Seminars in Oncology Nursing 39 (2023) 151470

Contents lists available at ScienceDirect

Seminars in Oncology Nursing

journal homepage: https://www.journals.elsevier.com/seminars-in-oncology-nursing

Effectiveness of Immersive Virtual Reality in People with Cancer Undergoing Antiblastic Therapy: A Randomized Controlled Trial

Francesco Burrai[a,*], Salvatorico Ortu[b], Marco Marinucci[c], Maria Grazia De Marinis[d,e], Michela Piredda[d]

[a] Department of Biomedicine and Prevention, PhD School in Nursing Sciences and Public Health, University of Rome "Tor Vergata", Rome, Italy
[b] Oncology Unit, John Paul II Hospital of Olbia, Olbia, Italy
[c] Psychology Department, University of Milano-Bicocca, Milan, Italy
[d] Department of Medicine and Surgery, Research Unit Nursing Science, Campus Bio-Medico of Rome University, Rome, Italy
[e] Fondazione Policlinico Universitario, Campus Bio-Medico, Rome, Italy

ARTICLE INFO

Key Words:
Antiblastic Therapy
Anxiety
Cancer
Fatigue
Pain
Virtual Reality

ABSTRACT

Objectives: This study aims to assess the effects of immersive Virtual Reality in people with cancer undergoing antiblastic therapy, on anxiety, fatigue and pain.
Data Sources: This is a randomized controlled three-arm trial. Seventy-four cancer patients were recruited from a regional hospital in Italy, and randomly allocated into three groups: a Virtual Reality group (n=25), a narrative medicine group (n=25) and a standard care group (n=24). The primary outcome was anxiety. Secondary outcomes included fatigue and pain. The outcomes were evaluated immediately before and after the interventions. The findings showed that anxiety decreased more in the Virtual Reality group (Δpre-post = 6.24, 95% CI 2.578 to 9.902, p=.001, d = 0.63) than in the narrative medicine group, whereas it did not change for those in the standard care group. Fatigue decreased in the Virtual Reality group (Δpre-post = 0.576, 95% CI 0.246 to 0.907, p=.001, d = 0.23), while remaining stable in the narrative medicine group, and increasing in the standard care group. Average levels of pain did not change before and after the intervention [F(1,71) = 1.06, p=.307, ηp2 = .015].
Conclusion: Findings show that virtual reality is effective to reduce anxiety and fatigue in people with cancer undergoing antiblastic therapy.
Implications for Nursing Practice: Virtual Reality can be recommended as an complementary intervention to manage anxiety and fatigue in people with cancer during antiblastic therapy.
Trial registration: ClinicalTrials.gov NCT05629507.
© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

INTRODUCTION

The introduction of innovative antiblastic therapy (AT) has increased the effectiveness of cancer treatment but has not reduced the side-effects of intravenous chemotherapy.[1] The symptoms frequently manifested by people receiving chemotherapy include anxiety, fatigue, and pain.[2]

Anxiety is present in about 10% of people during chemotherapy, while one-third of people with depression also show clinically significant anxiety states.[3] Cancer and treatments cause fear of dying, reduction in quality of life, loss of social relationships, loss of control over one's life, and anxious symptoms. Fatigue occurs in 60% to 90% of people receiving chemotherapy.[4] It negatively affects every aspect of quality of life, persisting even for months or years after chemotherapy, and sometimes reducing survival rates.[5] Pain is often produced by peripheral neuropathy, which occurs in 90% of people treated with neurotoxic chemotherapy.[6] Recipients report neuropathic pain either when a nerve is subjected to pressure from a tumor or as phantom limb pain.[7] Therefore, given the current persistence of these major healthcare problems, it appears crucial to find new interventions that can increase people's tolerance to chemotherapy, positively influencing anxiety, fatigue, and pain.[8] One of the most innovative and promising interventions is virtual reality (VR).[9]

VR can be defined as a simulated experience, consisting of an experiential environment created by hardware and software technology capable of eliciting sensations of real experiences.[10] There are three types of VR: 1) immersive,[11] 2) semi-immersive,[12] and 3) non-immersive.[13] Immersive VR uses a head-mounted display (HMD) system technology enabling individuals to isolate themselves from the physical environment in which they are and to become immersed in a multisensory virtual environment of a visual, auditory, and tactile

* Address correspondence to: Francesco Burrai. Department of Biomedicine and Prevention, University of Rome "Tor Vergata", PhD School in Nursing Sciences and Public Health, Viale Montpellier 1 00133 Rome, Italy.
E-mail address: francescoburrai@libero.it (F. Burrai).

https://doi.org/10.1016/j.soncn.2023.151470
0749-2081/© 2023 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/)

type. Semi-immersive is a mixture of nonimmersive and immersive VR, which uses a three-dimensional (3D) space or a virtual environment where users can act through a computer screen or a VR box/headset. This technology allows users to remain connected to physical environment. Nonimmersive VR is delivered through a monitor or projector, so users are not immersed in a virtual environment and still perceive the external environment totally. VR produces its effects on the mind–body axis through four fundamental mechanisms: 1) distraction, 2) presence, 3) immersion, and 4) interactivity.

VR produces the state of distraction because it simultaneously sends wide and diversified multisensory stimulations to the brain, influencing the cognitive process of attention and thus shifting the focus of attention from unpleasant to pleasant and interesting stimuli, through a remodeling of the perceived environment.[14] The activation of the cognitive variables able to affect the outcomes of this trial is the necessary condition for transferring participants' consciousness deep into virtual environments. Therefore, VR uses scenarios as a distraction cognitive strategy, immersing the individual in the virtual environment and activating several senses,[15] so that people can choose to retire from the stressful situation of chemotherapy, moving into another space–time situation in a pleasant, soothing environment and losing track of time. Presence can be defined as the experience of being in an environment while one is not physically in that environment; people respond by behaving consistently with the experience perceived.[16] Immersion can be described as a technological feature based on various input and output devices, capable of producing sensory and perceptual information that creates the illusion of being immersed in a real world.[16] The combination of more sensory and perceptual information with stereoscopic visual inputs and audio inputs can increase the level of immersion, generating depth in the perception of reality. VR, by causing deep immersion, distracts people from the hospital environment and prevents them from focusing on competing negative stimuli. Finally, interactivity, which can be defined as that perception process in which the user can interact with the virtual context, provides a high level of involvement and realism.[17]

Virtual Reality During Chemotherapy

Few systematic reviews and meta-analyses have studied the effects of VR on anxiety, fatigue, and pain in patients with cancer during chemotherapy.[18-22] Regarding anxiety, in a systematic review and meta-analysis including three trials and 117 patients with breast cancer, VR showed an improvement in anxiety level (standardized mean differences [SMD] = −2.07; 95% confidence interval [CI] = −3.81 to −0.34).[18] In another systematic review and meta-analysis with four trials and 227 patients with different types of cancer, VR significantly reduced anxiety levels (SMD = −3.03; 95% CI = −6.20 to 0.15).[19] In a systematic review with eight studies involving 475 patients with different types of cancer, VR improved anxiety but with high heterogeneity among the trials,[20] as confirmed by a systematic review with 14 studies.[22] These results differed from a systematic review and meta-analysis with three trials and 357 patients with different types of cancer (MD = −6.57; 95% CI = 11.59 to −1.54)[21] and from a systematic narrative review with six studies and 356 patients with different types of cancer.[22] VR showed statistically significant improvements on fatigue levels in a meta-analysis with two trials and a sample of 184 patients with breast cancer (SMD = −0.92; 95% CI = −4.47 to 2.62),[18] in a meta-analysis with two randomized controlled trials and a sample of 42 patients with different types of cancer (MD = −2.50; 95% CI = −4.28 to 0.73),[19] and in a systematic review with four trials, where three studies reported statistically significant reductions in symptom fatigue.[9] VR showed statistically significant reductions of pain in a meta-analysis including two trials with 112 patients with breast cancer (MD = 17.44; 95% CI = −21.93 to − 12.94),[18] in a meta-analysis with four studies (MD = −1.63; 95% CI = − 4.15 to 0.89),[19] in a mini-review of 19 studies, 18 of which showed a statistically significant reduction in 291 patients with different types of cancer ($P < .05$),[23] and in a comprehensive literature review of five studies.[24]

