Clinical Pain Research

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Neuropathy and pain after breast cancer treatment: a prospective observational study

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Abstract

Objectives: Neurological complications including pain are common after treatment for breast cancer. This prospective study investigated the symptoms, intensity and interference of chemotherapy-induced peripheral neuropathy. (CIPN) in the feet and hands compared to surgery- and radiation-induced neuropathy in the breast and upper arm.

Methods: Consecutive patients referred to surgery for breast cancer were included in a prospective study and completed a questionnaire at baseline and a follow-up questionnaire and interview after one year. CIPN was assessed with the CIPN20 questionnaire and the Michigan Neuropathy Screening Instrument questionnaire (MNSIq). Pain intensity was rated on a numeric rating scale (NRS, 0–10).

Results: In total 144 patients were included, of which 73 received chemotherapy. At one-year follow-up, symptoms of polyneuropathy were more common in patients treated with chemotherapy. Tingling or numbness in the feet in those treated/not treated with chemotherapy was reported by 44 (62%) and 15 (21%), respectively. Pain was present in 22 (30%) and 10 (14%), respectively. Pain in the area of surgery was reported by 66 (46%). Although less common, pain in the feet in those treated with chemotherapy was rated as more intense and with more daily life interference than pain in the surgical area (NRS 5.5 (SD 1.9) vs. 3.1 (SD 1.9).

Conclusions: Neurological complications including pain following surgery and chemotherapy represent a burden to breast cancer survivors. In those who had received chemotherapy, pain in the feet was less common than pain in the surgical area, but pain in the feet was more intense and had a higher interference with daily life. Our study emphasizes the need for either baseline data or a control population for improved estimation of the presence and severity of CIPN and pain from questionnaires.

Keywords: breast cancer; chemotherapy; CIPN; lumpectomy; mastectomy; polyneuropathy.

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Introduction

Breast cancer is treated with a combination of surgery, radiation therapy, and pharmacological treatment. Chemotherapy alone is estimated to prevent around one-third of

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deaths [1]. Patients may, however, experience treatment-related neurological sequelae, of which chemotherapy-induced peripheral neuropathy (CIPN) is considered the most common and disabling long-term condition [2]. Taxanes, including docetaxel and paclitaxel, are known to cause chronic CIPN in breast cancer patients [3]. Symptoms include tingling and numbness in the feet and occasionally in the hands and about one-third of patients experience neuropathic pain in these areas [4, 5]. Furthermore, breast cancer surgery, particularly axillary lymph node dissection, may damage sensory nerves and result in long-term post-surgical neuropathic pain in their innervation territory [6–9]. Neuropathic pain may be difficult to distinguish from pain that is induced by other cancer-related treatments (e.g., musculoskeletal pain caused by endocrine therapy, trastuzumab or bisphosphonates) [10, 11].

Previous prospective studies in patients with breast cancer have assessed the development of either CIPN [4, 12, 13] or persistent postsurgical pain [14–16]. Only few studies have assessed both complications in the same study. A prospective study including 475 patients with newly diagnosed breast cancer found that 43% presented with at least one cancer-related neurological complication at 1- and 3-year follow-ups [17]. The most frequently reported complications were CIPN, neuropathic pain after surgery, and cognitive impairment [17]. A cross-sectional study 2–6 years after surgery found that pain was most frequently reported in the breast (60%) followed by the axilla (48%), arm (29%), shoulder (26%), and fingers/feet (18%) [18].

This paper presents results of predefined secondary data from a prospective cohort study of patients undergoing breast cancer surgery. The objectives were to assess the symptoms, intensity and interference of neuropathy and pain due to chemotherapy. This study was conducted as part of the European Union's Horizon 2020 research project DOLORisk.

Materials and methods

Study design

This study was a prospective cohort study of consecutive patients scheduled for surgery due to breast cancer at the Breast Clinic, Regional Hospital Viborg, Denmark from September 2017 to October 2018. Details of the methods of the overall DOLORisk project have been presented previously [19]. The primary objectives of the study were to assess genetic and psychosocial risk factors for post-surgical neuropathic pain in two cohorts in France and Denmark and data will be presented separately. Here, only the methods related to this part of the prospective data from the breast cancer cohort performed only in Denmark will be described. The study was approved by the Central Denmark Region Committees on Health Research Ethics (no 1-10-72-23-17) and registered at the Central Denmark Region's internal notification for data protection (no 1-16-02-89-16). Patients provided written informed consent prior to enrolment in the study.

