Longitudinal Assessment of Balance Using Virtual Reality in Patients Receiving Potentially Neurotoxic Adjuvant Chemotherapy

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Research Article

Abstract

Purpose

Chemotherapy-induced peripheral neuropathy (CIPN) commonly affects people treated for cancer, with functional consequences of impaired balance and falls. Virtual reality technology (VR) may be able to assess balance, identifying patients at increased risk of falls. We aimed to assess the impact of neurotoxic chemotherapy on balance and falls risk using VR, and explore whether changes in balance threshold were associated with falls or validated CIPN measures.

Methods

We conducted a prospective, longitudinal cohort study at two Australian oncology centres. Eligible participants were commencing adjuvant chemotherapy containing a taxane for breast cancer, or oxaliplatin for colon cancer. Excluded: insufficient English to complete assessments, VR intolerance, or pre-existing balance disorder. VR balance threshold was recorded at baseline, intervals during chemotherapy, and 3- and 6-months after chemotherapy completion. Additional measures: 1) clinician-graded peripheral sensory neuropathy (Common Terminology Criteria for Adverse Events), 2) Total Neuropathy Score-clinical, 3) patient-reported neuropathy, 4) 'Timed Up-and-Go' test, 5) participant-reported falls/near-falls.

Results

Of 34 participants consented, 24 (71%) had breast cancer and 10 (29%) had colon cancer. Compared to baseline, balance threshold worsened in 10/28 (36%) evaluable participants assessed at the end-of-chemotherapy; this persisted in 7/22 (32%) at 6 months. CIPN affected 86% at end of chemotherapy, and 73% at 6-months post-chemotherapy . Falls/near-falls were reported by 12/34 (35%), and associated with impaired balance (p = 0.002).

Conclusion

VR balance assessment warrants further investigation as a surrogate method to objectively identify patients at risk of falls from CIPN, however was no better at diagnosing CIPN than existing tools.

Trial Registration: N/A

Introduction

Adjuvant chemotherapy improves survival in patients with breast and colorectal cancers. Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of agents used in the treatment of many common cancers. CIPN has a cumulative dose-dependent relationship with chemotherapy, limits the amount of adjuvant chemotherapy that can be safely delivered, and is a common reason for early cessation or dose reduction of treatment. CIPN can cause progressive sensory disturbances or pain in the

extremities, which can be long-lasting or permanent even after chemotherapy has been ceased[1]. Symptoms of CIPN in the lower extremities adversely affect balance, mobility and increase the risk of falls [2, 3]. This impairs the quality of life of cancer survivors and increases their use of health resources[4]. There is no consensus on the best method to identify and measure CIPN, with inconsistent prevalence and severity reported using the available patient-reported, clinician-reported and objective measures [5, 6]. There are no preventative agents for CIPN and exercise is one of the few evidence-based treatment options[1].

Oxaliplatin-based adjuvant chemotherapy is the mainstay of treatment for colon cancer but commonly causes neurotoxicity (89%). Acutely following infusion, oxaliplatin typically causes transient sensory paraesthesia, dysasthesia and cramping in almost all patients, with occasional laryngospasm. Chronic CIPN is dose dependent, cumulative, and can worsen even after ceasing oxaliplatin, a phenomenon known as 'coasting'[7].

Taxanes, namely paclitaxel and docetaxel, are commonly used in adjuvant therapy to improve survival in early breast cancer. Taxanes can acutely cause arthralgias or myalgias, with subsequent onset of paraesthesia, ataxia, proprioception deficits and loss of tendon reflexes[8]. Large randomised trials evaluating taxanes reported a 15–23% incidence of Grade 2–3 neuropathy[9]. Up to 80% of patients experienced symptoms of CIPN up to two years following completion of treatment[10].

Measuring CIPN

A systematic review and Delphi survey identified 117 CIPN assessment tools, with no consensus regarding the best method because no tool adequately and consistently addressed patient and clinical needs for routine use[6]. Clinician-based grading scales generally correlate poorly with patient-reported outcome assessments.