The literature shows several gaps: a) randomized controlled trials on the effects of VR on anxiety, fatigue, and pain are few; b) no randomized controlled trial has simultaneously studied the major outcomes affecting patients receiving chemotherapy; c) all of the randomized controlled trials evaluating the impact of VR on anxiety, fatigue, and pain showed very small sample sizes, which notably reduces their statistical power and generalizability; d) almost all randomized controlled trials had only two parallel groups, of which the control group was in 90% of cases standard care; e) no randomized controlled trial used a strong control group as narrative medicine; and f) only very few randomized controlled trials assessed cybersickness and used a structured satisfaction questionnaire.

This randomized controlled trial was therefore designed to overcome these issues by 1) including three groups: immersive VR, narrative medicine, and standard care; 2) simultaneously studying anxiety, fatigue, and pain outcomes; 3) calculating the sample size; 4) studying cybersickness; and 5) assessing user satisfaction with VR through a structured questionnaire.

Research Hypothesis

In patients with cancer receiving intravenous AT, the application of immersive VR prevents or reduces anxiety, prevents or reduces fatigue, and prevents or reduces pain, compared with people receiving narrative medicine and with people receiving standard care only.

METHODS

Trial Design

We conducted a randomized controlled trial with three parallel groups in a 1:1:1 allocation ratio, pre-post test, and longitudinal in people with cancer undergoing intravenous AT. The three groups were 1) VR, 2) narrative medicine, and3) standard care. This trial followed the CONSORT-outcomes 2020 extension for randomized trials.[25]

Participants

Eligible participants were recruited in a regional hospital in Italy, between July 1 and November 1, 2022. Inclusion criteria were 1) age >18 years, 2) diagnosis of cancer with indication for intravenous AT, 3) cognitively able to participate, 4) no significant acoustic deficit, 5) no significant visual impairment, and 6) sufficient ability to write and read in Italian. Exclusion criteria were 1) use of antipsychotic drugs, 2) epilepsy, and 3) use of drugs or alcohol. Participants were enrolled through consecutive sampling. This trial was registered on the US National Institutes of Health (www.clinicaltrials.gov) with registration number NCT05629507.

Interventions

The first group were people receiving AT who were treated with VR. To activate the cognitive variables able to impact on the outcomes (ie, distraction, presence, and immersion), as conditions necessary to move participants' consciousness deeply into virtual environments, we used high-quality technological equipment of the latest generation of immersive VR, with high onboard computing power, standalone, with sophisticated software and excellent optical components, producing low-latency, wide field of view and greatly improving the VR experience. This technology showed the best cost-effectiveness

and provided immersive and patient-friendly technology. Based on these characteristics, the Oculus Quest 2 HMD was chosen. This equipment allowed participants to observe specific virtual environments, named scenarios, in contemplative mode: a passive observation of the virtual environment with the possibility of navigating with a joystick. The scenarios were characterized by multimedia contents in VR, from 4K up to 8K for video definition, and 360° spherical video of images filmed in 360° in the real world. They were posted on a specific YouTube channel and protected by a password. The scenarios included 310 videos classified into nine categories: 1) Africa, 2) hills, 3) rivers, lakes, and waterfalls, 4) islands, 5) deserts, 6) beaches, 7) mountains, 8) sea, and 9) submarines. To increase the immersive experience, and the intensity of the sense of presence, it was also important to stimulate the auditory sensory modality. The audio contents of scenarios had a background of nature sounds and soothing musical stimuli, in high definition, panning stereo, listened to via earphones to ensure an immersive audiovisual experience with high-intensity multisensory immersion. This created an experience of being in another place with all the senses, rather than in the hospital receiving chemotherapy.

Our scenarios were natural environments, because immersion in such environments is able to activate a distraction that is both powerful, with near-total refocus attention, and positive, because it causes deep inner peace and relaxation.[26] Moreover, immersion in a virtual environment has an analgesic effect,[27] because attention to painful stimuli is reduced, and a block is activated at the neurological gateway level of transmission of pain signals to the brain, causing slower reaction to pain or a reduction of pain perception at conscious level.[27] The possibility of choosing between numerous different scenarios allows personalized intervention, higher flexibility in the cognitive stimulation, especially in maintaining attention to a scenario, and a wider range of emotional variations. VR was administered just after AT began. With participants sitting on outpatient chairs, after infusion started, a nurse helped each participant to position the VR headset and the joysticks. Participants could move their eyes and head freely, adjust the volume to their preferred level, and stop the VR session at any time for any reason. In accordance with previous study,[27] immersion duration was 30 minutes. After this period, the nurse removed the VR headset visor from the participant.

The second group consisted of participants treated with narrative medicine. Narrative medicine is an intervention able to collect and interpret the experiences expressed by people on their condition during an illness.[28] According to the hermeneutic approach, sharing the plurality of meanings that emerge from the encounter between nurse and person receiving treatment can contribute to a co-construction of the meaning of a lived experience.[29] In situations of suffering and illness, narration has a high evocative power and allows the re-elaboration of one's own experience by implementing reparative and beneficial mechanisms.[29] Nursing narrative was first developed in the studies of Paterson and Zderad,[30] considering the experiences as those arising from the person receiving treatment and the nurse sharing the same spatial and temporal dimension. Narration of these experiences can be enhanced through writing, speech, poetry, drawing, and photography. In this group, the writing method was used, which allows the individual story to emerge from the subjective experience and allows researchers to collect the different stories of participants, to study and highlight certain contents that unite and characterize a certain type of experience.[28] The narrative medicine intervention was administered just after AT began. With participants sitting on outpatient chairs, after infusion started, a nurse delivered a pen and notepad to them, explaining that for 30 minutes they could express through free writing the cognitive, emotional, and perceptual aspects of their subjective experience during the infusion of AT. The nurse also explained that during the writing he would always be available to guide participants in expressing cognitive, emotional, and perceptual contents if requested. After 30 minutes, the nurse collected the notepads.

The third group were people receiving AT in standard care. These participants were not treated with VR or narrative medicine, and they were free to choose different activities during AT infusion, such as talking with health personnel, reading, writing, watching TV, listening to music, or watching videos on their smartphone.