Patients

Patients scheduled for breast cancer resection aged ≥18 years with the ability and willingness to comply with study procedures and expected availability for follow-up and who provided written informed consent were included. Exclusion criteria were mental incapacity or language barriers, current alcohol or substance abuse, inability to participate in study procedures due to a serious underlying condition, and cancellation of their planned breast cancer surgery.

Study settings

Patients were enrolled by the Surgeon at their first visit to the Breast Clinic. Enrolled patients were asked to complete a set of questionnaires at home and bring them to the clinic when they returned for the scheduled surgery. All patients underwent standard treatment for breast cancer, which included surgery, chemotherapy, radiation therapy, and other adjuvant pharmacological treatments, depending on the cancer type and stage. After one year, they were sent the same set of questionnaires including a number of additional questions and were asked to return the completed questionnaires at the one-year control visit at the Breast Clinic. After the control visit, patients were asked to participate in an interview performed by the study laboratory technician.

Baseline questionnaire

The set of questionnaires included questions about age, sex, height and weight, smoking habits, and alcohol consumption. To assess neuropathy, the Michigan Neuropathy Screening Instrument questionnaire (MNSIq) was used [20]. A score of ≥4/13 was used as a cut-off for possible neuropathy, as previously proposed [20]. Next, the patients completed the EQ-5D rating of health using a 0–100 graphical rating scale [21] and the Patient-Reported Outcome Measurement Information System (PROMIS) short form 6a questionnaires to assess anxiety, depression, fatigue, and sleep disturbance. The PROMIS instrument assesses symptoms during the previous seven days using a 5-point ordinal scale. The scores were converted into PROMIS *T*-scores, with higher scores indicating more severe symptoms [22]. Patients were asked whether they were bothered by pain in the planned surgical area either all the time or on and off. If so, they were asked about the duration of their pain, the average pain intensity rated on a Numeric Rating Scale (NRS) from 0 to 10 over the past seven days. In addition, the PROMIS pain interference 6a questionnaire for interference with daily activities, homework, social activities, household chores, things they do for fun and enjoyment of social activities, rated as "not at all", "a little bit", "somewhat", "quite a bit", or "very much". Patients were also asked whether other types of pain bothered them, and how likely they thought it was that they would experience pain after one year due to the surgery, rated on the NRS (0–10).

One-year follow-up questionnaire

The one-year follow-up questionnaire set was almost identical to the baseline set. The item on pain expectation was removed, and the pain items now addressed the surgical area. In addition, the set included questions about concomitant cancer treatment and the European Organization for Research and Treatment of Cancer (EORTC) QLQ-CIPN20 questionnaire, which contains summary scores for sensory, motor and autonomic neuropathy symptoms [23].

Finally, the patients were asked whether they had experienced constant or recurrent unpleasantness (dysesthesia) and pain in the feet, and if so, they were asked to rate the average pain intensity over the past seven days on the NRS (0–10) and the pain interference on the PROMIS 6a questionnaire.

One-year follow-up interview

Patients were asked whether they had received chemotherapy and other adjuvant treatments (endocrine, trastuzumab, bisphosphonate, and radiation therapy), and if they had received a reduced number of chemotherapy cycles than planned and the reason why. The type of chemotherapy was not recorded, but at the time of study, the standard treatment was paclitaxel (80 mg/m^2) weekly for nine weeks and for 12 weeks in case of locally advanced cancer. Clinical information about cancer type, clinical stage, and surgery was obtained from the patients' medical records. Patients were asked whether they had experienced pain due to the cancer surgery during the past seven days and if not whether they had experienced unpleasantness, and they were also asked to describe these symptoms in detail. In addition, they were asked whether they had other diseases and if they took pain medication in general and for pain due to surgery or chemotherapy.

Statistical analyses

Descriptive data are reported as number (percentage) and numerical data as mean and standard deviations (SD) or median (range). Variables were compared using paired and unpaired t-tests, or Mann-Whitney U tests in case of a non-normal distribution of data. The Chi^2 test was used for testing independence between pain in the feet and breast and the McNemar test for testing consistency between the two. Logistic regression examined the effect of different causes of pain on health scores. $p<0.05$ was considered statistically significant. Statistical analyses were performed using SPSS, version 27 (IBM, Armonk, NY, USA).