Studies assessing the impact of CIPN on gait and balance in participants with symptoms of CIPN have demonstrated gait changes, increased disability scores and higher falls risk compared to asymptomatic patients. However, the objective measures used in the studies involved time-consuming testing or cumbersome equipment, which precludes implementation into the clinical setting due to time and resource constraints[4, 11, 12]. An appropriate tool to measure the functional impact of CIPN on falls risk would be sensitive, reproducible, and easy to use with minimal training.

Virtual reality technology (VR) for balance assessment

The BalanceRite app and visual perturbation program was developed by the University of Sydney Department of Psychology[13], using VR technology to assess and treat patients with balance and gait disturbances. This has been used in the research setting to monitor patients with vestibular disease and an age-matched cohort of healthy controls[14, 15]. VR has not been used to measure balance in patients with cancer but has been used for symptom management in acute cancer care to reduce anxiety, depression, pain, and aid cognitive function[16].

Our study objectives were to: 1) assess and quantify the effect of neurotoxic chemotherapy on balance using VR; 2) explore whether lower limb neuropathy assessed by validated clinical and patient-reported tools was associated with VR assessment of balance; and 3) to determine the safety and tolerability of VR assessment in the oncology clinical setting.

Methods

Study design

This prospective, longitudinal observational study assessed balance using VR and CIPN using multimodality neuropathy assessment tools in patients receiving platinum- or taxane-containing adjuvant chemotherapy for bowel or breast cancer.

Setting

Participants were recruited from two Australian tertiary oncology centres in New South Wales, Australia from November 2018 to July 2020. This study was approved by the Human Research Ethics Committee of Sydney Local Health District (Concord Repatriation General Hospital, HREC/18/CRGH/197) and conducted according to the Declaration of Helsinki. All patients provided written informed consent before study participation.

Participants

Eligible participants were chemotherapy naive, over 18 years of age and planned to receive adjuvant therapy containing docetaxel or paclitaxel for breast cancer, or oxaliplatin for colorectal cancer. Participants required sufficient English to complete study assessments. Specific exclusions were intolerance of VR, inability to stand unassisted in a stationary position, and pre-existing balance disorder such as myelopathy, Meniere's disease or Parkinson's disease. Participants with diabetes but without clinical neuropathy were eligible.

Patient and treatment characteristics extracted from the medical file included: age, cancer diagnosis, height, weight, chemotherapy regimen, and reasons for chemotherapy modifications (dose reductions, delays or early cessation).

Data sources/measurement

Assessments were performed at baseline, pre-specified intervals throughout chemotherapy, and 3- and 6-months following completion of chemotherapy. Assessment intervals throughout chemotherapy were scheduled to coincide with clinical reviews, which were every 3–6 weeks depending on the length of the chemotherapy cycle. After March 2020 and in the context of the COVID-19 pandemic, some participants had telehealth instead of face-to-face appointments; hence, some assessments were unable to be completed.

Balance assessment using VR

Postural sway was measured by a Wii Balance Board (WBB) connected by Bluetooth to an iPhone running the BalanceRite App. The participant was instructed to stand on the WBB or on the WBB plus a foam pad (WBB + foam, Airex AG, Sins, Switzerland, 41 cm × 50 cm × 6 cm thick) and to stay as still as possible for 20 seconds. Several visual conditions were presented: eyes open, eyes closed, and with an unpredictable visual perturbation VR at several amplitudes of movement. The visual perturbation consisted of a stereoscopic visual scene (Tuscany garden) projected into an Oculus Go VR headset. The visual perturbation was graded into levels from 0 (no perturbation) to 5 (highest amplitude of perturbation). Using eyes open, eyes closed, levels 0 to 5, with and without the foam pad, we effectively created 16 levels of difficulty in testing conditions[14]. The equipment is demonstrated in the supplementary material S1.

Each participant was assessed for their maximum tolerated VR level of difficulty (their 'balance threshold'). Stepping off the WBB, or requiring external support for balance constituted reaching the 'balance threshold'. At subsequent assessments, participants were initially tested at the balance threshold. If they were unable to maintain their balance at this level, the difficulty was progressively reduced until they were able to complete the level, and this became their new balance threshold. This protocol aimed to limit participant exposure to the testing environment, to avoid improving on the balance task performance due to a repetition/training effect. With each participant acting as their own control, the change in balance threshold level from baseline was determined at subsequent timepoints.