OUTCOMES

Primary Outcome

Anxiety was measured through the State-Trait Anxiety Inventory-Y (STAI-Y1).[31] This is a self-administered measure of the state of anxiety, through questions asking how the participant feels at the time of administration. It includes 20 items rated on a 4-point Likert scale, with 1 = "not at all," 2 = "a little," 3 = "enough," and 4 ="very much." The final score can vary from a minimum of 20 to a maximum of 80. The higher the score, the higher is the subject's level of anxiety. A Cronbach α coefficient of 0.86 showed optimal reliability.[31] A change of 10 points on the final score represents the minimal important difference. [32] In a population similar to our study sample, internal consistency showed a Cronbach α coefficient of 0.95.[33] Anxiety levels were assessed before the start of AT infusion and immediately afterward.

Secondary Outcomes

Fatigue was measured with the Revised Piper Fatigue Scale.[34] The scale is a self-administered questionnaire consisting of 22 items that measure four dimensions of fatigue: 1) behavioral severity, 2) cognitive severity, 3) affective meaning, and 4) sensory/emotional severity. Each item can produce scores on a scale from 0 to 10, with higher scores meaning a worsening of fatigue. A Cronbach α coefficient of 0.89 showed optimal internal consistency.[34] In a population similar to our sample, the Cronbach α coefficient was 0.93 for the Behavioral severity subscale, 0.94 for the Affective meaning subscale, 0.89 for the Sensory subscale, and 0.80 for the Cognitive/mood subscale, with 0.95 for the total Revised Piper Fatigue Scale showing excellent internal consistency.[35]

Pain was measured with a visual analogue scale scored from 0 to 10, where 0 indicates no pain and 10 indicates the worst possible pain.[36] This scale demonstrated consistency and diagnostic accuracy for evaluation of pain in a population similar to the study sample.[37] Fatigue and pain levels were assessed before the start of AT infusion and immediately afterward. The type of pain measured refers to any painful symptomatology that a cancer patient undergoing AT may experience.

In the VR group, the onset of symptoms of cybersickness, a type of motion sickness caused by exposure to VR, was evaluated at the end of the intervention. Cybersickness was assessed using the VR Symptom Questionnaire[38] that evaluates 23 different symptoms, 12 non-ocular and 11 ocular. The score for each symptom is measured by 7-point scales, from 0 to 6, where 0 = no symptoms, 1 and 2 = slight symptoms, 3 and 4 = moderate symptoms, and 5 and 6 = severe symptoms. If each symptom at any level of severity occurred with a frequency $<$20%, cybersickness is considered negligible.

In the VR group at the end of the session, we measured participant satisfaction through the VR participant satisfaction questionnaire, based on the framework of Buche et al.[39] Participants answered the eight items of the questionnaire on a 5-point Likert scale (from 1 = disagree completely to 5 = agree completely). Higher scores on the scale indicated higher participant satisfaction with the VR session.

To promote outcome data quality, during collection the data were stored every day in a cloud system with password, where every day an independent researcher checked each data set for any type of mistake. After data collection, another independent researcher checked the final dataset for missing data. All outcomes have been identified as per trial registration. Participants' socio-demographic and clinical information was collected at baseline.

Sample Size

With an a priori analysis approach, sample size was calculated based on an improvement on primary outcome anxiety measured by State-Trait Anxiety-Y Inventory scores. We computed an a priori power analysis G*Power[40] for an ANOVA with interaction (three groups, one numerator degree of freedom). A similar trial[8] showed a large effect of VR treatment across time ($\eta^2_p = 0.11$) on anxiety measured by State-Trait Anxiety-Y Inventory. Based on this previous research, we used a large effect size f = 0.40, a probability of error $\alpha = 0.05$, and a power of 0.80 $(1 - \beta)$ to calculate the total sample size for an ANOVA with interaction. The total sample was 64 subjects. Finally, to avoid possible dropouts, we enrolled at least 10% more patients. Interim analyses were not applicable.

Randomization

To generate the random allocation sequence, an independent researcher used a software random number generation (www.randomizer.org) with simple randomization. The randomization list included the allocation type for the 74 participants, using three numerical code for the three allocation groups: 1 for VR group, 2 for the narrative medicine group, and 3 for the standard care group. To implement the random allocation sequence, sequentially numbered, opaque, sealed envelopes were used.

A first nurse enrolled participants who met the inclusion criteria, offering the opportunity to participate in the study, informing each potential participant about the characteristics of the trial, and obtaining written informed consent from willing participants. A second nurse researcher assigned participants to one of the three interventions through the randomized list, by opening the next numbered, opaque, sealed envelope in the sequence. In line with previous studies,[10] for participants allocated to the VR group, a preliminary familiarization phase was introduced. In this phase, participants used the VR equipment before the start of the experiment, thus reducing a possible surprise effect and naive attractiveness. In the familiarization phase, participants were guided in their first manipulations, learned to use the viewer and the joysticks, and tried the scenarios for 5–10 minutes to optimize the effects of the virtual experience.[10] Participants were given a booklet listing the VR scenarios available including type, name, and length. Thus, participants could choose precisely in which scenario they wanted to immerse themselves during AT, in other words, which virtual environment they considered most effective for them. Due to the nature of VR and narrative medicine interventions, it was impossible to obtain a blinding between participant and knowledge of the group, so this study is open-label type.

Statistical Methods

To test the study hypotheses, we conducted 3 × 2 mixed between-within ANOVA, specifying the outcomes of anxiety, pain, and fatigue with its four subscales as dependent variables, the group as the between-subject predictor (3 levels: VR vs. narrative medicine *vs.* standard care), the time as the within-subject predictor (two levels: pre- *vs.* post-intervention), and their interaction. The group differences are reported using 95% CIs and effects size (Cohen d). Also, we conducted pairwise comparisons with Bonferroni correction to understand better how the outcomes changed over time for participants belonging to the three different groups.[34] A descriptive analysis was performed for baseline group characteristics, for cybersickness measure, and for participant satisfaction with VR. To study the reliability of instruments for anxiety and fatigue, Cronbach α coefficients were calculated. We conducted a new group comparison to check that participants were assigned randomly to the three interventions based on their sociodemographic and clinical variables. No outcome data from the analysis and reporting were excluded. Nonadherence to protocol was analyzed by number of dropouts in outcome analysis population. The threshold for level of significance was $\alpha = 0.05$ with two-tailed test for all analyses. The IBM SPSS Statistics v.28 software (IBM Inc., Armonk, NY, USA) was used to analyze the data.

Ethical Considerations

The study was approved by the local ethics committee with registration number 97/18/CE. The trial was conducted according to ethical principles of Declaration of Helsinki. Upon informing the patients about the study content, all participants provided written informed consent.

RESULTS

Participant Characteristics

A total of 84 potential participants were screened for eligibility; 10 were excluded and 74 participants were randomized into the three arms: 25 in the VR group, 25 in the narrative medicine group, and 24 in the standard care group. Recruitment was conducted from June to October 2022. All participants completed the interventions and all measurements without dropouts. The participants' flowchart is presented in Fig. 1. Participants' mean age was 59.3 (range: 33 to 83; SD: 10.8) years. Almost all (97.2%) were Italian, 74.3% were female, 47.2% were diagnosed with breast cancer, and 55.4% were in cancer stage IV. On average, the time since diagnosis or recurrence was 1.7 years (SD = 1.5), and 55.4% had undergone surgery. In 72.9% of cases, the AT session lasted less than 3 hours. Group comparisons to check that participants were assigned randomly to the three interventions based on their sociodemographic and clinical variables showed nonsignificant P values, confirming random assignment. Detailed participant characteristics are shown in Table 1.

