



The Use of Virtual Reality Technologies to Reduce Anxiety and Improve Experience in Chemotherapy Patients During Treatment

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The study explored the potential benefits of virtual reality as a psychological intervention to induce positive emotions and reduce pain levels in participants receiving IV chemotherapy treatment. Participants in the study had the opportunity to select a nature theme of their choosing during their treatment session. The study provided a noninvasive solution that promoted relaxation to reduce anxiety by shifting an individual's mood positively during treatment. The objective was met by measuring participants' mood and pain levels before and after the virtual reality experience and participant satisfaction with the use of the technology. The study was conducted in the chemotherapy treatment area at the INTEGRIS Cancer Institute and consisted of a mixed demographic of cancer diagnosed patients. Results of this study showed that participants felt more calm, relaxed, and content, as well as less tense after the use of VR. Participants showed high ratings of feeling immersed and distracted by feeling like they were visiting the places displayed and paid more attention to the said environment than their own thoughts. There was no significant difference in blood pressure, pain levels, feeling upset, or worried. A majority of participants preferred to have VR as part of their future experiences during treatment time.

Keywords: virtual reality, nature, chemotherapy, anxiety, pain, distraction, attention restoration theory, cancer

INTRODUCTION

The purpose of this study is to investigate the impact of nature scenes in a 3D virtual reality environment on patients receiving chemotherapy treatment. Virtual reality environments use a multi-sensory distraction technique that can help divert a person's attention away from painful or negative stimuli (Hoffman et al., 2003; Gershon et al., 2004; Gold et al., 2007; Jones et al., 2016; Maples-Keller et al., 2017). Focusing one's attention on pleasant, natural environments has shown to promote relaxation and enhance positive emotions, which can be influential in managing stress and decreasing feelings of anxiety (Carrougner et al., 2009; Chen et al., 2009; Banos et al., 2013; Shah et al., 2015; Flavian et al., 2019). Virtual reality has the potential to be more effective than other traditional methods due to its utilization of exposure-based therapy and immersion techniques (Powers and Emmelkamp, 2007; Opris et al., 2012; McCann et al., 2014; Fodor et al., 2018). The existing literature on virtual reality indicates that we know nature scenes can reduce anxiety for individuals. We also know that virtual reality serves as a distraction for patients to reduce pain levels, but we don't know how virtual nature scenes impact chemotherapy patients while receiving treatment. The research

study will test three hypotheses that expand on the use of virtual reality technology. Hypothesis 1: There is a statistically significant reduction in pain and blood pressure levels for patients who use a virtual reality intervention undergoing IV chemotherapy treatment than those levels before the VR session. Hypothesis 2: The use of virtual reality intervention provides an immersive atmosphere for cancer patients undergoing IV chemotherapy treatment. Hypothesis 3: Patients diagnosed with cancer undergoing IV chemotherapy treatment feel calmer and less anxious after using virtual reality than before the VR session.

BACKGROUND

Attention Restoration Theory

The Attention Restoration Theory categorizes attention into two types: directed and involuntary. Directed attention involves “hard fascination,” a higher-order, top-down mental processing that fully captures one’s attention (Berman et al., 2008; Valtchanov and Ellard, 2015; Ohly et al., 2016; Basu et al., 2019). In contrast, involuntary attention utilizes “soft fascination” via bottom-up processing and is less cognitively demanding (Berman et al., 2008; Gamble et al., 2013; Berto, 2014; Valtchanov and Ellard, 2015; Gerber et al., 2017; Basu et al., 2019). Attention is susceptible to fatigue, which can lead to adverse cognitive effects that, in turn, impact one’s physical and emotional well-being (Ohly et al., 2016; Gerber et al., 2017). One way to combat attention fatigue is through attention restoration, which involves activating involuntary attention while allowing directed attention to recover (Berman et al., 2008; Ohly et al., 2016). Research has shown that natural environments are an effective method to achieve attention restoration (Berman et al., 2008; Berto, 2014; Gamble et al., 2014; Ohly et al., 2016; Gerber et al., 2017; Navarro-Haro et al., 2017).

