Routine Cancer Treatment Regimens and Its Impact on Fine Motor Dexterity in Breast Cancer

Niklas Paul Grusdat^a Alexander Stäuber^a Marion Tolkmitt^b Jens Schnabel^b
Birgit Schubotz^c Henry Schulz^a

^aProfessorship of Sports Medicine/Sports Biology, Chemnitz University of Technology, Chemnitz, Germany;

^bDeutsches Rotes Kreuz Krankenhaus Chemnitz-Rabenstein, German Red Cross Hospital, Chemnitz, Germany;

^cTumorzentrum Chemnitz e.V., Clinical Cancer Registry Chemnitz, Chemnitz, Germany

Keywords

Breast cancer · Fine motor dexterity · Survivorship · Cancer treatment

Abstract

Introduction: Breast cancer can be a major challenge for those affected. Knowledge of changes in fine motor dexterity in affected women due to routine cancer therapies can help guide effective support. **Methods:** For this prospective observational study, we collected data of 79 women with a mean age 54.6 ± 9.5 years prior to, after breast cancer therapy (T1), and at 3-month follow-up. The fine motor dexterity was assessed for 4 treatment subgroups: SC = Surgery + Chemotherapy, SCR = Surgery + Chemotherapy + Radiotherapy, SR = Surgery + Radiotherapy, and S = Surgery. **Results:** Over time, women with breast cancer showed significant decreases in fine motor dexterity across all treatment groups ($p < 0.001$). The strongest negative effect was seen in the treatment groups receiving additional chemotherapy. SCR group showed pronounced limitations for dominant hand (DH) –12%; non-dominant hand (NDH) –15%; both hands (BH) –17%; assembly (ASSY) –11% at T1. Significant interaction was noticeable in DH ($F = 5.59, p < 0.001$), NDH ($F = 6.61, p < 0.001$), BH ($F = 13.11, p < 0.001$), and ASSY ($F = 5.84, p < 0.001$). **Discussion/Conclusion:** Our study showed that the extent of change in fine motor dexterity depends on the treatment regimen. The detection of unmet care needs

could help to personalize and optimize clinical and survivorship care. Based on our findings, multidisciplinary support initiated early in breast cancer therapy is required.

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Introduction

Breast cancer continues to be the most frequently diagnosed female cancer worldwide (2.26 million cases) [1]. The European Union reported 91,826 cases of death from breast cancer in 2020 [2]. In Switzerland, breast cancer is one of the most frequent cancers with 7,292 cases in 2020 [3]. Germany reports approximately 70,000 new cases every year [4]. Overall survival has improved in recent decades with new therapy options and personalized medicine [4]. Emotional challenges [5], functional limitations [6–8], cancer-related cognitive impairment (CRCI) [9–11], chemotherapy-induced peripheral neuropathy (CIPN) [12, 13] were all reported in women undergoing conventional breast cancer treatment. Especially at an early stage in life the ability to function in the workplace and employment issues are of great concern. Experiences may be highly individual and are sometimes underestimated in clinical routine assessments [14]. The Purdue Pegboard Test (PPT) has gained scientific credibility in measuring unimanual and bimanual finger and hand motor dexterity. In addition, it allows to draw conclusions

regarding cerebral lesions [15], cognitive processing [16, 17], and on executive and social functioning [18, 19]. Moreover, score changes have been shown to be of prognostic value in disease progression [20, 21] and the incidence of post-operative complications [22, 23].

Patients with breast cancer can receive various forms of medical therapy such as surgery, chemotherapy, hormone therapy, radiotherapy and may be confronted with adverse events. It can be assumed that treatment with chemotherapy certainly corresponds with more pronounced effects due to reported side effects, including hair loss, cardiotoxicity, and neurotoxicity [14, 24]. Peripheral neuropathy (PN) is one of the most common non-hematologic toxicities occurring among patients [25]. The severity and the prevalence of taxane-induced PN (TIPN) may still be underestimated in clinical routine assessments [26, 27].