Anxiety

Mean anxiety significantly decreased over time [$F(1.71) = 11.05$, $P < .001$, $\eta_p^2 = .135$]. The interaction of time by groups was marginal [$F(2.71) = 2.71$, $P < .074$, $\eta_p^2 = .071$]. Pairwise comparisons highlighted that anxiety decreased significantly for participants both in the VR group ($\Delta_{pre\text{-}post} = 6.24$, 95% CI = 2.578 to 9.902, $P < .001$, d = 0.63) and in the narrative medicine group ($\Delta_{pre\text{-}post} = 4.13$, 95% CI = 0.388 to 7.862, $P < .031$, d = 0.39), whereas it did not change for those in the standard care group ($\Delta_{pre\text{-}post} = 0.280$, 95% CI = −3.382 to 3.942, $P < .879$, d = 0.03). Comparisons between groups are presented in Fig. 2. The Cronbach α coefficient of the State-Trait Anxiety Inventory was 0.90.

Fatigue

Mean levels of fatigue before and after the intervention were not significantly different [$F(1.71) = 0.28$, $P < .870$, $\eta_p^2 = .000$]. However, differences between fatigue before and after the interventions varied according to the intervention received by participants [$F(2.71) = 11.19$, $P < .001$, $\eta_p^2 = .024$]. Specifically, pairwise comparisons

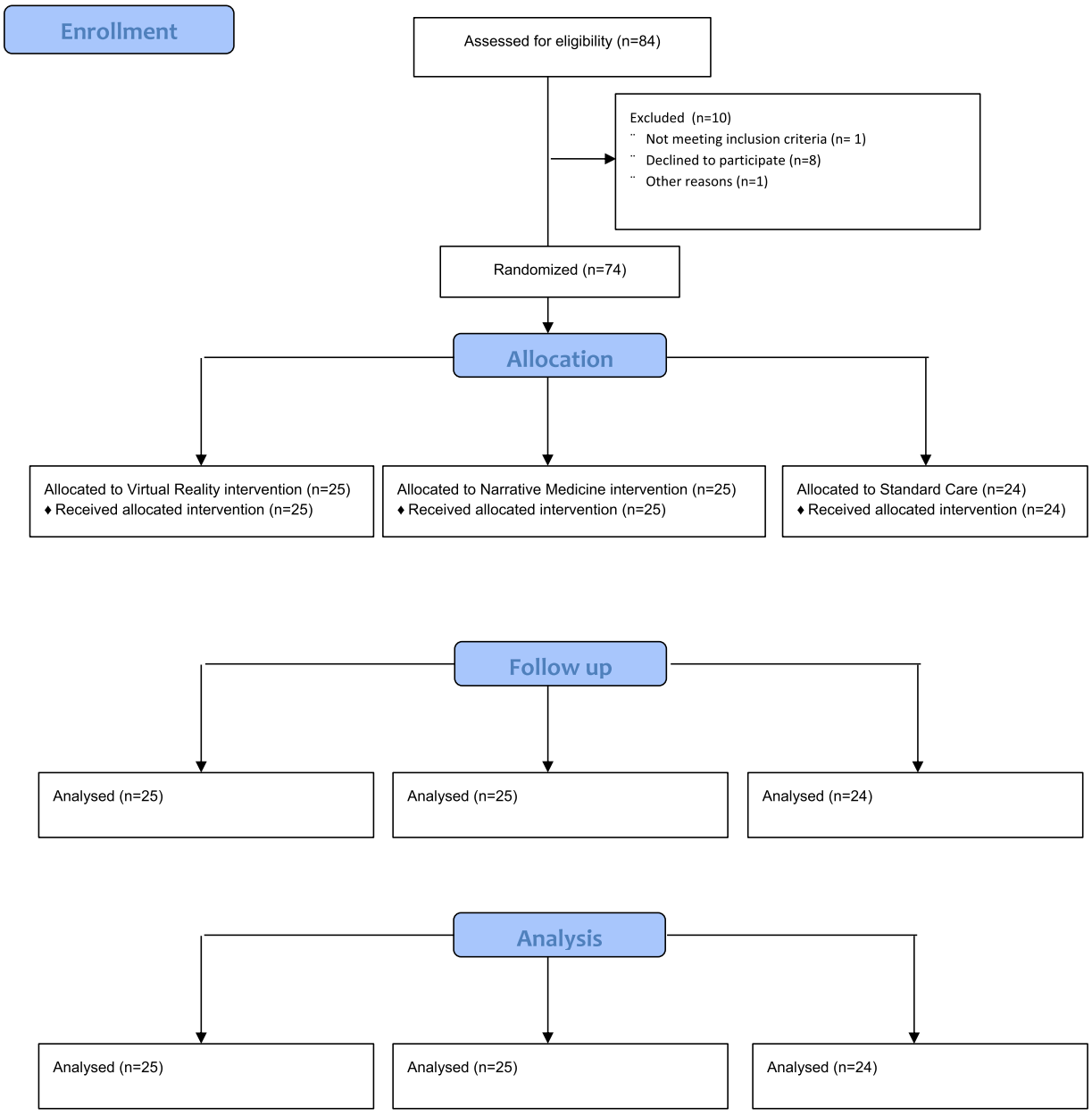


FIG. 1. Participants' flowchart.

suggested that the overall levels of fatigue decreased for participants in the VR intervention ($\Delta_{\text{pre-post}} = 0.576$, 95% CI = 0.246 to 0.907, $P < .001$, d = 0.23), remained stable for those in narrative medicine ($\Delta_{\text{pre-post}} = 0.02$, 95% CI = −0.335 to 0.339, $P < .991$, d = 0.00), and increased significantly for those in standard care ($\Delta_{\text{pre-post}} = -0.531$, 95% CI = −0.861 to −0.201, $P < .002$, d = 0.29). The estimated means between groups are presented in Fig. 3. The Cronbach α coefficient of the Revised Piper Fatigue Scale was 0.96.

Analyses focusing on the four subscales of fatigue as dependent variables showed the same pattern of results as the findings on the overall levels of fatigue. The interaction of the group by time was significant for behavioral severity [F(2.71) = 4.74, $P < .012$, $\eta_p^2 = .118$], affective meaning [F(2.71) = 3,70, $P < .030$, $\eta_p^2 = .094$], cognitive severity [F(2.71) = 6.24, $P < .003$, $\eta_p^2 = .149$], and sensory/emotional [F(2.71) = 7.03, $P = .002$, $\eta_p^2 = .165$]. For behavioral severity, pairwise comparisons showed that it significantly decreased for participants in VR ($\Delta_{\text{pre-post}} = 0.593$, 95% CI = 0.043 to 1.143, $P = .035$, d = 0.20), remained stable for those in narrative medicine ($\Delta_{\text{pre-post}} = 0.028$, 95% CI = −0.534 to 0.589, $P = .922$, d = 0.01), and increased for those in standard care ($\Delta_{\text{pre-post}} = -0.607$, 95% CI = −1.157 to −0.057, $P = .031$, d = 0.24). Also, cognitive severity significantly decreased for participants in VR ($\Delta_{\text{pre-post}} = 0.480$, 95% CI = 0.032 to 0.938, $P = .036$, d = 0.17), remained stable for those in narrative medicine ($\Delta_{\text{pre-post}} = -0.010$, 95% CI = −0.468 to 0.447, $P = .964$, d = 0.00), and increased for those receiving standard care ($\Delta_{\text{pre-post}} = -0.640$, 95% CI = −1.088 to −0.192, $P = .006$, d = 0.29). Similarly, sensory/emotional significantly decreased for participants in the VR condition ($\Delta_{\text{pre-post}} = 0.672$, 95% CI = 0.155 to 1.189, $P = .012$, d = 0.26), remained stable for those in the narrative medicine intervention ($\Delta_{\text{pre-post}} = -0.025$, 95% CI = −0.553 to 0.503, $P = .925$, d = 0.01), and increased for those in standard care ($\Delta_{\text{pre-post}} = -0.704$, 95% CI = −1.221 to −0.187, $P = .008$, d = 0.29). Lastly, affective meaning significantly decreased for VR participants ($\Delta_{\text{pre-post}} = 0.549$, 95% CI = 0.113 to 0.985, $P = .014$, d = 0.22), remained stable for those in narrative medicine ($\Delta_{\text{pre-post}} = 0.006$, 95% CI = −0.439 to 0.451, $P = .979$, d = 0.00), and increased, though not significantly, for those in