Anxiety and Chemotherapy

While receiving chemotherapy, patients are exposed to various objects, medications, and environments that can elicit negative emotions and symptoms, such as anxiety, nausea, vomiting, pain, and fatigue. Techniques to help patients cope with these stressors can improve their experience during chemotherapy sessions and increase the likelihood of adherence to their treatment regimens (Schneider and Hood, 2007). Several studies support that the use of virtual reality has far better outcomes than traditional evidence-based interventions (cognitive-behavioral therapy, *in vivo* exposure, ad imaginal exposure) for treating anxiety disorders. due to the accessibility, control of content, customization options, and cost-effectiveness (Powers and Emmelkamp, 2007; Opris et al., 2012). Powers and Emmelkamp’s (2007) study strengthen the conclusion of the effectiveness of virtual reality exposure therapy (VRET) by analyzing several case studies to explore the effectiveness of VRET compared to other forms of existing treatments and conclude that VRET has a larger effect on cognitive outcome measures than other control conditions (waitlist, *in vivo*, relaxation, attention control, and bibliotherapy) with Cohen’s $d = 1.11$ (SE = 0.15, 95% CI: 0.82–1.39). Opris et al. (2012)

highlight the advantages of VRET over traditional exposure specifically related to flexibility in the environment, the ability to repeat exposure as much as needed, and content selection per patient and anxiety disorder. When making a choice on type of treatment, PTSD patients highly preferred VRET over *in vivo* therapy which could be due to the patient’s perceptions of *in vivo* therapy and feeling threatened to confront fears in real life situations, objects, or activities (Opris et al., 2012).

Virtual reality utilizes distraction techniques by creating a greater sense of presence in the virtual environment, focusing a patient’s attention away from stressors and negative stimuli associated with treatment. Previous studies have identified a relationship between higher levels of distraction and lower levels of negative moods in chemotherapy and oncology patients (Schneider and Hood, 2007; Banos et al., 2013). An extensive literature review revealed only three studies that examined the effects of virtual reality on anxiety and pain levels in patients receiving chemotherapy treatment (Schneider et al., 2004; Schneider and Hood, 2007; Banos et al., 2013). Two of the three studies found a reduction in anxiety levels, whereas only one study found a reduction in both anxiety and pain levels (Schneider and Hood, 2007; Banos et al., 2013). Therefore, additional studies are needed to examine the effects of both anxiety and pain levels in chemotherapy patients. The following study will expand upon the existing body of research on anxiety and pain levels.

Virtual Reality in Pain Management

Existing literature shows that virtual reality can serve as a distractor and reduce pain levels for patients in the ICU, the inpatient environment, the emergency department, and in the outpatient setting (Schneider et al., 2004; Jones et al., 2016; Sikka et al., 2018; Tanja-Dijkstra et al., 2018; Spiegel et al., 2019; Ong et al., 2020). Distraction is widely accepted as a nonpharmacological intervention for pain relief and can be an effective adjunctive therapy to compliment pain management protocols (Schneider et al., 2004; Jones et al., 2016; Sikka et al., 2018; Tanja-Dijkstra et al., 2018; Spiegel et al., 2019; Ong et al., 2020). Immersive experiences can distract from a noxious stimulus by using multiple sensory systems, making it difficult to focus on stimuli outside the field of attention (Schneider et al., 2004; Sikka et al., 2019; Spiegel et al., 2019). This view supports the Multiple Resources Theory, which indicates that sensory systems function independently, and Gate Theory of Attention, which helps to explain that pain perceptions are reduced given the distraction of VR and the diversion of attention from pain (Jones et al., 2016; Sikka et al., 2019). The effects of VR can improve the patient’s experience in several healthcare settings by reducing pain levels at the moment and specifically reducing unavoidable discomforts involving ICU care (Ong, 2020).

Nature Scenes and Virtual Reality

Exposure to natural environments helps restore and improve attention by activating soft fascination, which has shown to have positive effects on mood and provide relief from psychological stressors (Felnhofer et al., 2015; Herrero et al., 2015; Valchanov

and Ellard, 2015; Gerber et al., 2017; Golding et al., 2018; Tanja-Dijkstra et al., 2018). Virtual reality provides the opportunity to simulate nature scenes and immerse the user in its environment, directing a patient's attention away from treatment-induced stressors. Natural settings have a more significant restorative potential than other environments because they require greater activation of involuntary attention (Berman et al., 2008; Gamble et al., 2014). These restorative effects of nature scenes can increase relaxation and peacefulness, decrease psychological stress, and improve cognitive function and attention (Berman et al., 2008; Gamble et al., 2014; Valtchanov and Ellard, 2015; Navarro-Haro et al., 2017).