Results

Patients

A total of 172 patients consented to participate among 182 invited, of which 144 (84%) were available for one-year follow-up data and were included in the analyses (Figure 1). The follow-up questionnaire set was completed on average 12.2 months (SD 1.25, range 9.6–17.8 months) after the baseline set. The examination was completed within 10 days after filling in the second questionnaire in 74% of patients.

All patients except one were women, and the average age was 62.3 (SD 10.5) years (Table 1). Most patients (62%) had a lumpectomy with sentinel lymph node biopsy, and 50.7% of the patients received chemotherapy (Table 1). In 38% (26/68), the chemotherapy dose was decreased; the reasons were sensory symptoms in the hands or feet (n=13), fever or abnormal blood cell count (n=3), or unknown causes (n=10).

Patients who received chemotherapy were younger than those who did not, and they were more often treated with invasive surgery (mastectomy and axillary lymph node dissection) and other cancer treatment modalities (Table 1).

Symptoms of polyneuropathy

On the CIPN20, patients who had received chemotherapy had significantly higher sensory and motor but similar autonomic scores than those who had not received chemotherapy (Table 2). Compared to patients who had not received chemotherapy, patients undergoing chemotherapy more often reported tingling or numbness in the feet on CIPN20 (62% (44/71) vs. 21% (15/71) $p<0.001$), had a higher MNSIq score (median 2.0 (0–11) vs. median 1.0 (0–5), $p=0.005$), and more often had a score of at least 4, indicating possible neuropathy (22 vs. 10%). At baseline, the median MSNIq score was 1 (range 0–7), and 8% (11/134) had a MNSIq score ≥4. The most common symptoms reported at follow-up in those undergoing chemotherapy compared to baseline and compared to follow-up in those who had not undergone chemotherapy were tingling, numbness, pricking, burning

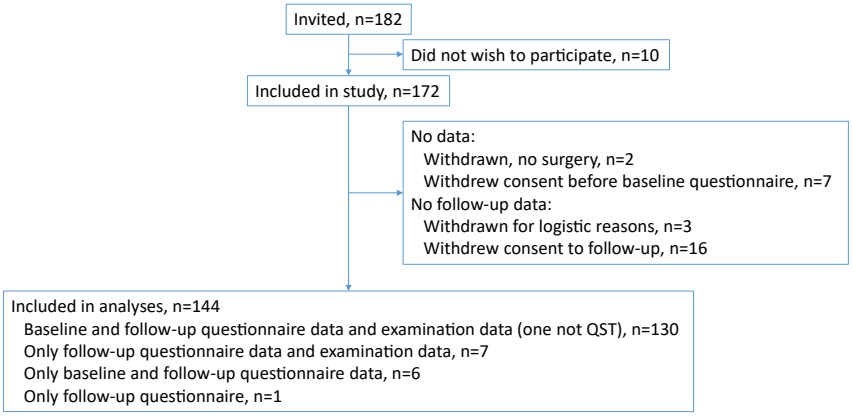

Figure 1: Study flow chart.

Table 1: Baseline characteristics and cancer treatment of all included patients and patients who did/did not receive chemotherapy.