More studies are needed that provide information on patients' perceived circumstances linked to routine cancer treatment regimes. Alongside the traditional clinical reports, transparency on performance-based outcome measures (OMs) is required to improve the quality of care [28, 29]. Close monitoring patient's care pathway appears to be of particular relevance as the option to conduct a risk stratification becomes available. Further differentiation on the perception of disease and the detection of unmet supportive care needs could help to personalize and optimize clinical and survivorship care.

However, to date few studies have examined the effects of different routine cancer treatment regimens on the neuropsychological performance with the PPT of women with newly diagnosed breast cancer. The purpose of the present study was to find out the extent to which performance-based OMs change over the course of the therapy. Based on this background, we conducted a study among 4 groups undergoing routine breast cancer treatment.

Methods

Between April 2018 and October 2020, a total of 149 patients with the first diagnosis of breast cancer were recruited within the research study, "RETURN" which was approved by the Ethics Committee of Chemnitz University of Technology (V-182-17-AS-Tumor-20012017) and registered with the German Clinical Trials Register (ID: DRKS00014263). All patients were recruited in the Red Cross Hospital in Chemnitz, Germany. Within 1 week after the diagnosis of breast cancer, affected women were invited by their doctor to a consultation and informed about possible participation in the present study. Participants had the opportunity to discuss their participation and read and consider the research information leaflet. Furthermore, sufficient time (>24 h) to reflect on the implications of participating in the study was given before the patients had to decide. Inclusion criteria for this analysis were – patients freely given written informed consent to participate in the study, recent diagnosis of untreated breast cancer, age <70 years. Patients with breast cancer were excluded if they had a previous

invasive malignancy, other malignant tumours, insufficiently treated pulmonary arterial hypertension, chronic obstructive pulmonary disease shown in Figure 1. Baseline demographics and patients' clinical characteristics were provided by the Clinical Cancer Registry Chemnitz (Tumorzentrum Chemnitz) (shown in Table 1). All assessments were carried out prior to (T0) and within 1 week after completing (T1) conventional cancer treatment (surgery, chemotherapy, and radiotherapy). The follow-up assessments were carried out 3 months after treatment (T2). Cases with long-term endocrine therapy continued beyond T2. Four treatment subgroups were included for the following analysis: SC = Surgery + Chemotherapy, SCR = Surgery + Chemotherapy + Radiotherapy, SR = Surgery + Radiotherapy and S = Surgery.

Materials

Assessment consisted of the PPT (Lafayette Instrument Co.; Model 32020A) following standardized directions for administration [30]. To evaluate the fine motor dexterity of the hands and fingers study participants were seated at a desk, and the Purdue Pegboard was placed in front of them. Participants were instructed to place as many pins and/or washers/collars as possible down the respective row in the given time interval prior to administering the 5 subtests: dominant hand (DH), number of pins placed in 30 s, non-dominant hand (NDH) number of pins placed in 30 s, both hands (BH), right + left + both (R + L + B) number of pins placed in 30 s and assembly (ASSY), number of pins, washers, and collars placed in 60 s. Each upper extremity was tested 3 times per session, and a mean score for each test was calculated. All assessments were performed by personnel trained examiners who administered all tests and documented all scores. The data analysis was performed with the statistical software package IBM SPSS statistics 26 (Chicago, IL, USA). Only those patients who completed all assessments were included in the analysis. Descriptive statistics are presented as mean, standard deviation (SD) of the outcome parameters. A significance level of $p < 0.05$ for data analyses was set. To ensure comparability between the study groups, demographic characteristics (age, height, weight, and BMI) were tested using ANOVA. All metric data were normally distributed (Shapiro-Wilk test), and sphericity was identified (Mauchly test). There was homogeneity of the error variances (Levene's test). Group differences over time were investigated with simple main effects of the between-subjects factor (Tukey-HSD), and secondary outcome variables with a repeated measure ANOVA for simple main effects of the within-subject factor (Bonferroni). Treatment-specific interactions between time and group (Greenhouse-Geisser) were tested by applying the mixed ANOVA for significant effects and post hoc analysis (Tukey, Games-Howell). The effect size was calculated by using the formula:

$$\text{partial } n^2 = \frac{SS_{\text{effect}}}{SS_{\text{effect}} + SS_{\text{error}}}.$$

Fig. 1. STROBE flow diagram of the prospective observational study in women with breast cancer.

