropathy and is easy to use (14). However, a limitation was, that only the first two parts of the questionnaire were used. This means that the patients filled in the questionnaire by themselves, without a clinical examination by the physician. Because of this, the DN4 questionnaire used in this study is not a validated tool anymore. This might be a potential weakness. On the other hand, the questionnaire is easy to fill in without assistance of a physician and it probably leads to a higher response percentage since patients do not have to visit the hospital to fill in the questionnaires. An aspect that caught the attention was the way the first two questions were filled in. It was not very clear for many patients, whether the second question should be answered, after answering "No" for all symptoms in the first question. Despite this being unclear, the total score was taken into account. Another tool that was used to grade neuropathic pain, was the CTCAE questionnaire (15). Despite the extensive use of this tool, it has not been validated yet.

Interpretation results

In this study, the prevalence of neuropathy two years after completing taxane chemotherapy was 57.5% in patients treated in the MST in the period 2017-2019. It is difficult to conclude whether this prevalence matches with prior studies on this topic, since many studies report very varying results (9) (11) (13). However, when looking at the systematic review that is mentioned before in this study, they reported a prevalence of 70.8% (12). This review looked at prevalence of neuropathy within 1 month, at 3 months and at 6 months or more after completion of chemotherapy (12). Since it had shorter follow-up times, prevalence rates were relatively high, because neuropathy symptoms gradually reduce with time. In comparison to this result, it is difficult to conclude that the hospital MST performed better by achieving a prevalence of 57.5%. Comparison of results between studies is difficult because of the different tools used to assess for neuropathy, which may under- or overestimate the prevalence of neuropathy. Other tools that have been used in other studies to assess for neuropathy include the neuropathic pain scale

(NPS), peripheral neuropathy score (PNS) and total neuropathy score (TNSc) (12). The DN4 tool that is used in this study to assess for presence of neuropathy consists of seven symptoms. In comparison to the other tools, only one of the seven symptoms has to be present to detect neuropathy in this study. In this way, it is relatively easier to detect neuropathy, which means that this tool in this study overestimates neuropathy compared to other tools.

Furthermore, the results have shown that when a dose reduction is made, that 29.7% of the patients recover from neuropathy two years after treatment. Without dose reductions it is highly likely that this percentage would be even lower. Therefore, dose reductions are effective, but are probably made too late which leads to a low percentage of patients recovering from neuropathy. Another important result is that 11 patients suffer from neuropathy two years after treatment, who have not reported any symptoms during treatment and thus did not receive a dose reduction. This means that either patients did not report neuropathy symptoms while they had symptoms or that they developed neuropathy symptoms at the end of the treatment. Therefore, it is very important for clinicians to emphasize the importance of the timeliness of a dose reduction, so that patients report symptoms in time.

Finally, treatment regimens including paclitaxel demonstrated to be more neurotoxic than docetaxel. Although this was already known, this study also confirms it (17). The results have shown that neuropathy is a more common side effect of paclitaxel compared to docetaxel. The relationship between paclitaxel treatment regimen and presence of neuropathy two years after treatment was found borderline significant. Given this small study size, it is difficult to find significant differences between variables. Also, these results cannot be generalized to other studies. Analyzing all seven treatment regimens with a large study population might be interesting for further research. Given this small study size, analyzing all treatment regimens had not been done, since it is difficult to find significant differences between variables and would not be generalizable to other studies. Although paclitaxel showed to be more neurotoxic than docetaxel, more patients received a paclitaxel regimen. This is because Dutch guidelines of breast cancer state that studies showed sequential (weekly) administration of chemotherapy to be more effective (5). Paclitaxel is given weekly, while docetaxel is given every 3 weeks. Therefore treatment regimens including paclitaxel are given more frequently than docetaxel treatment regimens.

General conclusion and implications

In summary, the findings of this study revealed insight into the prevalence of taxane-induced peripheral neuropathy (TIPN) two years after completion of taxane chemotherapy. Of the 73 patients, 43 patients suffer from TIPN two years after completion of treatment. Besides that, it also revealed insight into factors that increase the risk of developing TIPN, which remains present two years after treatment. Since we found that age is related to neuropathy, clinicians should take this into account when choosing a certain treatment regimen. For instance, older patients might be recommended docetaxel treatment regimens, which places these patients at less risk to develop long-term TIPN after treatment. Another finding was that dose reductions were effective to 29.7% of the patients, which fully recovered two years after treatment. This means that dose reductions were not effective to all patients in reducing neuropathy, because many dose reductions were probably made too late. Clinicians should learn to predict on neuropathy symptoms. This should be done by detecting neuropathy more timely. The role of the patient is also important in this process, since the patient must report neuropathy symptoms in time. Clinicians should clearly explain the importance of reporting symptoms in time to the patient, in order for the dose reduction to be effective. In this way dose reductions can be made in time, to effectively reduce neuropathy symptoms. This study also confirms that treatment regimens including paclitaxel are more neurotoxic than treatment regimens including docetaxel.

Moreover, the results found in this study are valuable to the MST, but may also be of great value for other hospitals. With these insights, the MST might adapt the treatment plans, to try and reduce the risk of TIPN.

Besides the risk factors that are associated with neuropathy two years after completion of taxane chemotherapy, understanding the underlying mechanisms of TIPN is also essential. Future research of the pathophysiology of TIPN is very important. As stated before, the underlying mechanisms of TIPN are poorly understood (7) (12) (18) (22). Because of this, there are barely any effective treatments for TIPN (7) (9) (12) (19) (20) (21) (22) (23) (24) (25). In order to develop and evaluate new effective prevention and treatment strategies for TIPN, the pathophysiology should be understood and studied well (7) (12) (18) (22). Treatments that have been proven effective include classical massage and exercising (20) (22) (26). Exercising is already being stimulated by the MST, but classical massage is not being used. This treatment is a prevention strategy, which is safe, low-cost and also has proven to be effective in preventing TIPN, but may require further research to increase the evidence base (26). Other treatment strategies that reduce TIPN are anti-neuropathic drugs including, gabapentin, pregabalin, vitamin E, glutamine, glutathione, N-acetylcysteine, oxcarbazepine, xaliproden and duloxetine (7) (10) (12) (19) (20) (21) (22) (23) (24). Of all these drugs, only duloxetine has proved to be beneficial in reducing TIPN (7) (10) (12) (19) (20) (21) (22) (23) (24). The other drugs are being tested by animal models and look promising but still require further research (7) (10) (12) (19) (20) (21) (22) (23) (24).

Another recommendation is that studies should use the same assessment methods to detect and grade TIPN. Many studies use different tools and instruments, which makes it very difficult to compare the findings of these studies, because different tools detect different outcomes.

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Table of Contents for Appendices

Appendix I: Theoretical framework

Taxanes

The taxanes belong to the category of anti-neoplastic drugs, which are derived from plants (27). Taxanes were considered among the most promising antitumor agents. In current practice, taxanes have been proven effective and are frequently used in medical oncology, such as: melanoma, lung cancer, breast cancer, ovarian cancer, gastric cancer and prostate cancer (27). Paclitaxel and docetaxel are known as the fundamental drugs in the treatment of breast cancer (27) (28) (29). Paclitaxel is derived from the bark of the Pacific yew tree (Taxus brevifolia) and is effective because unlike other drugs, paclitaxel promotes tubulin polymerization and overproduction of microtubules (27) (28) (29). Docetaxel is derived from needles extract of the European yew tree (Taxus baccata) and is effective because of its increased activity of microtubule proteins and cytotoxicity (27) (28) (29). At first, taxanes were used for metastatic breast cancer. Several randomized trials concluded that use of docetaxel and paclitaxel in neoadjuvant and adjuvant setting significantly improves disease-free and overall survival rates (27) (28) (29).