	All	Chemotherapy	No chemotherapy	p-Value[a]
Number	144	73	71	
Baseline data				
Sex, female, n (%)	143 (99)	73 (100)	70 (99)	0.49
Age, years, mean (SD)	62.7 (10.5)	60.8 (11.4)	66.8 (8.3)	0.007
Weight, kg, mean (SD)[b]	73.0 (14.4)	75.8 (17.0)	70.0 (11.7)	0.043
Height, cm, mean (SD)[b]	166.0 (6.7)	166.9 (6.7)	164.9 (6.7)	0.58
BMI, kg/m^2, mean (SD)[b]	26.5 (4.6)	27.1 (5.2)	25.8 (4.4)	0.61
Smoking, n=136, n (%)	15 (11)	9 (15)	6 (10)	0.48
Alcohol, >7 units/week, n=135, n (%)	26 (19)	15 (21)	11 (17)	0.51
Cancer type, n=142				0.43
Ductal, n (%)	125 (88)	61 (85)	64 (91)	
Lobular, n (%)	15 (11)	10 (14)	5 (7)	
Mucinous, n (%)	2 (1)	1 (1)	1 (1)	
Stage, n=140				<0.001
Stage 1, n (%)	31 (22)	5 (7)	26 (38)	
Stage 2, n (%)	66 (47)	39 (55)	27 (39)	
Stage 3, n (%)	31 (22)	24 (34)	7 (10)	
DCIS, n (%)	12 (9)	3 (4)	9 (13)	
Estrogen status positive, n=133, n (%)	120 (90)	59 (83)	61 (98)	0.003
HER2 positive, n=131, n (%)	28 (21)	23 (33)	5 (8)	<0.001
Cancer treatment				
Surgery type, n=143				0.008
Lumpectomy and SLNB, n (%)	88 (62)	37 (51)	51 (72)	
Lumpectomy and ALND, n (%)	13 (9)	9 (13)	4 (5)	
Mastectomy and SLNB, n (%)	17 (12)	8 (11.1)	9 (13)	
Mastectomy and ALND, n (%)	19 (13)	16 (22.2)	3 (4)	
Other, n (%)[c]	6 (4)	2 (3)	4 (6)	
Endocrine therapy, n=135, n (%)[d]	88 (65)	53 (77)	35 (53)	0.004
Trastuzumab, n=134, n (%)	21 (16)	21 (31)	0 (0)	<0.001
Bisphosphonates, n=137, n (%)	77 (56)	41 (59)	36 (53)	0.45
Radiation therapy, n=144, n (%)	124 (86)	67 (93)	57 (80)	0.046

[a]Chemotherapy vs. no chemotherapy, [b]in the 8 patients without baseline questionnaire data, weight and height from follow-up was used, [c]Mastectomy or lumpectomy alone or primary breast preserving surgery, [d]Letrozole in 63, tamoxifene in 15, other or unknown in 10. ALND, axillary lymph node dissection; BMI, body mass index; CIPN, chemotherapy-induced peripheral neuropathy; HER2, human epidermal growth factor receptor 2; SLNB, sentinel lymph node biopsy. Number of patients with data are indicated for each outcome in case of any missing data.

pain, and difficulty manipulating small objects in agreement with a mainly sensory neuropathy (Figures 2 and 3).

Painful chemotherapy-induced polyneuropathy

Pain in both feet was reported by 22% (32/144). It was more frequently reported in those who had received chemotherapy (30% (22/73)) than in those who did not (14% (10/71)) (p=0.021) and was also more intense over the past seven days on the NRS (mean 5.5 (SD 1.9) vs. 3.6 (SD 1.8), p=0.022). The 22 patients who had received chemotherapy and also had pain in both feet were considered to have possible painful CIPN. Of those, 82% reported moderate pain intensity (NRS ≥4/10), and the impact of pain was reported to be at least moderate on one of the six PROMIS parameters in 77% (17/22) (Figure 4). Although not specifically addressed, based on notes, other causes than CIPN for pain in feet could include Parkinson's disease, osteoarthritis, diabetes, spondylosis, and endocrine and bisphosphonate treatment. Constant or recurrent unpleasantness in the feet was reported by 40% (58/144) and was more common in patients who had received chemotherapy. Seven patients reported taking pain medication for what they considered to be

Table 2: One-year follow-up data.

	All	Chemotherapy	No chemotherapy	p-Value[a]
Number	144	73	71	
CIPN sensory score, n=135, median (range)	9 (8–22)	10 (8–22)	8 (8–18)	<0.001
CIPN motor score, n=126, median (range)	10 (8–22)	10 (8–20)	9 (8–22)	0.016
CIPN autonomic score, n=144, median (range)	2 (2–7)	3 (2–7)	2 (2–6)	0.32
MNSIq score≥4, n=142, n (%)	23 (16)	16 (22)	7 (10)	0.048
Dysesthesia in feet, n=144, n (%)	58 (40)	39 (53)	19 (37)	0.001
Pain in both feet, n=144, n (%)	32 (22)	22 (30)	10 (14)	0.021
Other pain, n=144, n (%)	102 (71)	54 (74)	48 (68)	0.40

[a]Chemotherapy vs. no chemotherapy. CIPN, chemotherapy-induced peripheral neuropathy; EORTC QLQ – CIPN20 questionnaire; MNSIq, Michigan Neuropathy Screening Instrument questionnaire. Number of patients with data are indicated for each outcome in case of any missing data.

chemotherapy-induced pain (1 morphine, 2 paracetamol, 4 paracetamol+NSAIDs).