Additional assessments

1. Clinician-graded peripheral neuropathy as per the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) [17]. This is a widely used assessment tool used in clinical and research settings; Grade 0 represents no neuropathy and Grade 4 represents life-threatening impairment.
2. Patient reported neuropathy using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group – Neurotoxicity (FACT/GOG-Ntx13), a validated 13-item patient-reported neuropathy questionnaire. Symptoms are scored between 0 'Not at all' to 4 'Very much' for an overall score between 0 and 52, with higher scores indicating greater symptom burden[18].
3. Clinical neuropathy using The Total Neuropathy score (clinical) (TNSc), a composite test comprising clinical examination including muscle weakness, pinprick and vibration sensation, tendon reflexes, and clinician-rated sensory, motor and autonomic symptoms. It is used as a clinical measure of CIPN severity with higher scores indicating greater neuropathy (range 0–28)[19].
4. Falls risk, using the validated 'Timed Up-and-Go' test. The score is the time taken for a participant to stand from a seated position, walk three metres to a marker, and return to their seat[20].
5. Patient-reported fall or near-fall (fall event) since the previous assessment.

Study size

The sample size of 35 participants was pragmatic based on anticipated uptake over a recruitment period of 18 months.

Statistical analysis

The primary endpoint was the difference in the measured balance threshold between the baseline and end-of-chemotherapy assessments. Descriptive statistics were used to compare scores for grade of neuropathy, FACT/GOG-Ntx13, TNSc, and 'Timed Up-and-Go' between baseline, end-of-chemotherapy and 3- and 6-month post treatment time-points.

The normality of the data was assessed using Normal Q-Q plot. Interval scale outcomes (FACT/GOG-Ntx13, TNSc, 'Timed Up-and-Go') were compared using repeated measures ANOVA. In case of non-normality, Friedman's test was applied. The binary outcome (fall event yes/no) was compared using Cochran's Q test followed by McNamara's test with Bonferroni's correction for post-hoc comparisons. Ordinal outcomes (CTCAE grade of neuropathy and VR balance threshold) were compared using Friedman's test followed by Wilcoxon's test with Bonferroni correction for post-hoc multiple comparisons. To account for patients with missing data, multiple imputation was used as recommended for the analysis of outcomes in longitudinal studies[21, 22]. Independent t-tests (Mann-Whitney U test) were used to compare VR balance threshold between participants who had a fall event, and those who did not. All statistical tests were performed at 0.05 level of significance. All analyses were performed using SPSS V26. Due to the limited sample size and the exploratory nature of the study, subgroup analyses were not performed.

Results

Participants

Of 35 participants who consented, 34 completed the baseline assessment and 32 completed at least two assessments while on chemotherapy. Most participants were female, who received adjuvant taxane chemotherapy for breast cancer. The demographic details of participants are summarised in Table 1.

Treatment intensity was > 75% of planned in 32/34 participants. Dose modification or early cessation of chemotherapy occurred in 26/34 (76%) patients. CIPN was the most common reason reported, affecting 50% of patients regardless of cancer diagnosis. Two participants only achieved 50% of planned treatment; one due to fever and infection, and one chose to stop chemotherapy due to the COVID-19 pandemic.

Outcome data

Participants completed a median of 4 assessments (range 2–5), dependent on their chemotherapy cycle length and duration of adjuvant therapy. Figure 1 outlines the flow of participants through the study.

The primary endpoint was evaluable for 28 participants. Reasons for missing data in 5 patients are: 1) 3 participants declined the VR assessment due to fatigue; 2) no assessor was available for 1 assessment; and, 3) one patient relocated treatment to a different hospital.

The reduced number of assessments at the 3- (n = 22) and 6- (n = 23) month post chemotherapy timepoints were predominantly due to reduced face-to-face visits in the context of the COVID-19 pandemic.