Suggested benchmarks for interpretation of the effect size are small (0.1–0.3), medium (0.3–0.5), and large (>0.5) [31].

Results

Seventy-nine women with breast cancer were included in the present analysis. Mean (SD) age of the total sample at diagnosis was 54.6 ± 9.5 years (range = 30–69 years).

ANOVA revealed comparability of demographic variables between the groups ($p > 0.05$). Mean (SD) time interval between diagnosis of breast cancer and initial data collection prior to starting treatment for breast cancer (T0) was 6.8 ± 1.3 days (range 6.0–9.0 days). For completing therapy all women with primary disease finished their cycles of chemotherapy, treatment sessions of radiotherapy and/or cancer surgery. Total mean (SD) time for completing therapy was 6.6 ± 3.0 months (range 1.0–13.4 months.). After breast cancer treatment, follow-up data

Table 1. Baseline demographics and patients' clinical characteristics of $n = 79$ women with breast cancer

Variable	Group SC	Group SCR	Group SR	Group S
<i>N</i> (%)	22 (27.9)	17 (21.5)	27 (34.2)	13 (16.5)
Age, years	51.9±11.6	54.4±8.5	56.7±9.0	55.3±7.3
Height, m	1.65±0.08	1.65±0.08	1.61±0.06	1.63±0.08
Weight, kg	72.1±14.2	82.7±20.2	68.6±12.4	72.6±12.5
BMI, kg m ⁻²	26.4±5.0	30.5±6.8	26.4±4.8	27.4±4.3
UICC, <i>n</i> (%)	IA: 5 (6.3) IIA: 10 (12.7) IIIA: 1 (1.3) IIIB: 6 (7.6)	IA: 7 (8.9) IIA: 7 (8.9) IB: 2 (2.5) IIIB: 1 (1.3)	IA: 25 (31.7) IIA: 2 (2.5) IB: 0 (0.0) IIIB: 0 (0.0)	IA: 5 (6.3) IIA: 8 (10.1) IB: 0 (0.0) IIIB: 0 (0.0)
Time of therapy, month	7.7±1.3 (6.0–10.5)	10.4±1.6 (7.1–13.4)	5.3±1.5 (3.0–9.3)	2.5±1.6 (1.0–5.6)
SNB, <i>n</i> (%)	21 (26.6)	15 (19.0)	27 (34.2)	13 (16.5)
ALND, <i>n</i> (%)	5 (6.3)	3 (3.8)	0 (0.0)	0 (0.0)
BCS, <i>n</i> (%)	8 (10.1)	16 (20.3)	27 (34.2)	0 (0.0)
MRM, <i>n</i> (%)	2 (2.5)	1 (1.3)	0 (0.0)	2 (2.5)
SCM, <i>n</i> (%)	9 (11.4)	0 (0.0)	0 (0.0)	10 (12.7)
BCS + SCM, <i>n</i> (%)	3 (3.8)	0 (0.0)	0 (0.0)	1 (1.3)
TMX, <i>n</i> (%)	1 (1.3)	4 (5.1)	6 (7.6)	1 (1.3)
ALs, <i>n</i> (%)	13 (16.5)	9 (11.4)	20 (25.3)	11 (13.9)
Anth-bCTx, <i>n</i> (%)	12 (15.2)	9 (11.4)	0 (0.0)	0 (0.0)
TaxAnth-C, <i>n</i> (%)	10 (12.7)	8 (10.1)	0 (0.0)	0 (0.0)
R, <i>n</i> (%)	0 (0.0)	17 (21.5)	27 (34.2)	0 (0.0)