Taxane-induced peripheral neuropathy

Despite the proven effectiveness of taxanes, patients can also experience adverse side effects during and/or after taxane chemotherapy. There are many side effects that can occur, including nausea, vomiting, mucositis (inflammation of the mucosa), neutropenia, leukopenia, hypotension or hypertension and myalgia (muscle pain) (27). In addition to these side effects, the most limiting side effect of taxane chemotherapy is taxane-induced peripheral neuropathy (TIPN) (7) (13). The most common side effects that arise during and/or after treatment are sensory and motor symptoms such as: paresthesia manifested as tingling, numbness, burning and itching, motor impairment and neuropathic pain (7) (10) (11) (13) (19). These side effects may ultimately lead to a significant decline in functionality and a diminished long-term quality of life (8) (11) (13).

The severity of TIPN is graded from grade 1 to 4, with grade 1 being mild symptoms (sensory disturbance), grade 2 being moderate symptoms (difficulty with instrumental activities) , grade 3 being severe symptoms (difficulty with self-care activities) and grade 4 being very severe symptoms (severe impairment in functioning) (15).

There are several risk factors that are associated with TIPN. Various studies have investigated these risk factors for patients receiving taxane chemotherapy. According to these studies, lifestyle factors are associated with TIPN (20). Firstly, the association between body mass index (BMI) and TIPN was examined. When someone's BMI is 30 kg/m^2 or higher, this indicates that the person has obesity (20). A prospective cohort study found an association between obesity and TIPN (20). The results of this study showed that obese patients are twice as much at risk of having increased TIPN compared to normal weight patients (BMI <25 kg/m^2) (20). Since taxane dosing is based on the body surface area (BSA) of the patient, it means that obese patients receive more chemotherapy because of a higher BSA, which makes them more vulnerable to worsening TIPN (11) (20). Other studies also found this association between obesity and increased TIPN (8) (10) (11) (19). Another lifestyle factor that has been identified by this prospective cohort study as risk factor for increased TIPN is physical activity (20). The results of this study showed that patients who spent at least five hours a week on moderate-to-vigorous physical activity (MVPA) were at 60% less risk of having increased TIPN (20). Lastly, this study found that

women who make adjustments in their use of antioxidants dietary supplements near chemotherapy are at twice to thrice as much risk of having increased TIPN (20).

Furthermore, other clinical and demographic factors have been examined and the following risk factors have been associated with an increased risk of TIPN: older age, high cumulative dose, greater number of positive lymph nodes and comorbidities, such as diabetes (8) (10) (13) (19) (20). Diabetes is a risk factor for TIPN, because high blood glucose levels may damage peripheral nerves, which increases the chance of developing TIPN (10). However, many studies state that the association between diabetes and increased risk of TIPN is not evident enough, because of inconsistent reports and limited data (8) (10) (11) (19).

Current treatments of TIPN

The pathophysiology of TIPN is very complex and not properly understood (7) (12) (18). Many studies have been conducted to evaluate prevention and treatment strategies for TIPN, such as pharmaceutical agents or so-called "anti-neuropathic drugs" (7) (10) (12) (19) (20) (21) (22) (23) (24). However, despite the many studies and high incidence of TIPN, effective treatments have not been established and there is no gold standard for treating and preventing TIPN (7) (9) (12) (19) (20) (21) (22) (23) (24) (25). Most of the interventions failed to show a significant improvement in TIPN and some even showed negative effects on TIPN (7) (9) (10) (12) (19) (20) (21) (22) (23) (24). Moreover, there are no available biomarkers to predict the relationship between the length and severity of TIPN (9) (25). The anti-neuropathic drugs that have been evaluated include gabapentin, pregabalin, vitamin E, glutamine, glutathione, N-acetylcysteine, oxcarbazepine, xaliproden and duloxetine, whereby solely the antidepressant duloxetine has showed any benefit in reducing neuropathic symptoms after 5 weeks (7) (10) (12) (19) (20) (21) (22) (23) (24). These drugs are being tested by animal models and look promising but still require further research (7) (10) (12) (19) (20) (21) (22) (23) (24). Recently more and more evidence suggests that lifestyle factors such as exercising may be effective in minimizing neuropathic symptoms and thus decreasing neuropathic pain, and also improves other taxane-related side effects, such as: fatigue, depression, strength and endurance (20) (22). These exercises include: sensimotor, endurance and strength training and should be done twice a week (20).

The current management of TIPN is mainly symptom-oriented and consists of the following three approaches (20) (23) (24):
1) Dose reduction;
2) Changing the treatment regimen;
3) Adjunct medications (including anticonvulsants, antidepressants, opioids and topical analgesics). Most of the times, the choice for dose reduction is supported over the other two options for patients with advanced breast cancer (23). For patients with early-stage breast cancer, the choice for adjunct medications is supported, although adding adjunct medications may cause new adverse effects and toxicities (23). Lastly, the choice for entirely changing the treatment regimen is mainly an option when other effective regimens are available (23). Since these are the only three approaches, and since the evidence of the effectiveness of these adjunct medications remains controversial, many patients seek new management and prevention strategies (26). One of these new strategies that may be beneficial to reduce and prevent TIPN, is classical massage (26). A randomized controlled trial (RCT) investigated the effect of classical massage on TIPN and quality of life in breast cancer patients receiving paclitaxel (26). In this RCT, each participant received a 30-minute massage, 10 minutes for the hands and 20 minutes for the feet (26). These massages were given on treatment day, before administration of the

chemotherapy (26). The results of this study have shown that classical massage is a safe and cost-effective approach that successfully prevents TIPN and also improves quality of life (26).

Relative dose intensity

As stated before, taxane dosing is based on the BSA of the patient. The relative dose intensity (RDI) is a tool that measures the effectiveness of this dosing, by calculating the ratio between the administered dose per m^2 of BSA per week and the optimal dose per m^2 of BSA per week (30). Given below is the formula that is used to calculate the RDI.

$$\text{RDI} = \frac{\text{Actual total dose}}{\text{Actual number of weeks}} \times \frac{\text{Planned number of weeks}}{\text{Planned total dose}}$$

Furthermore, there are variables that affect the RDI by affecting the actual period and/or actual dose. Variables that affect the actual period include: holidays, admission and patient preferences (30) (31). Variables that affect the actual dose include: weight, dose reductions and dose delays (30) (31). However, achieving 100% RDI is rarely found in studies, because of the fact that RDI can be easily affected by minor details, such as a 1-day delay because of a public holiday (31). This implies that such minor changes in RDI are not necessarily clinically relevant (31). Older age and obesity are known predictors of low RDI (30) (31). In several breast cancer studies, a RDI <85% was significantly associated with a lower disease-free survival (30) (31). Therefore, Dutch guidelines recommend that a RDI of at least 85% has to be achieved for optimal treatment (30).

Treatment in MST

In figure 4 below, a care pathway of breast cancer is illustrated from a patient's perspective when undergoing (neo)adjuvant chemotherapy with taxanes in the MST.