Primary endpoint: VR balance threshold

A reduction in balance threshold was observed in 10/28 (36%) of participants assessed at the end of chemotherapy, indicating that they could not maintain their balance at the same level of challenge as prior to chemotherapy. Most patients reduced their balance threshold by one level, but one participant patient dropped by 12 levels. Four participants (15%) had a balance threshold reduce by greater than two levels.

Table 2 summarises the neurotoxicity parameters assessed in the cohort. Violin plots (Fig. 2) summarise the distribution of scores for each outcome measured, with point estimates and 95% confidence interval (CI) reported in Supplementary material S2. Most participants (n = 24, 85%) developed CIPN during their chemotherapy treatment as assessed via CTCAE, with any-grade peripheral neuropathy symptoms persisting 6 months post-chemotherapy in 72% of patients (n = 16).

For clinician grade of neuropathy (CTCAE), Friedman's test on multiply imputed data set indicated a significant difference in neuropathy grade between baseline assessment and each of the timepoints (p = < 0.01). Wilcoxon's test indicated higher grade of neuropathy (median = 2) at post-treatment, 3 months post-treatment and six months post-treatment compared with neuropathy grade at baseline (median = 0).

For the FACT/GOG-Ntx13, results of the pooled set of multiply-imputed data indicated significant differences across the four periods. Compared to the mean score at baseline (M = 3.3, 95% CI: 1.9–4.8), the mean score at the three post-chemotherapy time points was significantly higher, indicating more severe neuropathy symptoms (M = 12.7, 95% CI: 9.8–15.6 at end of the treatment, M = 11.0, 95% CI: 7.5–14.4 at three months post-treatment, M = 11.2, 95% CI: 8.1–14.4 at six months post-treatment).

For clinically scored neuropathy (TNSc), results for the pooled set of multiply imputed data and multiply imputed data set indicated a significant difference in mean TNSc score across four periods. Compared to the mean score at baseline (M = 2.4, 95% CI: 1.5–3.2), mean scores at subsequent time-points were higher, indicating more neuropathy following chemotherapy (M = 4.5, 95% CI: 3.4–5.7 at end of the treatment), which persisted following cessation (M = 4.6, 95% CI: 3.5–5.7 at three months post-treatment, M = 5.2, 95% CI: 3.4–7.0 at six months post-treatment).

Results of the repeated measures ANOVA for complete cases data indicated no significant difference in the 'Timed Up-and-Go' across the four assessments (n = 9, Wilk's lambda = 0.57, F (3, 6) = 1.5, p = .31).

Frequency of falls

There were no participants or researcher injuries relating to the VR assessments. A fall/near fall was reported by 12 of 34 patients during the study period. Seven patients had falls, three had a near fall, and two had both. Three patients reported multiple episodes. Of the 18 falls or near falls reported, 13 occurred while on chemotherapy, two were within three months of completing chemotherapy, and three were between 3 and six months of treatment completion.

Balance threshold measured following the reported fall/near fall was significantly lower compared to times when no fall was reported (mean 10.3 vs 14.2, p value = 0.0002). Similarly, scores for clinical and patient reported neuropathy showed significantly more impairment from CIPN in participants who had experienced falls/near falls, compared to when no fall was reported (Table 3).

Discussion

This prospective cohort study used VR as a novel assessment of balance in people receiving potentially neurotoxic adjuvant chemotherapy. Balance deficits were identified in 36% of the participants at the completion of chemotherapy, and often persisted at 6 months following chemotherapy. The balance assessment findings were consistent with worsening CIPN identified by clinician- and patient-reported measures, which were also significantly and persistently higher following chemotherapy compared to baseline. Falls risk measured by 'Timed Up-and-Go' did not change significantly over time.

Participants who experienced a fall or near fall during the study (35%) were more likely to have balance deficits when assessed using VR assessment; they also had significantly higher CIPN scores assessed by clinician-grade, patient-reported outcome questionnaires and clinical parameters.

The findings of CIPN at 6 months following chemotherapy in 72% of our cohort is consistent with the prevalence of 58% (95% CI: 42–73) reported by our recent meta-analysis pooling prevalence of CIPN reported from clinical trials of adjuvant oxaliplatin[23].