METHODS

Design

Before beginning the VR session, each participant completed a pre-assessment of their pain and mood levels using a modified version of the State-Trait Anxiety Inventory (STAI) questionnaire. Developed in 1970 by Spielberger, Gorsuch, and Lushene, the STAI is a validated assessment that consists of 40 statements that address state and trait anxiety feelings (Rubin et al., 2009). For this study, a condensed version of the STAI was used using six questions that focus on state components that gauged the intensity of feelings of anxiety in the particular moment. The feelings related to the condensed STAI were: (calm, tense, upset, relaxed, content, and worried on a scale of "strongly agree," "agree," "disagree," and "strongly disagree." The pre and post assessments include assessing level of pain using the

Wong-Baker scale of 0–10 (see **Table 1**). The Wong-Baker face-pain scale was selected given its wide use in the healthcare industry, high usage as a study measure, and psychometric properties (McGrath, 2017). During this time, the investigator and study coordinator captured participant heart rates and blood pressure rates. After completing the pre-assessment, the VR headset was then given to the participant to place on their head and adjust as needed. The VR application used in this study, Applied VR, allows the participant to choose from 26 different nature scenarios that range from 2–30 min in duration (**Figure 1**). Each scenario contains relaxing music or interactive audio that is played through speakers built into the headset, providing an immersive audio-visual experience. Participants could adjust the volume to their desired level. Participants then navigated the 360-degree simulation by moving their eyes and head position. Participants were seated throughout the session and were informed they could stop at any time for any reason. Once the VR session ended, the headset was removed from the participant, and their heart rate and blood pressure were re-measured. The headsets and equipment were sanitized after each participant using the protocol provided by Applied VR. A post-assessment was then completed using the Wong-Baker faces and STAI questionnaire to evaluate pain and mood levels, as well as obtain patient satisfaction feedback regarding the overall VR experience.

Population and Sample

The theoretical population is chemotherapy patients undergoing treatment in an outpatient setting. The accessible population for this study is patients undergoing

TABLE 1 | Pre and post questionnaire.

Pre and post questionnaire			
Question	Answer scale	Source	Type
Select a number from the following scale to describe how much pain you are currently experiencing	0–10	Wong-baker	Pre and post
I Feel calm	Strongly agree, agree, disagree, strongly disagree	STAI	Pre and post
I Am tense	Strongly agree, agree, disagree, strongly disagree	STAI	Pre and post
I Feel upset.	Strongly agree, agree, disagree, strongly disagree	STAI	Pre and post
I Am relaxed	Strongly agree, agree, disagree, strongly disagree	STAI	Pre and post
I Feel content	Strongly agree, agree, disagree, strongly disagree	STAI	Pre and post
I Am worried	Strongly agree, agree, disagree, strongly disagree	STAI	Pre and post
I Felt I was visiting the places in the displayed environment	Strongly agree, agree, disagree, strongly disagree	ITC	Post
I Paid more attention to the displayed environments than I did my own thoughts	Strongly agree, agree, disagree, strongly disagree	ITC	Post
I Would recommend virtual reality during treatment time	Strongly agree, agree, disagree, strongly disagree	VR	Post
I Felt calmer and less anxious using virtual reality in my experience than not having it at all	Strongly agree, agree, disagree, strongly disagree	VR	Post
I Would prefer to have virtual reality as part of my future experiences	Strongly agree, agree, disagree, strongly disagree	VR	Post

Wong-Baker Faces Pain Rating Scale, State-Trait Anxiety Inventory Questionnaire, ITC Sense of Presence Inventory, Patient Experience Survey VR.