Data are expressed as means ± SD; *n* = number of patients (%). SC, Surgery + Chemotherapy; SCR, Surgery + Chemotherapy + Radiotherapy; SR, Surgery + Radiotherapy; S, Surgery; ALND, Axillary lymph node dissection; ALs, Aromatase inhibitors; Anth-bC, Anthracycline-Based Chemotherapy; BCS, Breast-conserving surgery; MRM, Modified Radical Mastectomy; R, Radiotherapy; SCM, Subcutaneous mastectomy; SNB, Sentinel node biopsy; TMX, Tamoxifen; TaxAnth-C, Anthracycline-Taxane-Based Chemotherapy; SD, standard deviation.

were collected within 1 week (mean 5.7 ± 0.8 days, range 4.0–7.0). The second follow-up took place 3 months after T1 (mean 91.4 ± 1.5 days, range 86.0–97.0). The statistical comparison of the data is summarized in Table 2. The longitudinal comparison indicated significant main effect (time) for the parameters: DH ($F [1.55, 116.63] = 57.76$ $p < 0.001$, $\eta^2 = 0.44$), NDH ($F [1.69, 126.34] = 63.13$ $p < 0.001$, $\eta^2 = 0.46$), BH ($F [1.86, 139.81] = 163.80$ $p < 0.001$, $\eta^2 = 0.69$), and ASSY ($F [1.88, 140.64] = 140.37$ $p < 0.001$, $\eta^2 = 0.65$). The highest effect sizes were shown in BH and ASSY (large effect).

A significant group $\times$ time interaction was shown for DH ($F [4.67, 116.62] = 5.59$, $p < 0.001$, $\eta^2 = 0.18$), NDH ($F [5.05, 126.34] = 6.61$, $p < 0.001$, $\eta^2 = 0.21$), BH ($F [5.59, 139.81] = 13.11$ $p < 0.001$, $\eta^2 = 0.34$), and ASSY ($F [5.63, 140.64] = 5.84$ $p < 0.001$, $\eta^2 = 0.19$) as significantly greater restrictions were experienced in the SC and the SCR group compared to the SR and the S group. The effect sizes for the primary outcome variable were small to moderate.

Discussion/Conclusion

Based on the preliminary data of the research study "RE-TURN", we conducted a sub-analysis of neuropsychological OMs in women with breast cancer. This study is the first

to perform a detailed characterization of the PPT in regard to the routine cancer treatment regimens. For monitoring of the neuropsychological performance in the early time course of breast cancer treatment, the clinically established PPT was used prior (T0) and post-cancer treatment (T1, T2). Our main findings provide evidence that women with breast cancer showed impaired hand and finger function immediately following cancer treatment and at 3-month follow-up. Across all treatment groups, the most pronounced impact was found in the SCR group following multi-modular treatment. Women with breast cancer who were exposed to chemotherapy performed worse in the 5 subtests of the PPT than patients of S and SR group.

Using PPT to evaluate changes of fine motor dexterity, we found that treatment subgroups in the present study showed 3–12% lower values in the ASSY subtest prior to cancer treatment than reference norms of healthy women aged 50–59 years [10, 30]. Differences at baseline could be based on emotional distress associated with the breast cancer diagnosis causing disrupted functional dynamics [32, 33]. Moreover, sex and age regarding guideline values for the Purdue Pegboard (3 Trials per Subtest) [10, 30] were undercut by our study groups to varying degrees T1; DH (SC –9%, SCR –9%, SR –3%, S –3%), NDH (SC –9%, SCR –10%, SR –1%, S –3%), BH (SC –12%, SCR –11%, SR +2%, S –1%) and in ASSY (SC –22%, SCR –14%, SR –15%, S

Table 2. The primary OMs of the Purdue pegboard test of the cancer treatment subgroups T0, T1, and T2