A recent review has highlighted the negative impact of CIPN on physical function, contributing to postural instability and falls risk[24]. Prior studies examined standing balance in patients treated with chemotherapy using different tools and different populations. Balance deficits were linked with CIPN severity but authors did not report on near or actual falls[25, 26].

This is the first study to explore the use of VR technology to assess balance in the oncology clinical setting, and compare the results with near or actual falls. VR technology has been utilised in oncology care with a systematic review indicating benefit in inpatient rehabilitation, and as a distraction therapy to alleviate pain and anxiety around procedures[16].

Strengths and limitations

The main strengths of this study are its prospective longitudinal design, and 'real world' cohort of participants with common cancer diagnoses requiring adjuvant chemotherapy. These allow for applicability of the findings to the clinical context. It assessed balance in a novel way using readily accessible equipment, and is 'proof of concept' of how VR technology might be integrated into the clinic setting. Feedback from clinicians was not a prespecified outcome of this study, and would be required to determine the role of VR as an assessment tool in a clinic setting.

The limitations of this study are the modest sample size, and missing data in the follow up period due to the uptake of telehealth consultations in the context of the COVID-19 pandemic. This limits the ability to perform subgroup analyses, and the precision of our point estimates. There is the potential for bias given the missing data; if participants refused assessments due to feeling unwell, side-effects from either chemotherapy of VR use may be underreported. As this was an observational study, feedback from the CIPN measures and balance assessments performed as part of the study was not fed back to the treating clinicians in real time. A further interventional study validating the test and evaluating the utility of treatment modifications on the basis of the VR assessment would be required prior to applying an individual's results to changes in clinical care. Our study population did not include patients with advanced disease or who received other cancer treatments with the potential to cause neurotoxicity such as cisplatin, bortezomib, or nab-paclitaxel. These factors need to be considered when applying our findings.

Interpretation

This novel test is simple, safe, uses equipment that is easily accessible. Its utility in identifying CIPN was no better than the existing assessment strategies available. However, it allows for an objective assessment on the functional disability of CIPN on an individual's falls risk. It would assist with identifying functional limitations when patients are unwilling to disclose symptoms, either due to a lack of insight or a fear of ceasing chemotherapy early. These and other factors were identified in a qualitative study exploring reasons for under-reporting of CIPN[27]. Poor correlation between patient self-report of balance and objective balance testing has been described in a prior study using the same VR equipment and methods used in this study[15].

Rather than being limited to CIPN measurement, VR balance assessment is likely to measure a multitude of falls and balance risk factors which are not necessarily captured solely by CIPN tools. Peripheral nerve function plays a small but important part in maintaining balance. Other factors such as sensory input, cognitive function and physiological aspects also play an important role[28, 29]. Each of these factors can be impacted by chemotherapy treatment in different ways and affect the overall falls risk.

Exercise has shown to be beneficial in the prevention and treatment of CIPN [30, 31]. VR exercise programs offer the potential for a patient-led physical activity with data feedback to clinicians or exercise physiologists. VR may be a useful tool for the prevention or rehabilitation in populations at risk of falls, regardless of the aetiology.

Conclusion

Impaired balance threshold using VR was associated with actual or near falls in patients receiving neurotoxic chemotherapy. VR is safe and provides objective measurement of falls risk in the oncology clinic setting, although in our population was no more effective at identifying CIPN than existing measures. Further research into the use of VR as a prevention or rehabilitation strategy in patients at risk of falls is warranted.

Declarations

Conflicts of interest: None to declare.

Availability of data and material: The authors have full control of primary data. Any data sharing will be at the discretion of the corresponding author following a written request.

Code availability: Not applicable.

Authors contributions: CT, PB, JV developed the study concept and protocol. EC and HG developed the VR assessment strategy, and instructed the research team on the use of the equipment.

CT, EC, DT and TB collected data and performed participant assessments. CT and V performed data analysis.

Ethics approval: This study was approved by the Human Research Ethics Committee of Sydney Local Health District (Concord Repatriation General Hospital), (HREC/18/CRGH/197) and performed in accordance with the ethical standards of the Declaration of Helsinki.