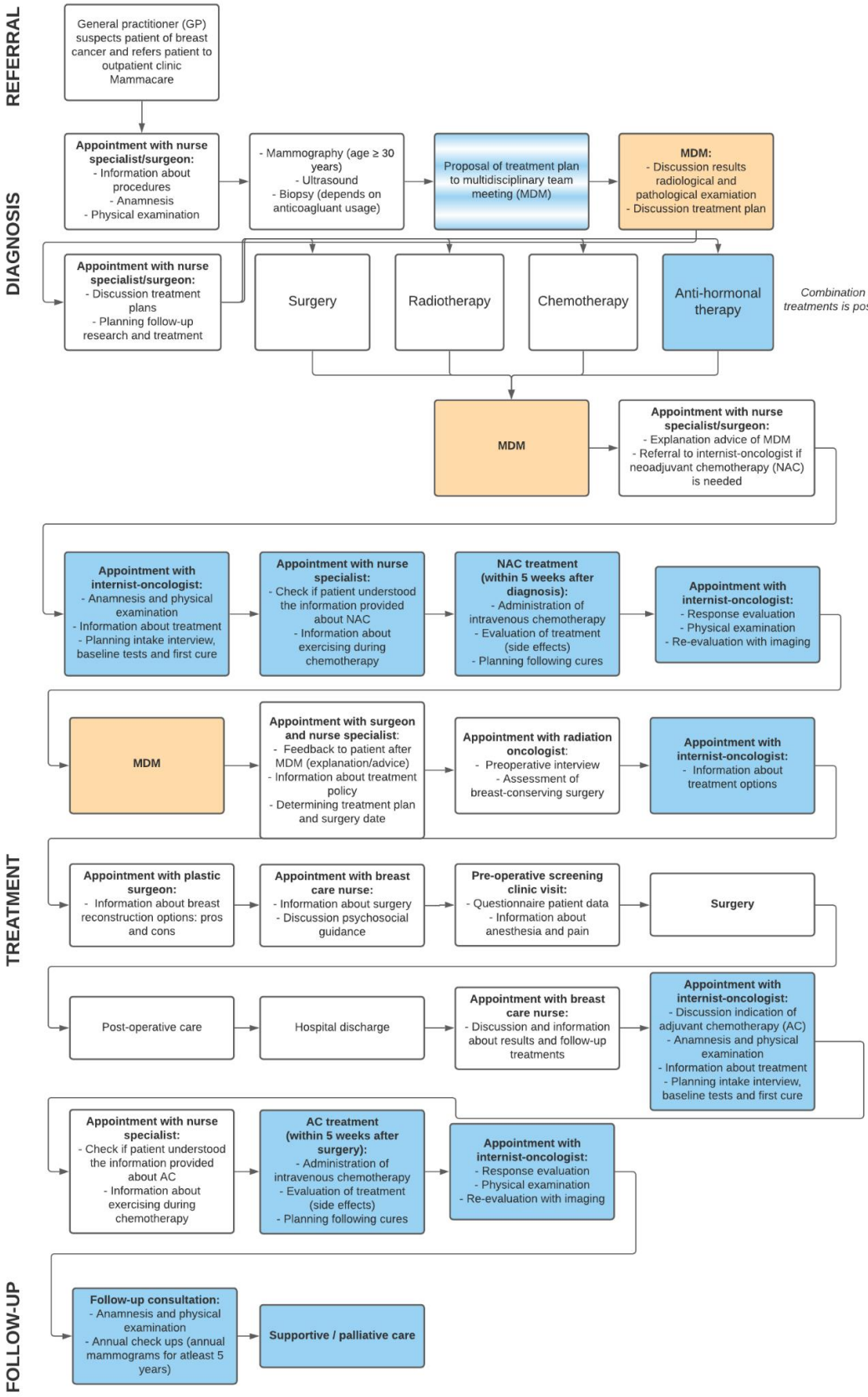

Figure 4. Care pathway MST.

In table 7 below, an overview is shown of all (neo)adjuvant treatment regimens in this study of breast cancer in the MST.

Table 7
(Neo)adjuvant treatment regimens of breast cancer in the MST

Treatment regimen	
AC-Paclitaxel	4x doxorucin/cyclophosphamide (=AC) intravenously every 3 weeks followed by 12x paclitaxel intravenously weekly
ACdd-Paclitaxel	4x doxorucin/cyclophosphamide (=AC) intravenously every 2 weeks followed by 12x paclitaxel intravenously weekly
AC-Paclitaxel/Trastuzumab	4x AC cycles every 3 weeks, followed by paclitaxel/trastuzumab every week for 12 times, followed by trastuzumab monotherapy for an additional 13 times every 3 weeks intravenously
ACdd-Paclitaxel/Trastuzumab	4x AC cycles every 2 weeks, followed by paclitaxel/trastuzumab every week for 12 times, followed by trastuzumab monotherapy for an additional 13 times every 3 weeks intravenously
AC-PDT	4x AC cycles every 3 weeks followed by 4x pertuzumab/trastuzumab/docetaxel every 3 weeks, followed by trastuzumab monotherapy for an additional 13 times every 3 weeks intravenously
ACdd-PDT	4x AC cycles every 2 weeks followed by 4x pertuzumab/trastuzumab/docetaxel every 3 weeks, followed by trastuzumab monotherapy for an additional 13 times every 3 weeks intravenously
TAC	6x TAC cycles intravenously (docetaxel/doxorubicine/cyclofosfamide) every 3 weeks

Appendix II: Patient Information Folder (PIF)

Informatie- en toestemmingsformulier voor deelname aan een medisch-wetenschappelijk onderzoek

Onderzoek naar de aanwezigheid en ernst van neuropathie bij patiënten die behandeld zijn met docetaxel of paclitaxel vanwege borstkanker.

Geachte heer/mevrouw,

Met deze brief willen wij u vragen of u wilt meedoen aan medisch-wetenschappelijk onderzoek. Meedoen is vrijwillig. U krijgt deze brief omdat u tussen 2017 en 2019 bent behandeld met chemotherapie vanwege borstkanker. U leest hier om wat voor onderzoek het gaat, wat het voor u betekent en hoeveel tijd het u kost. Wilt u de informatie doorlezen en beslissen of u mee wilt doen? Als u wilt meedoen kunt u het bijgevoegde toestemmingsformulier en de vragenlijsten invullen.
Het onderzoek wordt uitgevoerd door O. Gourie, student master Health Sciences bij Universiteit Twente en begeleid door M.C.H. Pleunis – van Empel, internist-oncoloog bij Medisch Spectrum Twente. Mochten er nog vragen of onduidelijkheden zijn, dan kunt u contact opnemen via de contactgegevens onderaan deze brief.

Doel van het onderzoek

In dit onderzoek willen we inventariseren of patiënten 2 jaar of langer na hun chemotherapie voor borstkanker klachten hebben van neuropathie. En zo ja, in welke mate zij hier last van hebben in hun dagelijks functioneren.

Achtergrond

Tussen 2017 en 2019 bent u behandeld met chemotherapie vanwege borstkanker. Eén van de middelen die u hebt gekregen was paclitaxel of docetaxel. Deze middelen kunnen de volgende bijwerkingen hebben: doof gevoel in vingertoppen en/of voeten, gevoel van lopen op watten en het gevoel van een sok die dubbel zit. Deze symptomen vallen onder neuropathie, oftewel een aandoening van de zenuwen van armen en benen.
Tijdens de chemotherapie is er herhaaldelijk aan u gevraagd of u hiervan klachten had. Soms is daarom de dosering van de chemotherapie aangepast of is de behandeling voortijdig gestopt. Neuropathie kan zowel vroeg in de behandeling als pas aan het einde van de behandeling optreden. Bovendien kunnen neuropathische klachten ook lang aanhouden en zelfs blijvend zijn. Deze klachten kunnen grote impact hebben op het dagelijks leven.

Het kan ook zijn dat u helemaal geen klachten (meer) heeft van neuropathie. Ook dit is belangrijk voor het onderzoek en wij willen u dan ook nog steeds vragen om deel te nemen.