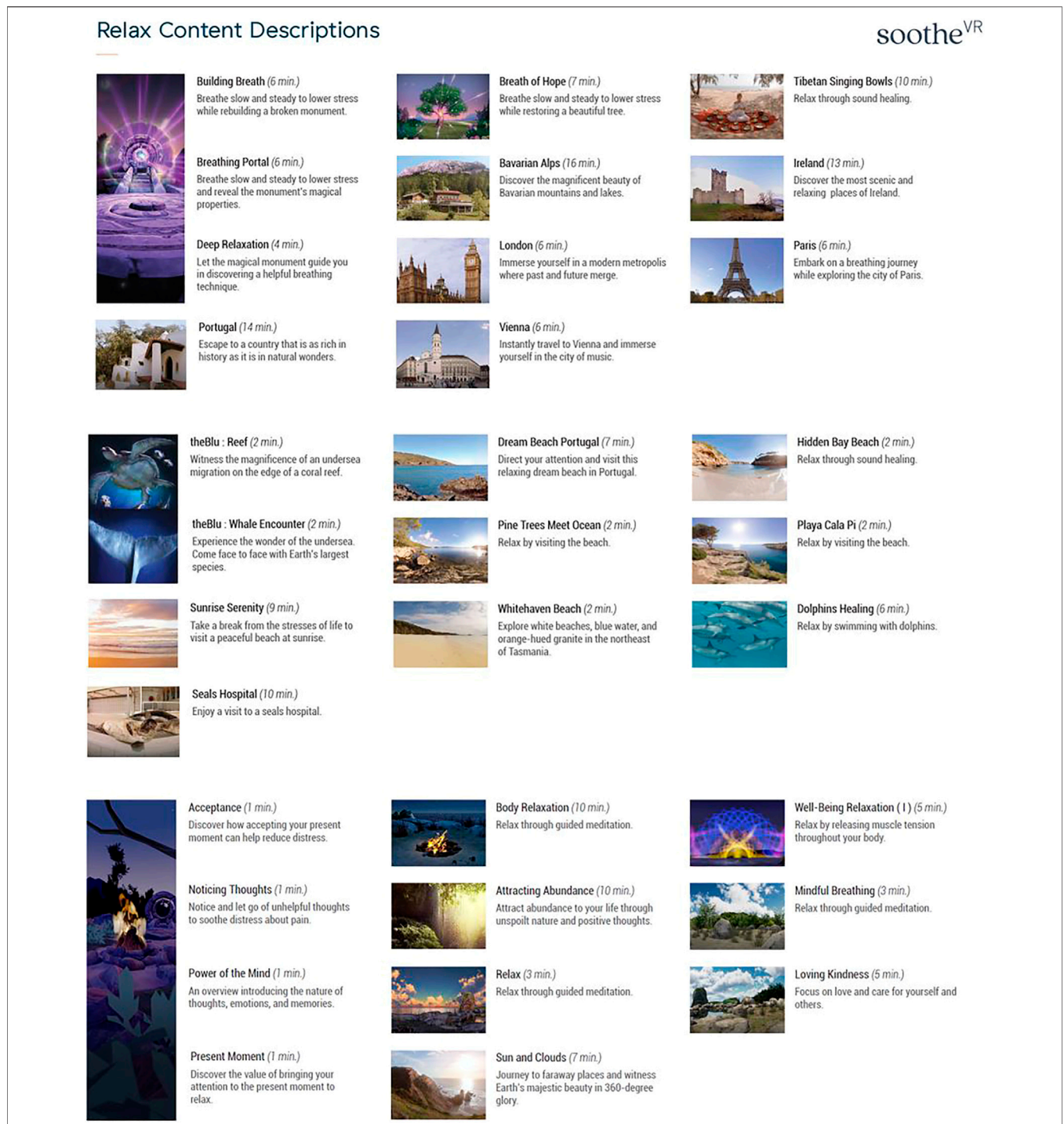


FIGURE 1 | Screenshots, titles, durations, and descriptions of VR experiences available to patients in study. Complete list of content provided, with permission, from AppliedVR (2021).

chemotherapy treatment at the INTEGRIS Cancer Institute. The population consists of male and female individuals who are actively undergoing chemotherapy treatment with a current cancer diagnosis. The minimum age range for the population is 18 years old. All races will be open to inclusion

in this study, with a breakdown of all demographic information.

The sample for this study is a convenience sample of available patients at the INTEGRIS Cancer Institute who had an appointment based on the investigator's availability to recruit

patients for the study between May 7, 2019, and February 20, 2020. The sampling frame is the daily clinic schedule provided by EPIC. Patients are identified by name, date of birth, and appointment time.

Eligibility criteria for inclusion in this study are that subjects must be 18 years of age or older, male or female, and currently receiving chemotherapy treatment. Exclusion criteria would be an individual with a history of epilepsy, seizures, vertigo, or motion sickness. The virtual reality setting could possess potential side effects, specifically visually-induced motion sickness (VIMS), for individuals with a history of one of the clinical conditions (Lorenz, 2017).