Consent to participate: All participants provided written informed consent before study participation.

Consent for publication: All participants have provided written consent for their de-identified data to be publishes, and all authors have provided consent to publish the manuscript.

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Tables

Table 1
Participant characteristics

	Breast cancer (n = 24)	Colorectal cancer (n = 10)	Total (%) (n = 34)
Median age (range)	55.5 (37−77)	55.5 (34−70)	55.5 (34−77)
Sex			
Male	0	6	6 (18)
Female	24	4	28 (82)
Chemotherapy regimen			
Paclitaxel	19		19 (56)
Docetaxel	5		5 (15)
FOLFOX		5	5 (15)
CapOx		5	5 (15)
Median BMI (range)	28 (18−36)	27 (19−40)	27 (18−40)
BMI > 25	16	6	22 (65)
Fall within 6 months	1	1	2 (6)
Chemotherapy dose modifications	18	8	26 (76)
Reason			
Neuropathy	12	5	17 (50)
Myelosuppression	1	2	3 (9)
Other	5	1	6 (18)

FOLFOX: 5-fluorouracil, folinic acid, oxaliplatin; CapOx: capecitabine, oxaliplatin; BMI: Body-mass index; Other: nausea, infection, fatigue.

Table 2
Neurotoxicity outcomes measured at study time points

CIPN measure	Baseline	End of chemotherapy	3-months post chemotherapy	6-months post chemotherapy
Number of Participants assessed (n)	34	28	23	22
Highest balance level achieved: Mean (SD) Range	14 (2.9) 6−16	14 (3.9) 1−16	13 (3.8) 3−16	13 (3.9) 4−16
Median change from baseline (range) Participants whose highest level: Worsened from baseline (n, %) Stable/ improved from baseline (n, %)	- - -	0 (-11, 4) 10, 36% 18, 64%	0 (-4, 10) 5, 22% 18, 78%	0 (-5, 5) 7, 32% 15, 68%
CTCAE Grade of neuropathy[a] (n, %) 0 1 2	32, 94% 2, 6% 0, 0%	4, 14% 18, 64% 6, 21%	7, 30% 8, 35% 8, 35%	6, 27% 8, 36% 8, 36%
FACT/GOG-Ntx13 score[b] Mean (SD) Range	3.3 (4.3) (0, 16)	11 (8.1) (1, 33)	10 (10) (0, 38)	11 (8.8) (0, 38)
Mean change from baseline (SD)	-	8 (6)	7 (10.3)	7 (11.2)
Total Neuropathy Score (clinical)[c] Mean (SD) Range	2.4 (2.6) (0−9)	4 (2.9) (1, 11)	4 (2.6) (0, 11)	5 (4.2) (0, 12)
Change from baseline (mean, SD)	-	2 (2.2)	2 (2.6)	1.8 (4.5)
Median Timed 'up and go' (seconds) (mean, SD) Range	10 (2.1) (6.9−18.4)	9.7 (2.2) (6.4, 15.9)	10.1 (5.5) (6.2, 34.6)	9.5 (4.1) (6.9, 27.3)
Mean change from baseline (SD)	-	0.2 (2.04)	0.01 (3.9)	0.58 (5.0)

CIPN: chemotherapy-induced peripheral neuropathy; SD: standard deviation; CTCAE: Common Terminology Criteria for Adverse Events; FACT/GOG-Ntx13: Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group Neurotoxicity questionnaire-13 items. a. higher grade indicates worse impairment, b. higher score indicates worse symptoms, c. higher score indicates worse neuropathy.