Variable	Mean (SD)		Percentage, %				F value		Effect size				
	Group	T0	T1	T2	T0-T1	T1-T2	n	p – time *	F – time	F – group	F – GxT	η ² (time)	η ² (GxT)
D ^H s	SC	15.3±1.3	13.7±1.3	14.0±1.1	-10.5	+2.2	22	a, b					
	SCR	15.5±2.1	13.6±2.2	13.7±2.3	-12.3	+0.7	17	a, b					
	SR	15.5±1.5	14.6±1.3	15.0±1.5	-5.8	+2.7	27	a, b, c	57.76***	1.11 NS	5.59***	0.44	0.18
	S	14.8±2.2	14.5±2.5	14.7±2.4	-2.0	+1.4	13						
NDH ^S	SC	14.5±1.4	13.1±1.7	13.3±1.8	-9.7	+1.5	22	a, b					
	SCR	15.1±1.7	12.9±1.5	13.0±1.7	-14.6	+0.8	17	a, b					
	SR	14.9±2.1	14.2±1.7	14.4±1.5	-4.7	+1.4	27	a	63.13***	1.68 NS	6.61***	0.46	0.21
	S	14.6±1.9	14.0±1.7	14.3±1.8	-4.1	+2.1	13						
BH I	SC	12.8±1.4	10.7±1.2	11.1±1.2	-16.4	+3.7	22	a, b, c					
	SCR	13.0±1.7	10.8±1.6	11.0±1.6	-16.9	+1.9	17	a, b					
	SR	13.2±1.3	12.4±1.3	12.6±1.2	-6.1	+1.6	27	a, b	163.80***	3.79 NS	13.11***	0.69	0.34
	S	12.8±1.9	12.0±1.8	12.2±1.8	-6.3	+1.7	13	a, b					
ASSY II	SC	31.2±7.9	27.1±7.9	27.7±7.9	-13.1	+2.2	22	a, b					
	SCR	33.5±7.4	29.9±7.1	30.2±7.7	-10.7	+1.0	17	a, b					
	SR	31.6±7.2	29.5±6.8	29.7±7.2	-6.6	+0.7	27	a, b	140.37***	0.41 NS	5.84***	0.65	0.19
	S	30.5±8.4	28.9±8.7	29.2±7.8	-5.2	+1.0	13	a, b					

Data are expressed as means ± SD; n = number of patients; Change in per cent (%). a = T1 differed significantly from baseline; b = T2 differed significantly from baseline; c = T2 differed significantly from T1. SC, Surgery + Chemotherapy; SCR, Surgery + Chemotherapy + Radiotherapy; SR, Surgery + Radiotherapy; S, Surgery; n, number of patients; s, number of pins; I, number of pairs of pins; II, Number of pins, collars and washers; DH, dominant hand; NDH, non-dominant hand; BH, both hands; R + L + B, right + left + both; ASSY, assembly; NS, not significant; OM, outcome measure; SD, standard deviation; T0, prior to treatment; T1, after cancer therapy; T2, at follow-up. * $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$.

–16%) which may be associated with changes in cognitive, sensory, and motor functions [10, 34]. Underlying mechanisms resulting in lower performance of the PPT in our study participants might be influenced by the state of inflammatory tumour [20, 35], the effect of anaesthetic drugs received [36], changes in hormone levels [37–39], attentional fatigue and neurotransmitter deregulation [40–42].

Our findings of strongest performance impairments within the chemotherapy-exposed groups may be related to neurotoxicity causing neurologic damage [43, 44], CRCI [9, 45], and interhemispheric transfer deficits [46]. However, the cause of the defect often remains undefined and is still not fully understood. Nevertheless, patients can get overwhelmed by impaired functional abilities and concurrent-related symptoms, including tingling, burning pain, and paraesthesia [47, 48]. The PPT is a reliable and time-efficient measure that can be helpful in identifying limitations for hand dexterity. There is a considerable amount of research available in support of its use in clinical practice and research [49–51]. The manual provides detailed directions, scoring, and reference norms across the lifespan (ages 5–89 years old) [10, 30], which makes the conduction of routine assessment in large target groups possible. The PPT is easily applicable for an oncology nurse as no special training is required and due to the portable use in a variety of settings. Based on the quick feasibility, long-term monitoring in survivorship care may be advantageous. Along with nerve conduction velocity testing, medical complications can be minimized by providing adequate intervention [52].