Uitvoering van het onderzoek

Doet u mee aan het onderzoek dan vragen we u de bijgevoegde vragenlijsten in te vullen en samen met het toestemmingsformulier terug te sturen. In vragenlijst 1 wordt gevraagd naar klachten die kunnen passen bij neuropathie. Als u minstens 1x JA hebt ingevuld bij vragenlijst 1, gaat u verder met vragenlijst 2. Hierin wordt gevraagd naar de invloed van uw klachten op uw functioneren. Als u bij vragenlijst 1 overal NEE invult, dan hoeft u vragenlijst 2 niet in te vullen.
Het invullen van de vragenlijsten duurt 5-10 minuten.

Uit uw medisch dossier worden de volgende medische gegevens verzameld:

- Uw lengte en gewicht
- Welke chemotherapie u heeft gehad (paclitaxel of docetaxel), het aantal kuren en de dosering
- Of u neuropathieklachten hebt benoemd tijdens de behandeling van paclitaxel of docetaxel
    - Zo ja, of er dan een verandering in dosering is geweest
- Of u diabetes mellitus (suikerziekte) hebt.

Wanneer vindt het onderzoek plaats?

Het onderzoek duurt tot en met 1 oktober 2021. Als u mee doet, wilt u dan binnen 1 maand het toestemmingsformulier en de vragenlijsten terug sturen?

Wat zijn de voordelen en nadelen als u meedoet aan het onderzoek?

Er zijn voor uzelf geen voordelen of nadelen van dit onderzoek te verwachten. Uw deelname helpt de onderzoekers om meer inzicht te krijgen in de lange termijns bijwerking neuropathie van chemotherapie voor borstkanker. Dit zal de behandelinformatie voor toekomstige patiënten verbeteren.

Wat gebeurt er als u niet wilt deelnemen aan het onderzoek?

Deelname aan het onderzoek is geheel vrijwillig. Als u niet wilt deelnemen heeft dit geen gevolgen voor u.

Wat gebeurt er met de gegevens van het onderzoek?

Door dit formulier te ondertekenen geeft u de onderzoeker toestemming om uw persoonlijke gegevens te verzamelen en te gebruiken voor het onderzoek. Uw gegevens worden door de onderzoeker gebruikt volgens de wet Algemene Verordening Gegevensbescherming (AVG). De onderzoeksgegevens die tijdens het onderzoek gebruikt worden, zullen worden beschermd met een codenummer. Alleen de onderzoeker weet welke persoon bij dit codenummer hoort. De onderzoeker kan uw gecodeerde onderzoeksgegevens delen met andere onderzoekers en instellingen die betrokken zijn bij het onderzoek of belang hebben bij de onderzoeksresultaten. Ook kan het onderzoek gepubliceerd worden. Hierbij zijn gecodeerde onderzoeksgegevens dus geanonimiseerd, waardoor deze gegevens niet herleidbaar zijn naar u.

De onderzoeksgegevens worden 5 jaar bewaard. U heeft te allen tijde recht om uw

onderzoeksgegevens in te zien of om uw toestemming voor het gebruik van uw gegevens in te trekken. U kunt hiervoor contact opnemen met de onderzoekers.

Meer informatie over uw rechten bij de verwerking van uw persoonsgegevens

Meer informatie over uw rechten bij de verwerking van uw persoonsgegevens kunt u vinden in het privacy statement van het Medisch Spectrum Twente (https://www.mst.nl/patienten/privacy/#9) en op de website van de Autoriteit Persoonsgegevens: https://autoriteitpersoonsgegevens.nl.

Extra kosten van het onderzoek

Er zijn geen extra kosten voor u. Er is bij de vragenlijsten een gefrankeerde retourenvelop bijgesloten.

Is het onderzoek ethisch getoetst?

Voor dit onderzoek is goedkeuring afgegeven door de Raad van Bestuur van Medisch Spectrum Twente.

Klacht

Indien u gedurende het onderzoek niet tevreden bent over de wijze waarop het onderzoek verloopt, kunt u contact opnemen met de onderzoeker. Indien u dit liever niet doet kunt u contact opnemen met de onafhankelijke klachtencommissie van Medisch Spectrum Twente. De klachtencommissie is te bereiken tijdens kantooruren op telefoonnummer: 053-4872045.

Bij vragen of klachten over de verwerking van uw persoonsgegevens kunt u ook contact opnemen met de onderzoeker. Of met de Functionaris voor de Gegevensbescherming van het Medisch Spectrum Twente, mevrouw mr. P.J.F. van Paridon via privacy@mst.nl.

Hoe doet u mee aan het onderzoek?

U kunt eerst rustig nadenken over dit onderzoek. Wilt u meedoen, dan vult u het toestemmingsformulier in dat u bij deze informatiebrief vindt en de vragenlijsten. Dit alles stuurt u naar de onderzoeker in de bijgevoegde gefrankeerde retourenvelop.

Vragen

Ongeveer twee weken na het opsturen van deze brief wordt er mogelijk telefonisch contact opgenomen met u. In dit contact is verdere uitleg mogelijk over de studie en kunnen mogelijke vragen worden beantwoord. Indien u na het lezen van deze brief of vragenlijst nog vragen heeft, kunt u ook zelf contact opnemen met de onderzoeker O. Gourie. Dit kan in augustus en september 2021 op maandag, dinsdag en vrijdag van 12.00 – 13.00 uur.

Orkino Gourie
Stagiair/Master Student Health Sciences aan de Universiteit Twente
Telefoonnummer: 06-36317787

Drs. M.C.H. Pleunis – van Empel
Internist-oncoloog Medisch Spectrum Twente
Onderzoeksbegeleider

Toestemmingsformulier

Onderzoek naar de aanwezigheid en ernst van neuropathie bij patiënten die behandeld zijn met docetaxel of paclitaxel vanwege borstkanker.

Ik verklaar dat ik:

- De schriftelijke informatie over het onderzoek heb ontvangen, gelezen en begrepen.
- Voldoende tijd heb gehad om na te denken over mijn deelname.
- De mogelijkheid heb gehad om aanvullende vragen te stellen over het onderzoek.
- Op de hoogte ben dat deelname aan het onderzoek vrijwillig is en dat ik te allen tijde kan stoppen met deelname.
- Toestemming geef aan de onderzoeker om mijn gegevens te verzamelen en te gebruiken voor het doel van dit onderzoek.
- Op de hoogte ben dat voor controle van het onderzoek sommige mensen al mijn gegevens kunnen inzien. Die mensen staan in deze informatiebrief genoemd.

Ik wil meedoen aan dit onderzoek.

Naam:_____

Datum: _____

Handtekening:

Mocht de onderzoeker, naar aanleiding van dit onderzoek, nog vragen hebben, gaat u er dan mee akkoord dat u nogmaals wordt benaderd? (aankruisen wat van toepassing is)

☐ **Ja**

☐ **Nee**

Ik verklaar dat ik deze proefpersoon volledig heb geïnformeerd over het genoemde onderzoek.

Naam onderzoeker (of diens vertegenwoordiger): _____

Datum: _____

Handtekening:

N.B. Wilt u dit getekende formulier samen met de 2 vragenlijsten retour sturen in de gefrankeerde envelop.

Appendix III: DN4-questionnaire

Vragenlijst 1 (DN4)

Onderzoek naar de aanwezigheid en ernst van neuropathie bij patiënten die behandeld zijn met docetaxel of paclitaxel vanwege borstkanker.

Graag onderstaande tabel invullen. Heeft u 1 of meerdere keren “Ja” ingevuld, vul dan vragenlijst 2 in. Indien alles met “nee” is beantwoord, hoeft u vragenlijst 2 niet in te vullen.