Table 3

Comparing outcome measures between participants who reported fall/near fall vs. no fall

Assessment tool	Mean value		p-value (Mann Whitney U test)
	Fall/Near fall	No fall	
Balance threshold (level)	10.3	14.2	0.002
FACT/GOG-NTx13[a]	12.8	7.2	0.002
Total Neuropathy Score (clinical)[b]	5.8	3.1	0.002

FACT/GOG-Ntx13: Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group Neurotoxicity questionnaire-13 items. a. higher score indicates worse symptoms, b. higher score indicates worse neuropathy.
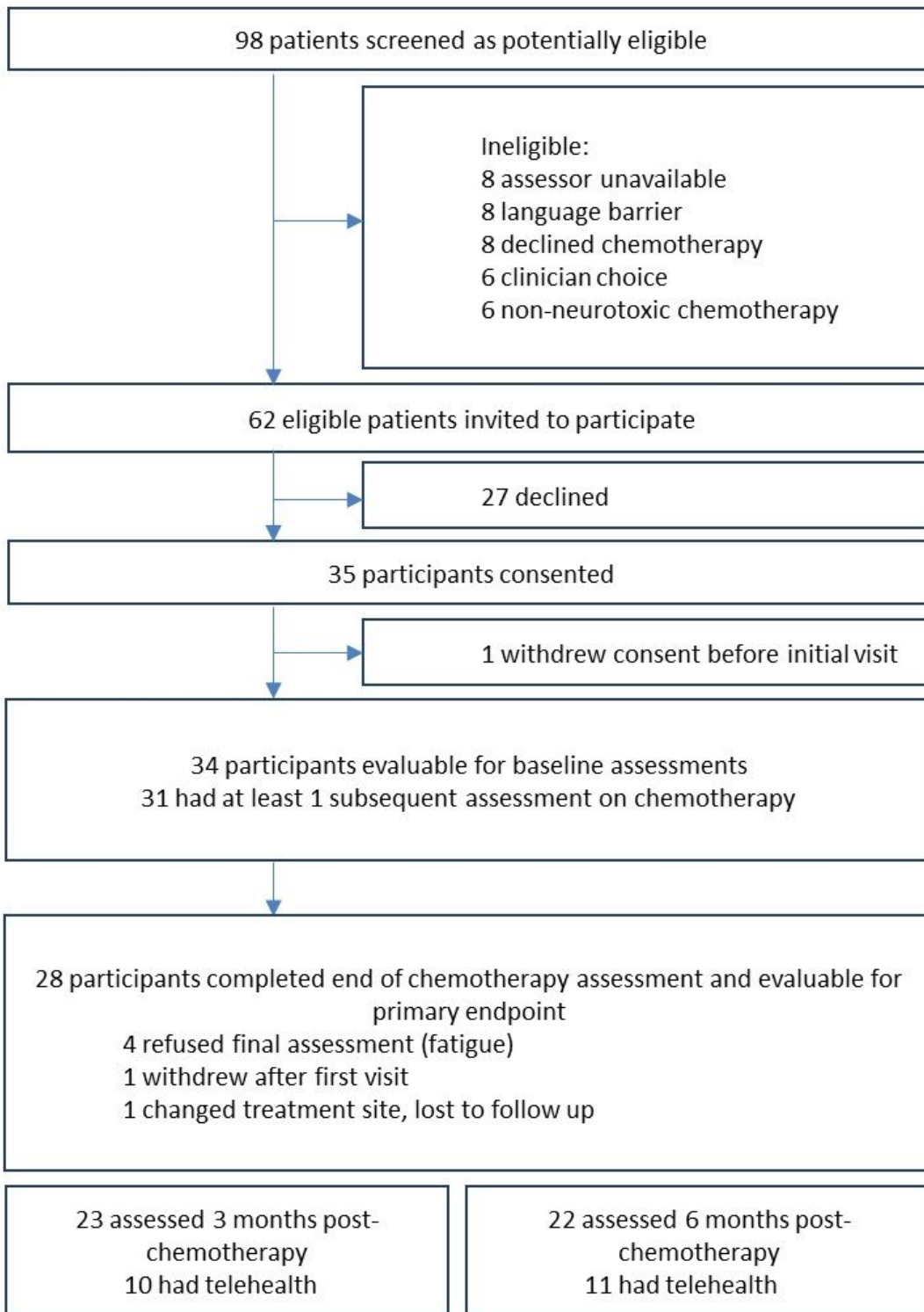