Postsurgical pain

Pain in the area of surgery at one-year follow-up was reported by 46% (66/144). Twenty patients (8.3%) also reported pain in the area where surgery was planned at baseline, which was before surgery but after the diagnostic breast biopsy and possible lymph node biopsy. Only five had pain of more than three months duration at baseline, of which 1 also had pain at one-year follow-up. At follow-up, pain in the arm was reported by 17% (24/144) and was more common following axillary lymph node dissection than sentinel lymph node biopsy (31 vs. 14%, p=0.021). Pain in the breast was reported by 33% (48/144) and was independent of surgery type (mastectomy vs. lumpectomy or lymph node dissection vs. biopsy, p>0.16).

The average pain intensity over the past seven days was 3.1 (SD 1.9). Moderate pain (NRS≥4) was reported by 36% (24/66), and 35% (23/66) reported at least moderate impact on one of the six PROMIS parameters (Figure 4).

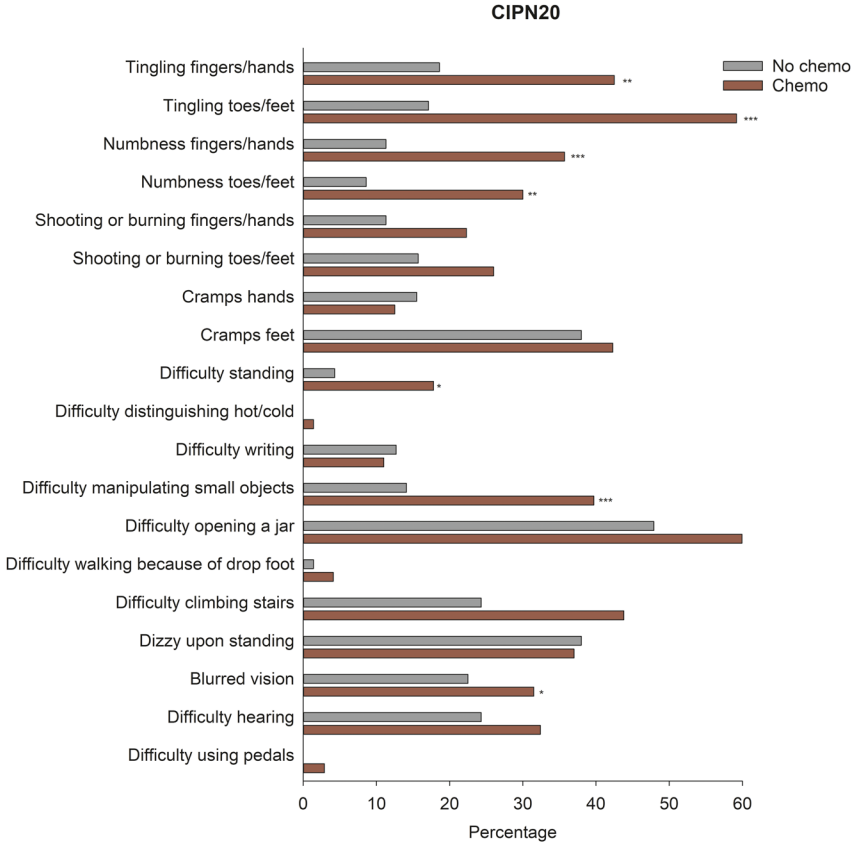

Figure 2: Symptoms reported on the European Organization for Research and Treatment of Cancer (EORTC) QLQ – CIPN20 questionnaire. Percentage of patients at one year reporting different symptoms with a score of at least "a little". Patients who had received chemotherapy (n=73) are shown as red columns, and those who had not received chemotherapy (n=71) as dark grey columns. Missing data were less than four for all questions except for difficulty using pedals, which was answered by 68 and 60, respectively. *p<0.05, **p<0.01, ***p<0.001.