<u>Vraag 1</u>: Heeft de pijn in uw handen en/of voeten één of meer van de volgende kenmerken?

1. Branderig gevoel	☐ Ja ☐ Nee
2. Pijnlijk koude gevoel	☐ Ja ☐ Nee
3. Elektrische schokken	☐ Ja ☐ Nee

<u>Vraag 2</u>: Gaat de pijn in uw handen en/of voeten gepaard met één of meer van de volgende symptomen in hetzelfde gebied?

4. Tintelingen	☐ Ja ☐ Nee
5. Prikken	☐ Ja ☐ Nee
6. Doofheid	☐ Ja ☐ Nee
7. Jeuk	☐ Ja ☐ Nee

Appendix IV: CTCAE questionnaire

Vragenlijst 2 (CTCAE)

Onderzoek naar de aanwezigheid en ernst van neuropathie bij patiënten die behandeld zijn met docetaxel of paclitaxel vanwege borstkanker.

Graag een kruisje plaatsen in het laatste vak van de rij zodra dit op u van toepassing is. U mag ook meerdere kruisjes plaatsen.

Ernst van bijwerkingen	Mate van impact op dagelijkse activiteiten	Voorbeelden	Kruis aan indien van toepassing
Graad 1) Lichte bijwerkingen	• Symptomen verstoren dagelijkse activiteiten niet	• Gevoelsstoornis: onprettig prikkelend, branderig, doof gevoel, tintelingen in de vingertoppen en/of voeten	
Graad 2) Matige bijwerkingen	• Symptomen veroorzaken duidelijke klachten, maar minimale verstoringen van de dagelijkse activiteiten	• Moeite met instrumentele activiteiten zoals: - toetsenbord computer of telefoon bedienen - knoopjes open-/dichtdoen - veters strikken - schrijven - eten klaarmaken	
Graad 3) Ernstige bijwerkingen	• Symptomen verstoren algemene dagelijkse levensverrichtingen (ADL)	• Moeite met zelfverzorgende activiteiten zoals: - zelfstandig aan-/uitkleden - wassen, haren wassen en kammen - bestek vasthouden en eten - lopen - deuren open-/dichtdoen - autorijden	
Graad 4) Zeer ernstige bijwerkingen	• Symptomen die gepaard gaan met ernstige beperkingen in uw functioneren	• Lopen gaat niet meer • Voor algemene dagelijkse activiteiten volledig op hulp aangewezen	

Bewerkt naar National Cancer Institute Neurotoxicity Disability Criteria en Common Toxicity Criteria V5.0

Appendix V: Ethical review BMS

UNIVERSITY OF TWENTE.

FACULTY BMS

211075 REQUEST FOR ETHICAL REVIEW

Request nr:	211075
Researcher:	Oude Wesselink, S.F.
Supervisor:	-
Reviewer:	Lubbe, R.H.J. van der
Status:	**Approved by commission**
Version:	2

1. START

A. TITLE AND CONTEXT OF THE RESEARCH PROJECT

1. What is the title of the research project? (max. 100 characters)

Neuropathy after chemotherapy treatment for breast cancer

2. In which context will you conduct this research?

Master's Thesis

3. Date of the application

23-07-2021

5. Is this research project closely connected to a research project previously assessed by the BMS Ethics Committee?

No/Unknown

B. CONTACT INFORMATION

6. Contact information for the lead researcher 6a. Initials:

S.F.

6b. Surname:

Oude Wesselink

6c. Education/Department (if applicable):

BMS-OMD

6d. Staff or Student number:

76677053

6e. Email address:

s.f.oudewesselink@utwente.nl

2021-07-26 15:06:14

Appendix VI: Ethical review MST

Medisch Spectrum Twente

Postbus 50 000
7500 KA Enschede
Koningsplein 1
7512 KZ Enschede
www.mst.nl

Aan de heer Orkino Gourie
Interne Geneeskunde
Medisch Spectrum Twente

Datum	Ons kenmerk	Pagina
15-07-2021	RvB//jvdp/2081-21/73.0	1 van 2

Uw kenmerk	Contactpersoon
Neuropathy after chemotherapy: long term consequences for patients	

Onderwerp

Goedkeuring onderzoeksproject niet-WMO-plichtige studie

Geachte heer Orkino Gourie,

De Raad van Bestuur gaat akkoord met het starten van de studie *Neuropathy after chemotherapy: long term consequences for patients*, bekend onder nummer K21-27.

De lokale adviescommissie uitvoerbaarheid heeft vastgesteld dat uw projectvoorstel nietWMO-plichtig is en dat ook verder aan gestelde voorwaarden is voldaan.

Wij wensen u veel succes met de uitvoering van dit onderzoek en worden te zijner tijd graag geïnformeerd over de uitkomsten.

Met vriendelijke groet, namens de Raad van
Bestuur*,

Mw. C. Pinners,
Bedrijfskundig manager

I.a.a.: RVE-management mevrouw drs. M.C.H. Pleunis – van Empel
Adviescommissie lokale uitvoerbaarheid

*Bij mandaat van de Raad van Bestuur d.d. 31-10-2017

In verband met de Corona-crisis:
In verband met de thuiswerksituatie van de medewerkers van het wetenschapsbureau wordt deze brief niet voorzien van een "natte handtekening" of in hard copy verzonden.
Bewaart u deze mail met bijlage dus goed, de brieven worden ook niet naderhand verzonden.

Declaration:

The Board of Directors agrees with the start of study *Neuropathy after chemotherapy: long term consequences for patients*, known as number K21-27.

The Institutional Review Board of Medisch Spectrum Twente has concluded that your study does not fall under the remit of the Medical Research Involving Human Subjects Act.

We wish you a successful conduct of your study. We herewith would like to emphasize that we need to be informed about the outcomes of the study.

Appendix VII: nWMO questionnaire MST

Niet-WMO vragenlijst

In te vullen bij statusonderzoek

Toelichting:
Onderzoek dat niet onder de Wet Medisch Wetenschappelijk Onderzoek met Mensen (WMO) valt, dient te voldoen aan andere wetten en richtlijnen op het gebied van patiënten rechten, privacy en informatieveiligheid (AVG, WGBO, code goed gedrag). Om te beoordelen of dataonderzoek in overeenstemming is met geldende wet- en regelgeving, dienen onderzoekers de niet-WMO vragenlijst (digitaal) in te vullen en op te sturen naar het wetenschapsbureau (nietwmo@mst.nl). De niet-WMO commissie zal de vragenlijst

beoordelen en bij akkoord een bevestiging per e-mail sturen. Als er nadere acties gewenst zijn, zal dit eveneens per e-mail gecommuniceerd worden.