TABLE 1
Participants' Characteristics.

		Virtual Reality (n = 25)		Narrative Medicine (n = 24)		Standard Care (n = 25)		Group Differences
		No.	%	No.	%	No.	%	
Gender	Male	6	24.0	6	25.0	7	28.0	$\chi^2(2) = .113$
	Female	19	76.0	18	75.0	18	72.0	$P = .945$
Age	Mean (SD)	62.56 (10.08)		58.92 (10.20)		58.80 (11.54)		F(2,71) = 1.00 $P = .372$
Nationality	Italian	24	96.0	24	100.0	24	96.0	$\chi^2(2) = .987$
	Not Italian	1	4.0	0	0.0	1	4.0	$P = .611$
Employment status	Employed	18	72.0	15	62.5	19	76.0	$\chi^2(4) = 1.322$
	Unemployed	1	4.0	2	8.3	1	4.0	$P = .858$
	Retired	6	24.0	7	29.2	5	20.0	
Education level	Primary school	1	4.0	1	4.2	1	4.0	$\chi^2(6) = 5.039$
	Secondary school	11	44.0	10	41.7	6	24.0	$P = .539$
	High school	11	44.0	10	41.7	11	44.0	
	Graduate	2	8.0	3	12.5	7	28.0	
Primary cancer	Breast	12	48.0	11	45.8	12	48.0	$\chi^2(28) = 33.933$
	Colon	2	8.0	2	8.3	6	6.0	$P = .203$
	Rectum	2	8.0	2	8.3	2	8.0	
	Melanoma	2	8.0	0	0.0	0	0.0	
	non-Hodgkin lymphoma	0	0.0	0	0.0	1	4.0	
	Stomach	1	4.0	1	4.2	0	0.0	
	Ovary	1	4.0	4	16.7	0	0.0	
	Pancreasr	2	8.0	1	4.2	1	4.0	
	Uterine cervix	0	0.0	0	0.0	1	4.0	
	Larynx	0	0.0	2	8.3	0	0.0	
	Esophagus	1	4.0	0	0.0	0	0.0	
	Testicle	1	4.0	0	0.0	0	0.0	
	Prostate	1	4.0	0	0.0	0	0.0	
	Lung	0	0.0	0	0.0	2	8.0	
	Biliary tract	0	0.0	1	4.2	0	0.0	
Cancer stage	I	2	8.0	0	0.0	0	0.0	$\chi^2(6) = 10.165$
	II	6	24.0	1	4.2	2	8.0	$P = .118$
	III	6	24.0	7	29.2	9	36.0	
	IV	11	44.0	16	66.7	14	56.0	
Duration of chemotherapy session	< 3 hours	20	80.0	15	62.5	19	76.0	$\chi^2(2) = 2.077$
	> 3 hours	5	20.0	9	37.5	6	24.0	$P = .354$
Time since diagnosis or recurrence	Years, Mean (SD)	1.56 (1.29)		1.71 (1.78)		1.84 (1.46)		F(2,71) = 0.21 $P = .810$
Surgical Intervention	Yes	15	60.0	15	62.5	11	44.0	$\chi^2(2) = 2.019$
	No	10	40.0	9	37.5	14	56.0	$P = .364$
Antineoplastic treatment	Chemotherapy	17	68.0	18	75.0	17	68.0	$\chi^2(6) = 3.157$
	Chemoimmunotherapy	1	4.0	1	4.2	0	0.0	$P = .789$
	Immunotherapy	2	8.0	0	0.0	2	8.0	
	Chemobiologic	5	20.0	5	20.8	6	24.0	

Note. Statistical tests: χ^2 = chi-squared test; F = Fisher F from one-way ANOVA.

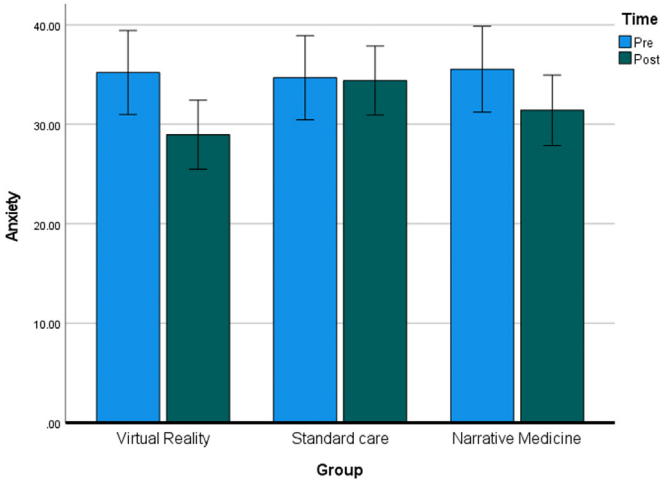


FIG. 2. Comparison between groups outcome anxiety.

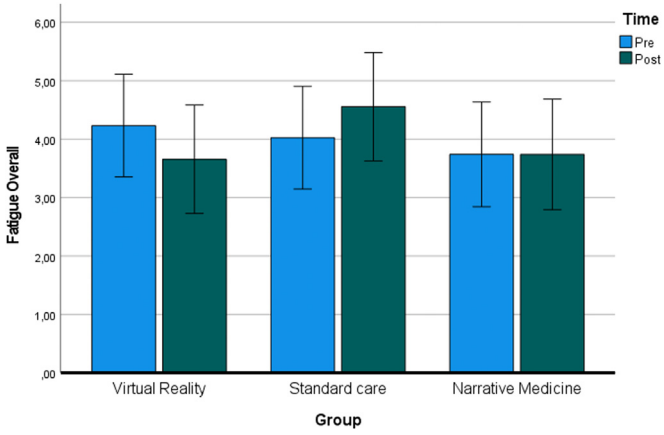


FIG. 3. Estimate mean of fatigue.

TABLE 2
Virtual Reality Symptom Questionnaire.