Ethical Considerations

From a beneficence standpoint, the focus is not to harm while maximizing benefits to participants with little to no risk (Belmont, 2007). As mentioned in the sampling plan, specific patients with the exclusion criteria will not participate in the study. The study's benefits are not justifiable to individuals who would be more susceptible to VIMS, given the underlying preexisting health conditions (Lorenz et al., 2017). Given the exclusion of such individuals, the research study to the proposed population would not expose participants to greater than normal daily risks. Integris Health Institutional Review Board (IRB) ensures the ethical concerns in all proposed research are addressed before approving such research. An essential step in this study is to comply with all the regulations for all institutional review boards. For INTEGRIS Health IRB, an IRB application consisting of consent to participate, confidentiality agreements, and rights protection will be submitted. IRB submission also includes informed consent, conflict of interest disclosure, protocol, ethical considerations, subject and recruitment methods, and research procedures. The protection of the participant's privacy will also be considered by ensuring all identifying information will be blinded, and all documents related to assessments will be anonymous. The anonymity technique is coding the pre and post assessments by completion date and using a randomly assigned letter of the alphabet to identify the patient.

RESULTS

Patient Characteristics

A total of 22 participants were recruited for the study. **Table 2** shows the types of diagnosis for the sample with the majority of the sample having a diagnosis of breast cancer. **Tables 3, 4** provide the ethnicity and gender demographics for the sample of the research study. From a gender standpoint, 59% were female, and 41% were male. The median age was 61, and the range was between 32 and 78 years of age. The demographic consisted of Caucasian (86%), African American (9%), and Asian (5%) participants.

Data Analysis

Following data collection, the data was entered into an SPSS data file for analysis. A paired T-test was used to determine the

TABLE 2 | Sample demographic by diagnosis.

	N	%
Mantle Cell lymphoma	1	4.5
Lung cancer	3	13.6
Adenocarcinoma of brain	1	4.5
Breast cancer	8	36.4
Colon cancer	1	4.5
Follicular lymphoma	1	4.5
Myeloma	1	4.5
Hodgkins lymphoma	1	4.5
Bial duct cancer	1	4.5
Mucinous adenocarcinoma of appendix	1	4.5
Breast neoplasm	1	4.5
Esophageal adenocarcinoma	1	4.5
14.00	1	4.5

TABLE 3 | Sample demographic by ethnicity.

	N	%
White	19	86.4
African american	2	9.1
Asian	1	4.5

TABLE 4 | Sample demographic by gender.

	Frequency	Percent
Valid	Male	9
	Female	13
	Total	22
		40.9
		59.1
		100.0

significance level, and the p -value was set at $p > 0.05$. According to **Table 5**, there was no significant difference in blood pressure (Pair 1 $p = 0.073$, Pair 2 = 0.508), pain levels (Pair 2 $p = 0.374$), feeling upset (Pair 6 $p = 0.576$, or worried (Pair 9 $p = 0.379$). The data supports the rejection of Hypothesis one since there was no significant reduction in blood pressure or pain levels. Even though there was no statistically significant difference in blood pressure for the sample, it is worth noting that out of the 22 participants, 12 participants had a decrease in systolic blood pressure levels. Additionally, six participants had a reduction in diastolic blood pressure levels. In regard to feeling calm, the T-test in **Table 5**, a T-test showed a p -value of 0.017, indicating that participants felt calmer after the virtual reality experience. In **Table 5**, a p -value of 0.042 indicates the significance of feeling less tense after the use of VR. The effect of VR was more pronounced in the feelings of being relaxed ($p = 0.002$) and content ($p = 0.000$).

To assess the distraction quality of the intervention, participants were asked to rate their level of feeling distracted and immersed on a Likert scale with the following ratings: strongly agree (4), agree (3), disagree (2), and strongly disagree (1). The average score of feeling distracted was 3.68. According to **Table 6**, the average score of feeling immersed was 3.33, concluding that most patients strongly agreed to feeling like they were visiting the places displayed and paid

TABLE 5 | Paired sample T-test, pre- and postintervention (virtual reality).

		Paired differences			95% Confidence interval of the difference		t	df	Sig. (2-Tailed)
		Mean	Std. Deviation	Std. Error mean	Lower	Upper			
Pair 1	Pre systolic blood pressure (mmHg) - post systolic blood pressure (mmHg)	5.000	10.741	2.605	-0.523	10.523	1.919	16	0.073
Pair 2	Pre diastolic blood pressure (mmHg) - post diastolic blood pressure (mmHg)	2.294	13.963	3.387	-4.885	9.473	0.677	16	0.508
Pair 3	Pre pain level - post pain level	0.600	1.342	0.600	-1.066	2.266	1.000	4	0.374
Pair 4	Pre calm - post calm	-0.364	0.658	0.140	-0.655	-0.072	-2.592	21	0.017
Pair 5	Pre tense - post tense	-0.364	0.790	0.168	-0.714	-0.014	-2.160	21	0.042
Pair 6	Pre upset - post upset	0.091	0.750	0.160	-0.242	0.424	0.568	21	0.576
Pair 7	Pre relaxed - post relaxed	-0.714	0.902	0.197	-1.125	-0.304	-3.627	20	0.002
Pair 8	Pre content - post content	-0.476	0.512	0.112	-0.709	-0.243	-4.264	20	0.000
Pair 9	Pre worried - post worried	-0.143	0.727	0.159	-0.474	0.188	-0.900	20	0.379

TABLE 6 | Postintervention descriptive statistics.