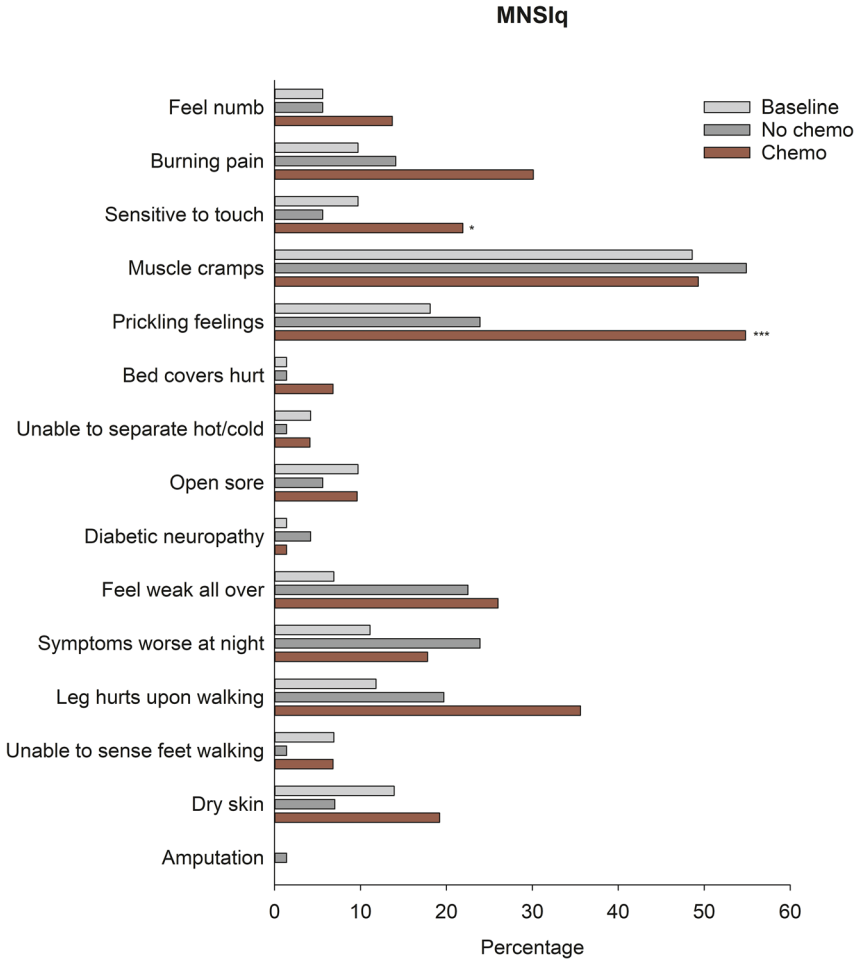

Figure 3: Symptoms reported on the Michigan Neuropathy Screening Instrument questionnaire (MNSIq).
Percentage of patients reporting the different symptoms in legs/feet. Baseline results are indicated with light grey and one-year results with red for the patients who had received chemotherapy and dark grey for those who had not received chemotherapy. Missing data were less than four for all questions except for prickling feelings (missing n=5) and symptoms worse at night (missing=4). *p<0.05, ***p<0.001, follow-up compared to baseline.

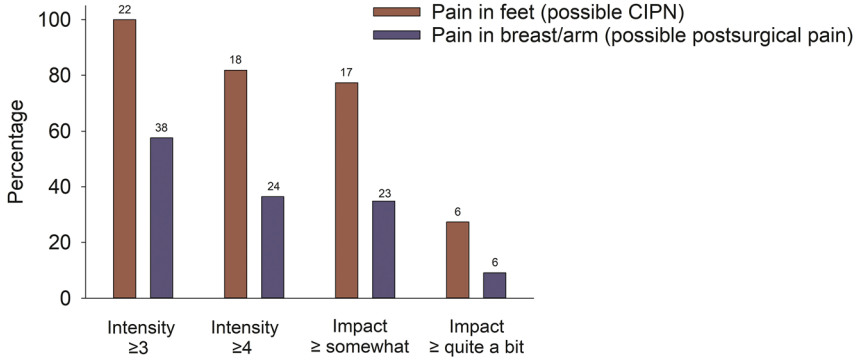

Figure 4: Intensity and impact of pain possible related to cancer treatment.
The percentage of patients with average weekly pain intensity on the NRS (0–10) reported as at least 3 and 4 and impact on one of the six PROMIS parameters of at least “somewhat” or “quite a bit”. Patients with possible painful CIPN (n=22, 30% of patients treated with chemotherapy) are indicated with red and patients with possible postsurgical pain (n=66, 46% of all patients) are indicated with blue. Absolute numbers are indicated above each column.