Symptoms	None	Slight		Moderate		Severe	
	0	1	2	3	4	5	6
Nonocular Symptoms							
General discomfort	22 (88%)	1 (4%)	1 (4%)	0	1 (4%)	0	0
Fatigue	22 (88%)	1 (4%)	1 (4%)	0	1 (4%)	0	0
Boredom	23 (92%)	0	0	2 (8%)	0	0	0
Drowsiness	20 (80%)	3 (12%)	0	2 (8%)	0	0	0
Headache	23 (92%)	1 (4%)	1 (4%)	0	0	0	0
Sweating	24 (96%)	1 (4%)	0	0	0	0	0
Claustrophobia/Disorientation	24 (96%)	1 (4%)	0	0	0	0	0
Nausea	22 (88%)	1 (4%)	0	2 (8%)	0	0	0
Dizziness	23 (92%)	0	0	1 (4%)	1 (4%)	0	0
Stomach awareness	22 (88%)	1 (4%)	1 (4%)	0	1 (4%)	0	0
Exhilaration	11 (44%)	2 (8%)	2 (8%)	1 (4%)	3 (12%)	3 (12%)	3 (12%)
Difficulty concentrating	21 (84%)	1 (4%)	3 (12%)	0	0	0	0
Ocular Symptoms							
Tired eyes	21 (84%)	3 (12%)	1 (4%)	0	0	0	0
Sore/aching eyes	25 (100%)	0	0	0	0	0	0
Irritated eyes	24 (96%)	1 (4%)	0	0	0	0	0
Watery eyes	23 (92%)	2 (8%)	0	0	0	0	0
Dry eyes	24 (96%)	1 (4%)	0	0	0	0	0
Eyestrain	22 (88%)	2 (8%)	1 (4%)	0	0	0	0
Hot/burning eyes	22 (88%)	2 (8%)	1 (4%)	0	0	0	0
Blurred vision	18 (72%)	1 (4%)	2 (8%)	0	3 (12%)	0	1 (4%)
Difficulty focusing	22 (88%)	1 (4%)	1 (4%)	0	0	1 (4%)	0
Double vision	25 (100%)	0	0	0	0	0	0
Vision discomfort	20 (80%)	1 (4%)	2 (8%)	1 (4%)	0	0	1 (4%)

standard care ($\Delta_{pre\text{-}post} = -0.280$, 95% CI = −0.716 to 0.156, $P = .204$, d = 0.13).

Pain

Average levels of pain did not change before and after the intervention [$F(1,71) = 1.06$, $P = .307$, $\eta_p^2 = .015$], and pain remained stable over time for participants in all groups [$F(2,71) = 0.19$, $P = .828$, $\eta_p^2 = .005$]. A closer inspection of the single item measuring pain revealed that 50 of the 74 (67.57%) participants reported absence of pain both before and after the intervention.

Cybersickness Symptoms

Possible VR-associated cybersickness symptoms as ocular and nonocular symptoms were not experienced after the VR intervention, as shown by the average scores of the ocular (M = 0.24, SD = 0.50) and nonocular (M = 0.39, SD = 0.45) VR symptoms (Table 2).

Participant Satisfaction using VR

The average score (M = 4.47, SD = 0.69) on the VR participant satisfaction questionnaire indicated that participants were highly satisfied with the session. Overall, descriptive analyses suggested that the VR session was a pleasant and satisfactory experience that did not yield any downside risk (Table 3).

DISCUSSION

This trial studied the effects of immersive VR in people with cancer undergoing AT infusion on anxiety, fatigue, pain, cybersickness symptoms, and participant satisfaction using VR compared to standard care and a powerful distractive strategy, the narrative medicine. Only in three previous trials[8,41,42] was VR compared with another distractive intervention. Furthermore, our sample size was larger than that of all previous clinical trials on immersive VR intervention during chemotherapy,[41-43] so our findings are able to show more precise estimates and demonstrate that this study has a greater power to draw conclusions.

Our intervention was a contemplative VR immersion, without any interaction with the scenarios, and this experimental condition might be assumed as being less effective than a participatory-type VR immersion.

VR and narrative medicine were both effective in reducing anxiety, but VR showed a stronger effect than narrative medicine. These results showed that VR was an excellent distraction technique, where

TABLE 3
Virtual Reality Patients Satisfaction Questionnaire.

	Disagree at all	Disagree	Agree	Quite agree	Very much agree
Virtual reality was easy to use	0	1 (4%)	0	6 (24%)	18 (72.0%)
The virtual reality scenarios were pleasant	0	0	4 (16%)	3 (12%)	18 (72.0%)
The use of virtual reality during chemotherapy is useful	0	0	4 (16%)	1 (4%)	20 (80%)
I felt like I was experiencing the scenes as if I was actually there	0	3 (12%)	2 (8%)	3 (12%)	17 (68%)
When I was with virtual reality it felt like I wasn't in the hospital	1 (4%)	1 (4%)	2 (8%)	8 (32%)	13 (52%)
The virtual reality headset was comfortable	1 (4%)	2 (8%)	4 (5.4%)	5 (6,8%)	13 (52%)
I would recommend virtual reality to other patients as well	0	0	3 (12%)	1 (4%)	21 (84%)
The experience with virtual reality met my expectations	0	1 (4%)	3 (12%)	4 (16%)	17 (68%)

participants regulated the emotional response associated with stressful chemotherapy by moving the focus of attention onto pleasant stimuli by selecting the different scenarios. In accordance with the stress and adaptation model of Lazarus and Folkman,[44] VR acted as a coping technique, because our scenarios stimulated in participants a set of cognitive skills to control, reduce or tolerate the stressful situation. In accordance with the positive psychology of Fredrickson,[45] VR increased positive emotions by reducing the negative ones such as anxiety, and this condition produced and empowered sustainable and useful inner resources to face difficult situations. The reduction of anxiety could be produced by immersing participants in virtual scenarios that recalled places they had physically visited and where they felt good, with stimulation of the medial temporal lobe and the hippocampal region.[22] Our findings are in line with several trials[41,42,46] that reported a significant decrease in anxiety after VR intervention during chemotherapy. In only one study[47] in 20 people with breast cancer was the decrease in anxiety after VR intervention not statistically significant.

Our findings suggest that VR is effective in reducing fatigue, whereas narrative medicine is not. These results are consistent with several studies,[10,41,48] while only one showed findings not statistically significant.[45] The choice of natural scenarios for the reduction or prevention of fatigue also accords with the Stress Reduction Theory,[49] where nature scenes improve the person's well-being by activating the restoration of attention. Pain did not change before and after the intervention and it remained stable over time in the three arms. An important aspect is that almost three-quarters of participants showed absence of pain both before and after the intervention. This aspect meant that the possible impact of the VR on pain could not be studied in our trial. Our findings are consistent with two previous trials,[38,50] where pain means at baseline were clinically not significant. Other studies of the effects of VR on pain showed no statistical significant effects[41,42,50] while one trial showed statistically significant effects.[42] These differences could be due to heterogeneity of the population, VR equipment, length of intervention and type of scenarios, among studies. In our study, participants did not show ocular or nonocular symptoms after the VR intervention, with results well below the cut-off of 20%, so cybersickness can be considered negligible. These finding are consistent with previous trials[48,50] and with the study by Chirico and colleagues, except for a slight difficulty in concentrating (21.4%).[8] The familiarization phase we used helped to reduce anxiety and fatigue, in line with findings from previous study.[8] Participants using VR showed high satisfaction scores, in line with other trials.[43,44,47]

Limitations

This trial shows some limitations. Due to the nature of the VR intervention it was impossible to blind the participants, so the risk of bias is high for detection and performance bias. Moreover, this trial analyzed only short-term effects, as measurements were taken only at two time points (pre and post intervention) and each person participated in only one session. In the participants' characteristics, the number of the AT cycle was not considered. Finally, data were collected via subjective answers obtained from questionnaires only.