CONTACTGEGEVENS	
Titel van het onderzoek:	Neuropathy after chemotherapy: long term consequences for patients
Hoofdonderzoeker:	Orkino Gourie
Lokale (hoofd)onderzoeker MST	
Afdeling:	Interne Geneeskunde
Datum van invullen:	11-05-2021

1	**ALGEMENE INFORMATIE OVER DE STUDIE**		
1.1	a) Is er reeds een bestaande database met verzamelde data (data hoeft niet meer uit patiëntendossier gehaald te worden)?	☐ ja Ga naar 2.1	☒ nee
	b) Indien nee, geef aan of de data prospectief (metingen moeten nog plaatsvinden) of retrospectief (metingen hebben al plaatsgevonden) uit patiëntendossier gehaald wordt.	☒ prospectief ☐ retrospectief Ga naar 2.5	

2	**PRIVACY ASPECTEN**		
LET OP: Onderstaande vragen (2.1 t/m 2.4) alleen invullen als er sprake is van dataonderzoek met een <u>bestaande</u> database!			
2.1	Is er in het kader van dit onderzoek toestemming gevraagd aan patiënten voor het gebruik van hun (medische) gegevens?	☐ nee	☐ ja
2.2	a) Is het in het kader van het onderzoek noodzakelijk om patiëntendossiers in te zien?	☐ ja	☐ nee Ga naar 2.3
	b) Licht toe waarom patiëntendossiers ingezien dienen te worden.	Klik hier als u tekst wilt invoeren.	
	c) Geef aan door wie de patiëntendossiers ingezien worden (naam en functie).	Klik hier als u tekst wilt invoeren.	
	d) Zijn de personen die de patiëntendossiers inzien hiertoe gerechtigd uit hoofde van een behandelrelatie met de desbetreffende patiënt (of is hiervoor toestemming aan de patiënt gevraagd)?	☐ nee	☐ ja Ga naar 2.3
	e) Indien nee, staan de personen die de gegevens uit de patiëntendossiers inzien onder directe supervisie van een behandelaar die uit hoofde van de behandelovereenkomst wel gerechtigd is tot inzage in de dossiers? *Als een lid van het onderzoeksteam zelf geen behandelrelatie heeft met de desbetreffende patiënten en daarom niet gerechtigd is tot inzage van het dossier, dient de behandelaar die wél gerechtigd is tot inzage de gegevens uit het dossier ter beschikking te stellen, dan wel dient de persoon die de gegevens uit de dossiers haalt onder directe supervisie van de behandelaar te staan.*	☐ nee	☐ ja, naam / functie supervisor: Klik hier als u tekst wilt invoeren.
2.3	Is er aantekening gemaakt in de status van de desbetreffende patiënten van het gebruik van (medische) gegevens voor wetenschappelijke doeleinden?	☐ nee	☐ ja

	Voor de verstrekking van (medische) gegevens in het kader van wetenschappelijk onderzoek, zonder uitdrukkelijke toestemming van de patiënt, vereist de wet dat de behandelaar die de gegevens verstrekt daarvan aantekening maakt in het patiëntendossier.	
2.4	a) Hoe zijn de onderzoeksgegevens opgenomen in de database? *Indien patiënten geen uitdrukkelijke toestemming hebben gegeven voor het gebruik van gegevens uit hun patiëntendossier, mogen in de database geen identificerende gegevens worden opgenomen (zoals patiëntennummer, NAW-gegevens, volledige geboortedatum). Indien het voor het beantwoorden van de onderzoeksvraag onmogelijk is onderzoek te doen met anonieme gegevens, dienen de in de database opgenomen gegevens te worden gecodeerd. Gegevens zijn alleen anoniem als de gegevens op geen enkele manier zijn te herleiden tot de patiënt. Dus ook niet via een code/sleutel. Als er een sleutelbestand wordt bewaard waarmee onderzoeksgegevens terug zijn te herleiden tot de patiënt spreken we van gecodeerde data.*	☐ Geanonimiseerd ☐ Gecodeerd ☐ Niet gecodeerd of geanonimiseerd
	b) Indien de onderzoeksgegevens gecodeerd zijn, geef aan op welke wijze dit gedaan is (hoe is deze opgebouwd).	Klik hier als u tekst wilt invoeren.
	c) Indien de database tot de persoon te herleiden gegevens bevat, geef aan om welke gegevens het gaat.	Klik hier als u tekst wilt invoeren. Ga naar 3.1
LET OP: onderstaande vragen (2.5 t/m 2.8) alleen invullen als er sprake is van dataonderzoek waarbij de <u>database</u> nog <u>gegenereerd</u> dient te worden!		
2.5	a) Wordt er in het kader van dit onderzoek toestemming gevraagd aan patiënten voor het gebruik van hun (medische) gegevens?	☐ nee ☒ ja
	b) Zo ja, wordt de template van MST gebruikt voor de patiënteninformatie (PIF) en toestemmingsverklaring (TSV)? *De template van MST (zie website MST) dient verplicht gebruikt te worden. Deze voldoet aan wettelijke vereisten.*	☒ nee ☐ ja
	c) Zo nee, licht toe waarom er geen toestemming gevraagd wordt.	Klik hier als u tekst wilt invoeren.
2.6	a) Is het in het kader van het onderzoek noodzakelijk om patiëntendossiers in te zien?	☒ ja ☐ nee Ga naar 2.7
	b) Geef aan door wie de patiëntendossiers ingezien worden (naam en functie).	- Orkino Gourie, stagiair/afstudeerder master Health Sciences bij Universiteit Twente - drs. M.C.H. Pleunis-van Empel, Internist-oncoloog
	c) Zijn de personen die de patiëntendossiers inzien hiertoe gerechtigd uit hoofde van een behandelrelatie met de desbetreffende patiënt (of is hiervoor toestemming aan de patiënt gevraagd)?	☐ nee ☒ ja Ga naar 2.7
	d) Indien nee, staan de personen die de patiëntendossiers inzien onder directe supervisie van een behandelaar die uit hoofde van de behandelovereenkomst wel gerechtigd is tot inzage in de dossiers?	☐ nee ☐ ja, naam/functie supervisor:

	Als een lid van het onderzoeksteam zelf geen behandelrelatie heeft met de desbetreffende patiënten en daarom niet gerechtigd is tot inzage van het dossier, dient de behandelaar die wél gerechtigd is tot inzage de (gecodeerde of geanonimiseerde) gegevens uit het dossier ter beschikking te stellen, dan wel dient de persoon die de gegevens uit de dossiers haalt onder directe supervisie van de behandelaar te staan.	Klik hier als u tekst wilt invoeren.
2.7	Wordt er aantekening gemaakt in de status van de desbetreffende patiënten van het gebruik van (medische) gegevens voor wetenschappelijke doeleinden? *Voor de verstrekking van (medische) gegevens in het kader van wetenschappelijk onderzoek, zonder uitdrukkelijke toestemming van de patiënt, vereist de wet dat de behandelaar die de gegevens verstrekt daarvan aantekening maakt in het patiëntendossier.*	☒ nee ☐ ja
2.8	a) Hoe worden de onderzoeksgegevens opgenomen in de database? *Indien patiënten geen uitdrukkelijke toestemming hebben gegeven voor het gebruik van gegevens uit hun patiëntendossier, mogen in de database geen identificerende gegevens worden opgenomen (zoals patiëntennummer, NAW-gegevens, volledige geboortedatum). Indien het voor het beantwoorden van de onderzoeksvraag onmogelijk is onderzoek te doen met anonieme gegevens, dienen de in de database opgenomen gegevens te worden gecodeerd. Gegevens zijn alleen anoniem als de gegevens op geen enkele manier zijn te herleiden tot de patiënt. Dus ook niet via een code/sleutel. Als er een sleutelbestand wordt bewaard waarmee onderzoeksgegevens terug zijn te herleiden tot de patiënt spreken we van gecodeerde data.*	☐ Geanonimiseerd ☒ Gecodeerd ☐ Niet gecodeerd of geanonimiseerd
	b) Indien codering plaatsvindt, geef aan wanneer dit plaatsvindt, door wie (naam en functie) en op welke wijze (hoe is deze codering opgebouwd).	Het patiëntennummer wordt alleen gebruikt voor het dossieronderzoek en daarna met zal met een willekeurig onderzoeksnummer gewerkt worden op het toestemmingsformulier door stagiair/afstudeerder Orkino Gourie.
	c) Indien de database tot de persoon te herleiden gegevens bevat (bijvoorbeeld geboortedatum, ziekenhuisnummer, adres), geef aan om welke gegevens het gaat.	Klik hier als u tekst wilt invoeren. Ga naar 3.1