Only 41 (30%) reported any pain on interview compared to 46% in the questionnaire. An additional 30 reported non-painful dysesthesia and many patients spontaneously reported paresthesia such as tightness, soreness, pricking, tingling, and rare short-duration electrical shock-like sensations. Seven patients reported taking pain medication for postsurgical pain (1 amitriptyline, 6 paracetamol).

Patients who experienced pain in the area of surgery at one-year follow-up did not score higher at baseline on the likelihood that they would experience pain than those who did not experience pain (median 1 (0–5) vs. median 1 (0–10), p=0.37).

Surgical vs. chemotherapy-induced pain

Among the 73 patients who had received chemotherapy, 40% (17/43) with pain in the surgical area had pain in both feet compared to 17% (5/30) without pain in the surgical area (Chi^2, p=0.036). These data also show that there is a higher risk of developing pain in the breast than in the feet (McNemar, p=0.0002). However, as illustrated in Figure 4, the intensity and impact of pain in the feet is higher than pain in the breast. This is supported by analyses on the 17 who had pain in the feet (possible CIPN) as well as possible postsurgical pain. The average weekly pain intensity in the feet was more severe than pain intensity in the surgical area (median 5 (range 3–8) vs. median 3 (range 1–7), p=0.008) and more often had at least moderate impact on one of the six PROMIS parameters (76 vs. 35%, p=0.039).

Health state – differences between baseline and follow-up

Patient-reported health state on the EQ-5D VAS score was significantly higher at baseline (median 85, range 30–100) than at follow-up (median 80, range 10–100; p=0.009), but patients had significantly higher anxiety (55.0 (SD 7.5) vs. 47.6 (SD 9.4), p<0.001) and depression scores (48.9 (7.3) vs. 47.1 (SD 8.4), p=0.01) at baseline than at follow-up. There was no difference in fatigue (48.7 (SD 9.5) vs. 49.4 (SD 10.3), p=0.33) and sleep problems (51.6 (SD 7.7) vs. 50.6 (SD 8.2), p=0.15) scores. In logistic regression models, the presence of any pain and pain in the feet at one-year follow-up predicted health scores on the EQ-5D VAS with the model explaining only 14%, whereas none of the pain types were associated with a change in health score (Supplementary Table A1).

Discussion

The main finding of this prospective one-year follow-up study of patients with breast cancer was a high impact of chemotherapy in terms of frequency and severity of neuropathy symptoms including pain. Pain in both feet was reported by about one-third of patients treated with chemotherapy and only by half as many among those who had not received chemotherapy. Pain in the area of surgery was more common and present in almost half of the patients. However, pain was more severe in those with possible CIPN-related pain than those with possible surgery-related pain.

We found lower scores of patient-reported health state on the EQ-5D VAS score at follow-up compared to baseline. Pain in the feet and any pain was related to a lower quality of life. This findig is in line with previous studies revealing a higher symptom burden and decline in well-being in breast cancer patients treated with chemotherapy and endocrine therapy [24, 25]. Despite a higher quality of life at baseline compared to follow-up, we found high anxiety and depression scores at baseline, when they had just received a cancer diagnosis, and lower scores at follow-up. A previous study also found a decrease in anxiety and depression scores at one-year follow-up in patients with breast- and colorectal cancer treated with chemotherapy [24, 25]. This study reported further that patients with persistent pain had less improvement in anxiety and depression scores than those without [24, 25].

It is well-known that the estimated prevalence of CIPN varies depending on the type of scale used [2, 26]. In agreement with a previous study [4], a diagnosis of symptomatic CIPN was higher when based on the presence of symptoms of tingling/pricking or numbness in the feet than based on a cut-off score of ≥4 on the MNSIq, a questionnaire originally developed for diabetes-related neuropathy resulting in similar symptoms as CIPN. Among patients treated with chemotherapy, 22% had an MNSIq score ≥4 indicating possible polyneuropathy compared to 10% in patients treated without chemotherapy. At baseline 8% had a MNSIq score ≥4. Tingling or numbness was present in 62% of those who had received chemotherapy compared to 21% of those who had not. This was higher than previously found at one-year follow-up, where 45% of patients who had received docetaxel had tingling or numbness [25]. This may partly be explained by a potentially higher risk of developing CIPN from paclitaxel than docetaxel [27–29].