Implications for Practice

We recommend that nurses implement VR to reduce anxiety and fatigue in people with cancer during AT. Oncology nurses should introduces patient-centered new interventions to improve the patient's experience during AT. VR is an innovative intervention, safe and easy to use, that has the characteristic of quickly and effectively distracting the patients from the negative stimuli in which they are immersed during AT. VR represents the most promising innovative digital healthcare intervention for oncology nursing care and will play an increasingly important role in healthcare, offering a new perspective for cancer nursing. The effective implementation of VR in oncology nursing care requires specific training in digital health for the management of this new technology.

Conclusion

VR was effective in reducing anxiety and fatigue, without cybersickness symptoms, and is a pleasant and satisfactory experience for people receiving AT. Future studies should use a single-blind randomized controlled trial design, consider the number of the AT cycle, increase the sample size, and use a small effect size to improve the study power. Moreover, they should increase longitudinal pre-post treatment with repeated VR sessions to assess possible long-term benefits. Finally, to obtain a more objective measurement of VR effects on emotional states, an electrodermal recording should be added to the questionnaires.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Funding Sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgements

We would like to thank Diana Giannarelli, PhD, statistician, for statistical consultation; Stefano Chirigoni, MSc, for collaboration in VR programming; and Giovanna Maria Schintu, MD, Giancarla Soru, MD, Antonella Delogu, RN, Lucia Poloni, RN, Patrizia Domenica Sini, RN, Giulia Cadeddu, RN, and Veronica Arminu Davidica, RN, for contributing to the trial by recruiting participants and implementing the intervention.

REFERENCES

1. Schirrmacher V. From chemotherapy to biological therapy: A review of novel concepts to reduce the side-effects of systemic cancer treatment (Review). *Int J Oncol*. 2019;54(2): 407419. https://doi.org/10.3892/ijo.2018.4661.
2. Beaver CC, Magnan MA. Managing chemotherapy side-effects: achieving reliable and equitable outcomes. *Clin J Oncol Nurs*. 2016;1(6): 589591. https://doi.org/10.1188/16.CJON.589591. 20.
3. Mitchell AJ, Chan M, Bhatti H, et al. Prevalence of depression, anxiety, and adjustment disorder in oncological, haematological, and palliative-care settings: a meta-analysis of 94 interview-based studies. *Lancet Oncol*. 2011;12:16074. https://doi.org/10.1016/S14702045(11)70002.
4. O'Regan P, McCarthy G, O'Reilly S, et al. Cancer-related fatigue and self-care agency: a multicentre survey of patients receiving chemotherapy. *J Clin Nurs*. 2019;28(23-24):4424–4433. https://doi.org/10.1111/jocn.15026.
5. Bower JE. Cancer-related fatigue-mechanisms, risk factors, and treatments. *Nat Rev Clin Oncol*. 2014;11(10):597–609. https://doi.org/10.1038/nrclinonc.2014.127.
6. Fallon MT. Neuropathic pain in cancer. *Br J Anaesth*. 2013;111(1):10511. https://doi.org/10.1093/bja/aet208.
7. Brant JM, Stringer LH. Cancer pain. In: Yarbro CH, Wujcik D, Gobel BH, eds. *Cancer Nursing: Principles and Practice*. Burlington, MA: Jones and Bartlett; 2018:781–816.
8. Chirico A, Maiorano P, Indovina P, Milanese C, Giordano GG, Alivernini F, et al . Virtual reality and music therapy as distraction interventions to alleviate anxiety and improve mood states in breast cancer patients during chemotherapy. *J Cell Physiol*. 2020;235(6):5353–5362. https://doi.org/10.1002/jcp.29422.9.
9. Ioannou A, Papastavrou E, Avraamides MN, Charalambous A. Virtual reality and symptoms management of anxiety, depression, fatigue, and pain: a systematic review. *SAGE Open Nurs*.. 2020;27(6): 2377960820936163. https://doi.org/10.1177/2377960820936163.
10. Radianti J, Majchrzak TA, Fromm J, Wohlgenannt I. A systematic review of immersive virtual reality applications for higher education: design elements, lessons learned, and research agenda. *Comput Educ*. 2020;147: 103778. https://doi.org/10.1016/j.compedu.2019.103778.
11. Burrai F, Othman S, Brioni E, Silingardi M, Micheluzzi V, Luppi M, et al . Virtual reality in dialysis: a new perspective on care. *J Ren Care*. 2018;44(4):195–196. https://doi.org/10.1111/jorc.12264.