3	**TOEGANG TOT EN OPSLAG VAN DATA**	
3.1	a) Worden er onderzoeksgegevens op papier opgeslagen?	☒ ja ☐ nee Ga naar 3.2
	b) Zo ja, waar worden de papieren onderzoeksdata opgeslagen?	In een afgesloten kast op de kamer van drs. M.C.H. Pleunis-van Empel
	c) Voldoet deze opslagplek aan vereisten? *Kast kan op slot, gegevens zijn alleen toegankelijk voor leden van het onderzoeksteam.*	☐ nee ☒ ja

3.2	a) Waar worden de digitale onderzoeksgegevens opgeslagen? *De onderzoeksdata behoren, bij voorkeur, te worden opgeslagen op een MST netwerkschijf en mogen alleen toegankelijk zijn voor leden van het onderzoeksteam. Gebruik van een onbeveiligde USB stick of harde schijf is niet toegestaan (tenzij enkel anonieme gegevens opgeslagen zijn).*	De onderzoeksgegevens worden opgeslagen op een MST netwerkschijf.	
	b) Indien van toepassing: waar wordt de sleutel, waarmee gecodeerde gegevens zijn te herleiden tot de patiënt, bewaard? *De sleutel blijft in MST.*	Er zal gewerkt worden met sleutelbestanden. Deze worden bewaard op het MST netwerkschijf.	
	c) Hoe wordt de toegankelijkheid van de digitale onderzoeksgegevens beschermd?	☒ wachtwoord	☐ anders, namelijk: Klik hier als u tekst wilt invoeren.
	d) Worden er back-ups gemaakt?	☐ nee	☒ ja
	e) Zo ja, hoe vaak?	Er wordt dagelijks een back-up gemaakt. De back-ups worden gemaakt tijdens het invoeren en analyseren van de data.	
3.3	a) Wie hebben er toegang tot de digitale onderzoeksgegevens?	De onderzoeker O. Gourie en begeleider M.C.H. Pleunis-van Empel	
	b) Indien van toepassing: wie hebben er toegang tot de sleutel van de gecodeerde data?	De onderzoeker O. Gourie en begeleider M.C.H. Pleunis-van Empel	
3.4	Hebben stagiaires of andere medewerkers zonder een formele contractuele relatie met MST, die toegang hebben tot de privacygevoelige gegevens (hiertoe behoren ook de gecodeerde onderzoeksgegevens), een geheimhoudingsverklaring ondertekend?	☐ nee	☒ ja ☐ n.v.t.
3.5	a) Vindt er uitwisseling van (onderzoeks)gegevens plaats met (een) andere instelling(en) binnen Nederland en/of de EU? *Zo ja, dan dienen de gegevens bij voorkeur volledig anoniem te worden overgedragen aan de andere instelling. Indien dat niet mogelijk of wenselijk is, dienen de gegevens gecodeerd te worden overgedragen aan de andere instelling (vóórdat de onderzoeksgegevens worden verstuurd naar de andere instelling). Gebruik liever geen usb stick. Als het niet anders kan, bescherm dan de usb stick met encryptiesoftware.*	☒ ja	☐ nee
	b) Indien ja, geef de namen van de instellingen aan.	Santeon ziekenhuizen en Universiteit Twente	
	c) Indien ja, is er een verwerkersovereenkomst of data transfer agreement afgesloten met degene met wie de data gedeeld worden?	☒ nee	☐ ja, namelijk: Klik hier als u tekst wilt invoeren.
3.6	a) Vindt er uitwisseling van de (onderzoeks)gegevens plaats met een andere instelling/instantie buiten de EU?	☐ ja	☒ nee
	b) Indien ja, geef de namen van de instellingen aan.	Klik hier als u tekst wilt invoeren.	

	c) Indien ja, wordt aan de desbetreffende patiënten toestemming gevraagd voor het uitwisselen van persoonsgegevens met een land buiten de EU? *De uitwisseling van persoonsgegevens met land buiten de EU is aan strengere regels onderworpen met als doel dat een zelfde bescherming als binnen de EU wordt gewaarborgd. In beginsel is daarvoor toestemming van de desbetreffende patiënten vereist. Ook als gegevens gecodeerd zijn, zijn deze indirect herleidbaar tot de patiënt en is het strengere regime uit de AVG op de uitwisseling van deze gegevens van toepassing.*	☐ nee ☐ ja
	d) Indien ja, is er een verwerkersovereenkomst of data transfer agreement afgesloten met degene met wie de data gedeeld worden?	☐ nee ☐ ja, namelijk: Klik hier als u tekst wilt invoeren.
3.7	Hoelang worden de gegevens van het onderzoek bewaard? *De standaardbewaartermijn voor onderzoeksgegevens is 5 jaar (niet-WMO plichtig onderzoek).*	☒ 5 jaar ☐ Anders, namelijk: Klik hier als u tekst wilt invoeren.

Appendix VIII: nWMO application form MST

	Soort Document: **Aanmeldingsformulier**		Code:
	Titel: **Aanvullende gegevens voor Goedkeuring RvB niet WMO-plichtig onderzoek**		
	Dienst/afdeling: **Medisch Spectrum Twente**		
Versie: **2.0**	Status: **Final**	Datum: **30-03-2021**	Pagina's **51**

Informatie onderzoek

Volledige titel onderzoek:	Neuropathy after chemotherapy: long term consequences for patients
Verkorte titel onderzoek:	-
Korte omschrijving onderzoek (Hoe/met welk hulpmiddel)	The aim of the study is to investigate (using questionnaires) to which extent patients that have been treated in Medisch Spectrum Twente (MST) in 2017 – 2019 suffer from neuropathy symptoms on the long term. By mapping this, it contributes to better inform future patients about neuropathy to prevent it from getting worse.
Verwacht aantal proefpersonen in MST	200 borstkankerpatiënten

Verantwoordelijke(n)

Naam Onderzoeker:	Orkino Gourie
RVE Onderzoeker:	drs. M.C.H. Pleunis – van Empel
Kostenplaats:	84257
Betrokken RVE-en:	Interne Geneeskunde
Betrokken afdelingen:	Interne Geneeskunde
Opdrachtgever:	drs. M.C.H. Pleunis – van Empel
Financiële consequenties voor studie(handelingen): **NB: Altijd bijlage 1 invullen**	Nee

De onderzoeker verklaart hierbij:

- de aanvraag volledig en juist te hebben ingevuld;
- het onderzoek uit te voeren in overeenstemming met de toepasselijke wet- en regelgeving, waaronder de Code Goed Gedrag.

Onderzoeker	
Naam:	Orkino Gourie
Datum:	11-05-2021
Handtekening:	

Toestemming betrokken partijen

Akkoord RVE-management (bedrijfskundig manager* of medisch manager)	
Naam:	
RVE:	
Datum:	22-6-21
Handtekening:	

Niet-WMO verklaring ontvangen
☐ Ja, bijlage toevoegen
☒ Nee

Studie RVE overstijgend
☐ Ja, RVE-management overige afdelingen zijn akkoord, zie onder
☒ Nee

Contract en/of overeenkomst aanwezig?
☐ Ja, bijlage toevoegen (getekend of concept)
☒ Nee

*** = Handtekening van de Bedrijfskundig manager is vereist, indien er financiële consequenties zijn voor de betrokken afdeling(en).**

Overige betrokken managers, kunnen hieronder tekenen (naam, RVE, datum en handtekening melden).