Our study emphasizes the need for either baseline data or a matched reference material or control population to

estimate the presence and severity of CIPN from questionnaire studies as patients not treated with chemotherapy also had symptoms of polyneuropathy on the MNSIq and QLQ-CIPN20. Reference QLQ-CIPN20 scores from people who have not undergone chemotherapy increase with age and are higher in people with various health conditions such as osteoarthritis, cardiac disease, and hypertension [30]. It is thus expected that patients who have not received chemotherapy also have positive scores on questionnaires aiming to assess CIPN.

The symptoms on the QLQ-CIPN20 and MNSIq most likely related to chemotherapy were tingling, numbness, pricking, burning pain, and difficulty manipulating small objects, consistent with a mainly sensory neuropathy, with tingling/pricking feelings in the feet being present in around 60% compared to around 20% in those who had not received chemotherapy and baseline. In a large study including 884 patients with breast cancer, taxane chemotherapy was associated with higher risk of tingling in feet and hands, numbness in feet, shooting or burning of feet, problems standing, difficulty distinguishing between hot and cold water and manipulating small objects, opening a jar, and climbing stairs, as well as cramps in hands and feet and dizziness and blurred vision 1.5–7.3 years after treatment [29]. Except for cramps in the hands and dizziness upon standing, we found similar trends. Since patients who received chemotherapy more often received other cancer treatments, it cannot be ruled out that these other treatments are responsible for some of the symptoms that were more common in the chemotherapy group.

A total of 45% of patients reported pain in the area of surgery in the questionnaire, but only 30% of patients reported pain when interviewed. An additional 15% reported non-painful dysestesia/unpleasantness and several patients spontaneously reported paresthesia, although this was not systematically assessed. A higher prevalence of pain in studies using self-administered questionnaires compared with studies using face-to-face interviews has also been described for residual limb pain [31]. It is possible that patients experiencing dysesthesia or paresthesia tend to rate these sensations as pain in questionnaires when not offered the possibility to mention the sensations as non-painful abnormal sensations, thus leading to a false high prevalence of pain. At baseline, some patients also reported pain in the area of surgery of a duration of less than three months. Biopsies from the breast and possible lymph nodes were performed up to 10 days before the first visit and could explain this pain as breast cancer is most often painless.

Remarkably, except for one patient treated with amitriptyline, patients with pain in the feet or in the surgical area did either not receive pain medication or were treated with paracetamol with or without NSAIDs or morphine. Similar low frequencies of neuropathic pain drugs have previously been reported in patients with breast cancer [16]. It is unknown if they had previously tried medications recommended for neuropathic pain or if they had not been offered or not been interested in taking such medication.

We found a slightly higher likelihood of experiencing pain in the feet in patients with pain in the surgical area. A similar high intraindividual concordance of experiencing pain has been suggested in previous studies on neuropathic pain in patients undergoing bilateral amputations [32, 33], sternotomy and saphenectomy [34], and bilateral thoracotomy [35]. These results may point to an individual vulnerability to pain, which may consist of genetic, psychological or cognitive factors.

The advantage of our study is that it assessed unselected patients before surgery with a high response rate at one-year follow-up. Limitations include a relatively small number of patients recruited from a single surgical site. The follow-up time was one year, and it is likely that some symptoms may have resolved over time. Radiation therapy is, e.g., administered after chemotherapy treatment and was thus given closer to the time of the follow-up. In addition, the study did not include a clinical examination and detailed assessment of neuropathy nor data from the patients' medical records from oncology departments which would have provided us with more detailed data on their cancer treatment. Finally, we only assessed peripheral neuropathy and not cognitive impairment and other neurological complications.

Conclusions

The current study showed that neurological complications are common one year after diagnosis of breast cancer. Possible CIPN-related pain was less common than possible surgery-related pain, but when present, it was more intense and had a higher impact on daily life than possible surgery-related pain. The study also found an intraindividual uniformity of pain in the CIPN- and surgery-affected areas, suggesting that patient-related factors are important for the development of chronic pain.

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Informed consent: Informed consent has been obtained from all individuals included in this study.

Ethical approval: The research complied with all relevant national regulations, institutional policies and is in accordance with the tenets of the Helsinki Declaration (as amended in 2013), and has been approved by the Central Denmark Region Committees on Health Research Ethics (no 1-10-72-23-17).

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