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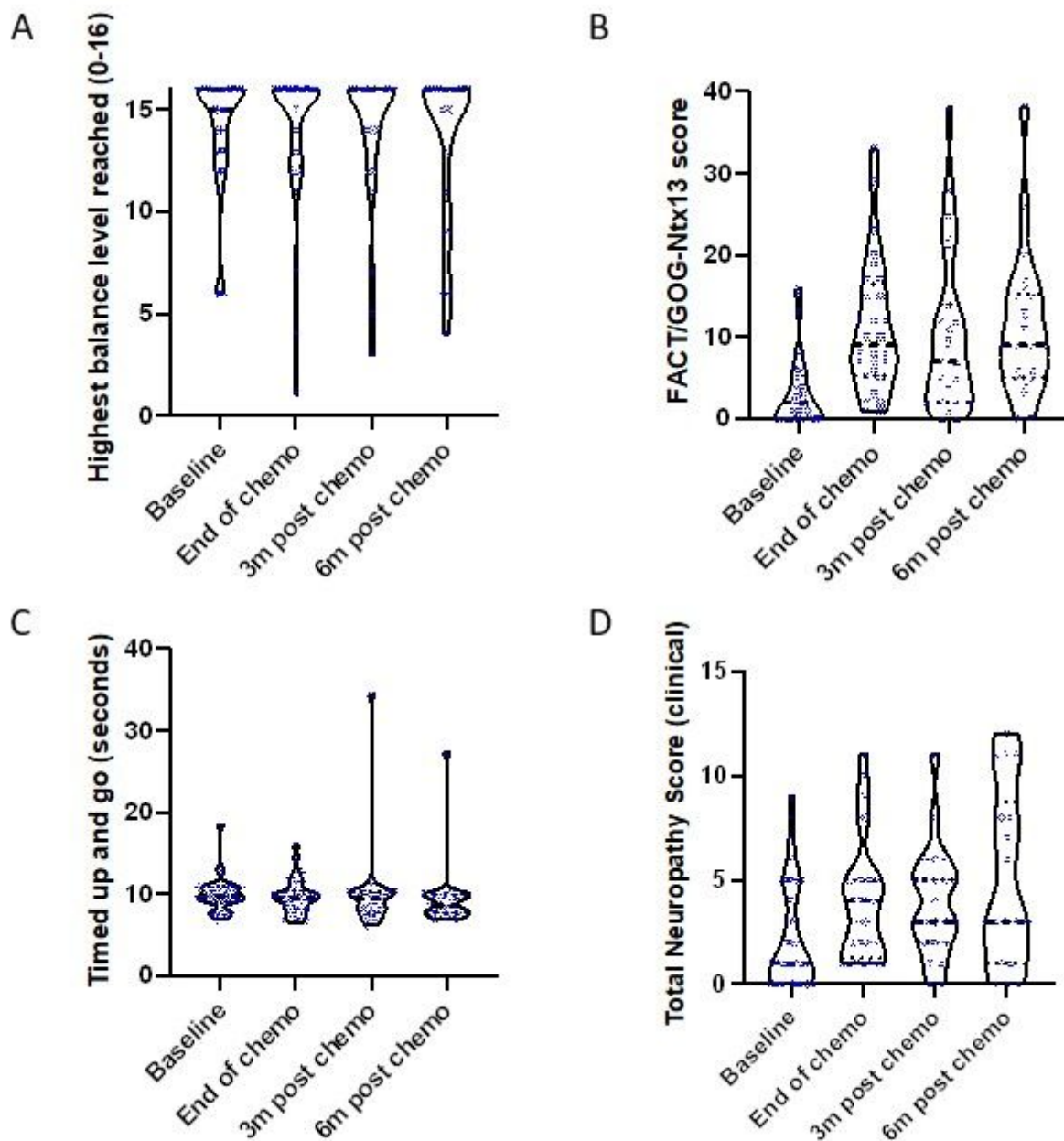
Figure 1

Participant flow diagram.

Figure 2

Outcome measures of participants. A) Highest balance level reached using virtual reality equipment (higher score indicates better balance); B) Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group (FACT/GOG) neurotoxicity questionnaire (higher score indicates more symptoms); C) Timed up-and-go (higher score indicates impairment); D) Total Neuropathy Score (clinical) (higher score indicates impairment)

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- VRBalanceSupplementaryfigures.pdf