<u>Bijlage 1 Financiële consequenties:</u> ***Altijd invullen***

☐Er zijn wel/deels financiële consequenties voor de studiehandelingen van het onderzoek. (Vul tabel in en omschrijf welke handelingen plaatsvinden)

☐Er zijn geen financiële consequenties, maar het onderzoek bevat wel studiehandelingen.(Vul tabel **ook** zoveel mogelijk in en omschrijf welke handelingen plaatsvinden)

☒Er zijn geen financiële consequenties, want het onderzoek is een data-onderzoek zonder studie-handelingen met de patiënt. (Tabel hoeft niet ingevuld te worden)

Tabel uitleg Financiële consequenties:

Alle handelingen in het kader van het onderzoek noemen Gewenst onderzoek per patiënt	Te beschouwen als **reguliere** patiëntenzorg (normale facturering) Aantal:	**Niet reguliere handelingen of bepalingen** Aantal:	Kosten:	**Voor niet standaard zorg: wie betaalt dit**? Voeg een mailbevestiging toe en/of begroting. **Indien geen kosten, graag onderbouwen.**

Indien andere RVE's/functieafdelingen/diensten zijn betrokken (inclusief Medlon en Labpon) bij het onderzoek, voeg dan een akkoord / handtekening toe van de functionaris die verantwoordelijk is voor trials binnen deze dienst. Voor een overzicht van verantwoordelijke functionarissen wordt verwezen naar de MST-website 'Wetenschap en Onderzoek'
[https://www.mst.nl/over-mst/wetenschap-en-onderzoek/onderzoek-indienen-en-uitvoeren/niet-wmo-plichtig-onderzoek/].

Toestemming betrokken partij(en)

Naam:	
Functie/dienst:	
Datum:	
Handtekening:	

Naam:	
Functie/dienst:	
Datum:	
Handtekening:	

Appendix IX: SPSS syntax

```
* Encoding: UTF-8.


* Recoding patient reported NP dummy .
RECODE Patient_Reported_NP ('No'=0) ('Yes'=1) INTO Patient_Reported_NP_Dummy.
EXECUTE.

* Recoding dose reduction dummy categories.
RECODE Dose_Reduction ('No'=0) ('Yes, because of NP'=1) ('Yes, because of neutropenia'=2) ('Yes, '+
    'because of mucositis'=3) ('Yes, because of dose delay'=4) ('Yes, because of epistaxis'=5) INTO
    Dose_Reduction_nr.
EXECUTE.

* Recoding dose reduction dummy categories into dummy yes/no .
RECODE Dose_Reduction_nr (0=0) (ELSE=1) INTO Dose_Reduction_Dummy_yesno.
EXECUTE.

* CTCAE_Results missing values to 999.
RECODE CTCAE_Results (SYSMIS=999).
EXECUTE.

*Computing new variable: total score.
DO IF MISSING(CTCAE_Results).
COMPUTE Total_Score=DN4_Results.
ELSE IF DN4_Results >=1 & CTCAE_Results >=1 | DN4_Results <1 & CTCAE_Results <1.
COMPUTE Total_Score=DN4_Results+CTCAE_Results.
ELSE.
COMPUTE Total_Score=0.
```

```
END IF.
EXECUTE.

* Recoding presence neuropathy dummy .
RECODE Total_Score (SYSMIS=SYSMIS) (0=0) (ELSE=1) INTO Presence_Neuropathy_Dummy.
EXECUTE.

* Compute new variable: severity of neuropathy .
DO IF MISSING(CTCAE_Results) | Presence_Neuropathy_Dummy = 1.
COMPUTE Severity_Neuropathy=CTCAE_Results.
ELSE.
COMPUTE Severity_Neuropathy=0.
END IF.
EXECUTE.

* Treatment regimen recoding  .
RECODE Treatment_Regimen ('AC-Paclitaxel'=1) ('ACdd-Paclitaxel'=2) ('AC-
Paclitaxel/Trastuzumab'=3)
    ('ACdd-Paclitaxel/Trastuzumab'=4) ('AC-PDT'=5) ('ACdd-PDT'=6) ('TAC'=7) INTO
Treatment_Regimen_nr.
EXECUTE.

* Determine normal distribution patient characteristics.
GRAPH
  /HISTOGRAM=Age_Patient.

GRAPH
  /HISTOGRAM=Treatment_Regimen_nr.

* Table 3 baseline characteristics .

FREQUENCIES VARIABLES=Age_Patient Treatment_Regimen_nr Patient_Reported_NP_Dummy
    Dose_Reduction_nr Presence_Neuropathy_Dummy Severity_Neuropathy
```

```
  /STATISTICS=STDDEV VARIANCE RANGE MINIMUM MAXIMUM SEMEAN MEAN
MEDIAN
  /ORDER=ANALYSIS.


* Figure 3 frequencies 1st research question .
FREQUENCIES VARIABLES=Presence_Neuropathy_Dummy
  /ORDER=ANALYSIS.


* Table 4 regression patient characteristics .
LOGISTIC REGRESSION VARIABLES Presence_Neuropathy_Dummy
  /METHOD=ENTER Age_Patient
    /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).


* Recoding dose reduction into dose reduction because of neuropathy .
RECODE Dose_Reduction_nr (1=1) (ELSE=0) INTO Dose_Reduction_Dummy_NP.
EXECUTE.


* Table 5 Relationship between dose reduction and presence of neuropathy two years after taxane
chemotherapy .
CROSSTABS
  /TABLES=Presence_Neuropathy_Dummy BY Dose_Reduction_Dummy_NP BY
Patient_Reported_NP_Dummy
  /FORMAT=AVALUE TABLES
  /CELLS=COUNT
  /COUNT ROUND CELL.


* Create AC-Paclitaxel dummy .
RECODE Treatment_Regimen_nr (1=1) (ELSE=0) INTO AC_Paclitaxel_Dummy.
EXECUTE.
```

```
* Create ACdd-Paclitaxel dummy .
RECODE Treatment_Regimen_nr (2=1) (ELSE=0) INTO ACdd_Paclitaxel_Dummy.
EXECUTE.

* Create AC-Paclitaxel/Trastuzumab dummy .
RECODE Treatment_Regimen_nr (3=1) (ELSE=0) INTO AC_Paclitaxel_Trastuzumab_Dummy.
EXECUTE.

* Create ACdd-Paclitaxel/Trastuzumab dummy .
RECODE Treatment_Regimen_nr (4=1) (ELSE=0) INTO ACdd_Paclitaxel_Trastuzumab_Dummy.
EXECUTE.

* Create AC-PDT dummy .
RECODE Treatment_Regimen_nr (5=1) (ELSE=0) INTO AC_PDT_Dummy.
EXECUTE.

* Create ACdd-PDT dummy .
RECODE Treatment_Regimen_nr (6=1) (ELSE=0) INTO ACdd_PDT_Dummy.
EXECUTE.

* Create TAC dummy .
RECODE Treatment_Regimen_nr (7=1) (ELSE=0) INTO TAC_Dummy.
EXECUTE.

* Recode into docetaxel dummy .
RECODE Treatment_Regimen_nr (5=1) (6=1) (7=1) (ELSE=0) INTO Docetaxel_Dummy.
EXECUTE.

* Recode into paclitaxel dummy .
RECODE Treatment_Regimen_nr (1=1) (2=1) (3=1) (4=1) (ELSE=0) INTO Paclitaxel_Dummy.
EXECUTE.
```

```
* Table 6 regression between age, paclitaxel and docetaxel and presence of neuropathy .
LOGISTIC REGRESSION VARIABLES Presence_Neuropathy_Dummy
  /METHOD=ENTER Paclitaxel_Dummy Docetaxel_Dummy Age_Patient
    /PRINT=CI(95)
  /CRITERIA=PIN(.05) POUT(.10) ITERATE(20) CUT(.5).
```