The total mean scores of SCR and SC group at T1 are similar to previously reported DH 13.8, NDH 12.9, and BH 11.1 values in women with breast cancer >20 years after adjuvant chemotherapy ($n = 196$) [11]. It transpired that women need to receive information about the possible effects of memory loss and advice about coping methods. Additionally, concerns on completing education or being able to meet job requirements to secure financial stability are debilitating and signal an adverse effect [53]. Follow-up data of our study participants may be an indicator of a lower capacity during everyday life [54] which requires therapeutic alignment to prevent deterioration of conditions [55, 56]. Further, survivors of breast cancer exposed to paclitaxel or docetaxel chemotherapy more often reported PN [57]. The management of CIPN [58] can be particularly severe and long-lasting [59]. Furthermore, CIPN may affect the quality of life to such an extent that a drug dose reduction is required [60]. This is accompanied by a potentially higher risk of mortality and morbidity due to the discontinuation of initial cancer treatment [61, 62]. Early implementation of regular exercise interventions of walking and resistance training, individually adapted to fitness with moderate-intensity counteracted illness-related symptoms in patients receiv-

ing taxane-based chemotherapy [63]. However, the evidence of studies focussing on improving CIPN and CRCI with exercise treatment is limited [64, 65]. In the light of apparent CIPN and CRCI, study designs must employ baseline assessments of PPT to detect changes accurately. More research is needed to identify how clinical characteristics, including older age, obesity, dietary supplements, stage of cancer, and side effects of chemotherapy, contribute to an increased risk of impaired fine motor skills. Assessing the fine motor dexterity should be integrated as a common measure in treatment process of women with breast cancer for advanced classifications. Performance-based OMs may give guidance to healthcare professionals as well as the team involved including oncologists, physiotherapists, and nurses for determining individualized needs of women with breast cancer and to initiate the appropriate supportive care, which may lead to better health outcomes and should thus be explored. For a beneficial approach in the subsequent oncological rehabilitation treatment, the optimal treatment modalities and timing for their implementation are required.

Limitations

There are limitations to the present study as we could not include an additional follow-up analysis. Since the number of patients, especially in group S was small ($n = 13$), our findings can only be regarded as preliminary, and future investigations are necessary for the generalizability of our findings. Treatment groups may not be representative for all cancer patients and especially not for those with a severe course of illness. Based on treatment regimens, differently distributed variables of clinical characteristics appeared in the final sample of patients. A multivariable risk-stratified approach with a larger sample size for identifying reduced fine motor dexterity is necessary. Socio-economic status as a possible influencing factor was not investigated. Screening patients for their levels of physical activity throughout the course of therapy may have led to a more differentiated assumption of study results.

Conclusion

In summary, women with breast cancer showed decreased unimanual and bimanual dexterity and across all groups, with the most pronounced impact in the SCR and SC group following a multi-modal treatment. Differences were particularly noticeable in the reduced performance with their NDH, their DH, with BH, and in ASSY. In order to strengthen health resources, especially for women undergoing combined cancer treatment, a multidisciplinary support is necessary. A permanent adoption of performance-based OMs in clinical research may increase the transparency of the patients' perceived circum-

stances. Routine assessment may help to personalize and optimize clinical and survivorship care and improve the overall patient's experience.

Statement of Ethics

Study approval statement: This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethical Review Board of Chemnitz University of Technology (reference number: V-182-17-AS-Tumor-20012017). The RETURN study is registered with the German Clinical Trials Register (ID: DRKS00014263).

Consent to participate statement: Written informed consent was obtained from all individual participants included in this study.

Consent for publication: N/A.

Conflict of Interest Statement

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Author Contributions

N.P.G. performed data collection, management, analysis, and manuscript writing; A.S. helped in data analysis and manuscript editing and provided scientific oversight for the manuscript; M.T. and J.S. helped in data collection; B.S. supplied clinical data and performed data management; H.S. provided editorial assistance for the manuscript. All the authors have read and approved the final manuscript.

Data Availability Statement

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

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