12. Burrai F, Othman S, Brioni E, Silingardi M, Micheluzzi V, Luppi M, et al . Effects of virtual reality in patients undergoing dialysis: study protocol. *Holis Nurs Prac*. 2019;33(6):327–337. https://doi.org/10.1097/HNP.0000000000000330.
13. Keshner EA, Weiss PT. Introduction to the special issue from the proceedings of the 2006 International Workshop on Virtual Reality in Rehabilitation. *J Neuroeng Rehabil*. 2007;4:18. https://doi.org/10.1186/1743-0003-4-18.
14. Rutkowska A, Rutkowski S, Szczepanska-Gieracha J. The use of total immersion in the rehabilitation process. *Med Rehab*. 2020;24(2):2730. https://doi.org/10.5604/01.3001.0014.412.
15. Freeman D, Reeve S, Robinson A, Ehlers A, Clark D, Spanlang B, et al . Virtual reality in the assessment, understanding, and treatment of mental health disorders. *Psychol Med*. 2017;47(14): 23932400. https://doi.org/10.1017/S003329171700040X.
16. Slater M. Place illusion and plausibility can lead to realistic behavior in immersive virtual environments. *Philos Trans R Soc B Biol Sci*.. 2009;364:3549–3557. https://doi.org/10.1098/rstb.2009.0138.
17. Sundar S, Xu Q, Bellur S. Designing interactivity in media interfaces: a communications perspective. In: *Proceedings of the SIGCHI Conference on Human Factors in Computing Systems*. 20102247–2256. https://doi.org/10.1145/1753326.1753666.
18. Zhang H, Xu H, Zhang ZX, Zhang Q. Efficacy of virtual reality-based interventions for patients with breast cancer symptom and rehabilitation management: a systematic review and meta-analysis. *BMJ Open*. 2022;12: e051808. https://doi.org/10.1136/bmjopen2021051808.
19. Zeng Y, Zhang JE, Cheng ASK, Cheng H, Scott Wefel J. Virtual reality-based interventions in cancer-related symptom management. *Integr Cancer Ther*. 2019;18: 1534735419871108. https://doi.org/10.1177/1534735419871108.
20. Leggiero NM, Armstrong TS, Gilbert MR, King AL. Use of virtual reality for symptom management in solid-tumor patients with implications for primary brain tumor research: a systematic review. *Neurooncol Pract*. 2020;28(5): 477489. https://doi.org/10.1093/nop/npaa012. 7.
21. Rutkowski S, Czech O, Wrzeciono A, Kiper P, Szczepańska-Gieracha J, Malicka I. Virtual reality as a chemotherapy support in treatment of anxiety and fatigue in patients with cancer: a systematic review and meta-analysis and future research directions. *Complement Ther Med*. 2021;61: 102767. https://doi.org/10.1016/j.ctim.2021.102767.
22. Chow H, Hon J, Chua W, Chuan A. Effect of virtual reality therapy in reducing pain and anxiety for cancer-related medical procedures: a systematic narrative review. *J Pain Symptom Manage*. 2021;61(2): 384394. https://doi.org/10.1016/j.jpainsymman.2020.08.016.
23. Chirico A, Lucidi F, De Laurentiis M, Milanese C, Napoli A, Giordano A. Virtual reality in health system: beyond entertainment. A mini-review on the efficacy of VR during cancer treatment. *J Cell Physiol*. 2016;231(2): 275287. https://doi.org/10.1002/jcp.25117.
24. Indovina P, Barone D, Gallo L, Chirico A, De Pietro G, Giordano A. Virtual reality as a distraction intervention to relieve pain and distress during medical procedures: a comprehensive literature review. *Clin J Pain*. 2018;34(9): 858877. https://doi.org/10.1097/AJP.0000000000000599.
25. Butcher NJ, Monsour A, Mew EJ, et al. Guidelines for reporting outcomes in trial reports: the CONSORT-Outcomes 2022 extension. *JAMA*. 2022. https://doi.org/10.1001/jama.2022.21022.
26. Scates D, Dickinson K, Sullivan JI, Cline H, Balaraman R. using nature-inspired virtual reality as a distraction to reduce stress and pain among cancer patients. *Environ Behav*. 2020.52(8):895918. doi:10.1177/0013916520916259.
27. Sharifpour S, Manshaee G, Sajjadian I. Effects of virtual reality therapy on perceived pain intensity, anxiety, catastrophising and self-efficacy among adolescents with cancer. *Couns Psychother Res*. 2020;21:2:18–226. https://doi.org/10.1002/capr.12311.
28. Charon R. *Narrative Medicine: Honoring the Stories of Illness*. New York, NY: Oxford University Press; 2006.
29. Molzahn A, Sheilds L, Bruce A, Stajduhar K, Makaroff KS, et al . People living with serious illness: stories of spirituality. *J Clin Nurs*. 2012;21(1516): 234756. https://doi.org/10.1111/j.13652702.2012.04196.x.
30. Paterson JG, Zderad LT. *Humanistic Nursing*. New York, NY: John Wiley and Sons; 1976.
31. Spielberger CD. *State-Trait Anxiety Inventory*. Palo Alto, CA: Mind Garden; 1983.
32. Corsaletti BF, Proença M-DGL, Bisca GKW, Leite JC, Bellinetti LM, Pitta F. Minimal important difference for anxiety and depression surveys after intervention to increase daily physical activity in smokers. *Fisioter Pesqui*. 2014;21(4). 10.590/18092950/1308782104201.
33. Mattsson S, Olsson EMG, Carlsson M, Johansson BBK. Identification of anxiety and depression symptoms in patients with cancer: comparison between short and long web-based questionnaires. *J Med Internet Res*. 2019;21(4):e11387.
34. Piper BF, Dibble SL, Dodd MJ, Weiss MC, Slaughter RE, Paul SM. The revised Piper Fatigue Scale: psychometric evaluation. *Oncol Nurs Forum*. 1998;25(4):67784.
35. Giacalone A, Polesel J, De Paoli A, Colussi AM, Sartor I, Talamini R, Tirelli U. Assessing cancer-related fatigue: the psychometric properties of the Revised Piper Fatigue Scale in Italian cancer inpatients. *Support Care Cancer*. 2010;18:1191–1197. https://doi.org/10.1007/s0052000907410.
36. Gagnon MC, Stanos PS, Ende G, Rader RL, Harden N. Treatment outcomes for Workers Compensation patients in a US based interdisciplinary pain management program. *Pain Practice*. 2013;13(4):282–288. https://doi.org/10.1111/j.15332500.2012.00586.x.
37. Ham OK, Kang Y, Teng H, Lee Y, Im EO. Consistency and accuracy of multiple pain scales measured in cancer patients from multiple ethnic groups. *Cancer Nurs*. 2015;38(4):305–311. https://doi.org/10.1097/NCC.0000000000000179.
38. Ames SL, Wolffsohn JS, McBrien NA. The development of a symptom questionnaire for assessing virtual reality viewing using a head-mounted display. *Optom Vis Sci*. 2005;82(3):168–176. https://doi.org/10.1097/01.OPX.0000156307.95086.6.
39. Buche H, Michel A, Blanc N. Use of virtual reality in oncology: from the state of the art to an integrative model. *Front Virtual Real*. 2022;3: 894162. https://doi.org/10.3389/frvir.2022.894162.
40. Faul F, Erdfelder E, Lang AG, Buchner AG*Power. 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. *Beh Res Methods*. 2007;39(2): 175191. https://doi.org/10.3758/bf03193146.
41. Ioannou A, Paikousis L, Papastavrou E, Avraamides MN, Astras G, Charalambous A. Effectiveness of virtual reality vs guided imagery on mood changes in cancer patients receiving chemotherapy treatment: a crossover trial. *Eur J Oncol Nurs*. 2022;61: 102188. https://doi.org/10.1016/j.ejon.2022.102188.
42. Verzwyvelt LA, McNamara A, Xiaohui X, Stubbins R. Effects of virtual reality v. biophilic environments on pain and distress in oncology patients: a case-crossover pilot study. *Sci Rep*. 2021;11(1):20196. https://doi.org/10.1038/s41598021997632.
43. Mohammad EB, Ahmad M. Virtual reality as a distraction technique for pain and anxiety among patients with breast cancer: a randomized control trial. *Palliat Support Care*. 2019;17(1):2934. https://doi.org/10.1017/S1478951518000639.
44. Lazarus RS, Folkman S. *Stress, appraisal, and coping. In:* Behaviour Research and Therapy. New York, NY: Springer; 1984.
45. Fredrickson B. The role of positive emotions in positive psychology. The broaden-and-build theory of positive emotions. *Am Psychol*.. 2001;56:218–226. https://doi.org/10.1037/0003066x.56.3.218.
46. Schneider SM, Ellis M, Coombs WT, Shonkwiler EL, Folsom LC. Virtual reality intervention for older women with breast cancer. *Cyberpsychol Behav*. 2003;6:301–307.
47. Schneider SM, Prince-Paul M, Allen MJ, Silverman P, Talaba D. Virtual reality as a distraction intervention for women receiving chemotherapy. *Oncol Nurs Forum*. 2004;31(1):81–88. https://doi.org/10.1188/04.ONF.8188.
48. Schneider SM, Hood LE. Virtual reality: a distraction intervention for chemotherapy. *Oncol Nurs Forum*. 2007;34(1):39–46. https://doi.org/10.1188/07.ONF.3946.
49. Golding SE, Gatersleben B, Cropley M. An experimental exploration of the effects of exposure to images of nature on rumination. *Int J Environ Res Public Health*. 2018;15(2):300. https://doi.org/10.3390/ijerph15020300.
50. Wilson K, Scorsone G. The use of virtual reality technologies to reduce anxiety and improve experience in chemotherapy patients during treatment. *Front*. 2021. https://doi.org/10.3389/frvir.2021.695449.