	N	Minimum	Maximum	Mean	Std. Deviation
Distraction	22	3	4	3.68	0.477
Calmer and less anxious	22	2	4	3.18	0.795
Prefer VR for future experiences	22	3	4	3.68	0.477
Recommend	22	3	4	3.86	0.351
Immersion	21	1	4	3.33	0.913
Valid N (listwise)	21				

more attention to the said environment than their own thoughts which validates Hypothesis 2. The feeling of distraction is validated through the qualitative feedback received from participants provided in **Table 1**. Participants reported the VR provided a distraction from their chemotherapy treatment and contributed to their positive experience, stating: "It engaged my mind and distracted me in a good way. The sound really enhances the experience"; "It took my mind off the itching. I thought it was great"; and "That is cool! This would be wonderful because it is a great distraction."

Upon completion of the VR session, participants were asked if they felt calmer and less anxious using the virtual reality in their chemotherapy experience than not having it at all. In **Table 6**, an average score of 3.18 indicates that participants felt calmer and less anxious than before using VR, which validates Hypothesis 3. The qualitative feedback from participants further validates the feeling of relaxation, which is associated with lower levels of anxiousness and feeling calmer. A majority of participants found the VR to be an overall positive experience. Several participants commented on the ability of the VR to induce relaxation, stating: "I felt my heartbeat slower. It was lovely"; "It is a really positive experience. I feel connected to the place. It is relaxing and makes you feel like you are there and not here. I got the chance to get out of my comfort zone and in a place that can be comforting. It is therapeutic"; "It was very calming. I felt like I was really there and could just let my mind go"; and "Good for tension and really helps me feel relaxed. I felt like I could just fall asleep."

Table 6 shows that a majority of participants preferred to have VR as part of their future experiences, with a mean score of 3.68. Participant feedback in **Table 7** validates the continued use of VR for future treatment sessions: "I feel like I'm sitting in a lounge chair. I love the sound. This would be beneficial in a private room by yourself"; and "I would like for it to cover the entire time of treatment." A mean score of 3.86 indicates that most participants would recommend having virtual reality as an option during chemotherapy treatment sessions. Open comments that validate recommending VR include: "This would also be great for pediatric oncology patients"; "It was pretty cool. It is nice to have when you don't have someone with you or don't want to watch TV"; and "I think you guys should definitely have this for cancer patients."

SUMMARY, DISCUSSION, AND LIMITATIONS

Results of this study show that although there was not a statistically significant decrease in blood pressure, we do know that 12 participants in the study had lower systolic blood pressure levels, and six participants had a lower diastolic blood pressure after their virtual reality session. The ability of virtual reality to reduce pain levels while receiving chemotherapy treatment remains inconclusive. The results of this research study

TABLE 7 | Themes and comments.

Theme	Participant quotes
Distraction	"It engaged my mind and distracted me in a good way. The sound really enhances the experience" "It took my mind off the itching. I Thought it was great."
Relaxation	"That is cool! this would be wonderful because it is a great distraction. " "I felt my heart beat slower. It was lovely." "It is a really positive experience. I Feel connected to the place. It is relaxing, and makes you feel like you are there and not here. I Got the chance to get out of my comfort zone and in a place that can be comforting. It is therapeutic." "It was very calming. I Felt like I was really there and could just let my mind go."
Enhancements	"Good for tension and really helps me feel relaxed. I Felt like I could just fall asleep." "I feel like I'm sitting in a lounge chair. I Love the sound. This would be beneficial in a private room by yourself." "I would like for it to cover the entire time of treatment."
General comments	"This would also be great for pediatric oncology patients." "It was pretty cool. It is nice to have when you don't have someone with you or don't want to watch TV." "I think you guys should definitely have this for cancer patients."

suggest that further research using a larger sample size to measure pain levels and blood pressure is warranted to validate if virtual reality impacts the two variables.

Participants indicated a significant reduction in levels of feeling tense, as well as an increase in levels of feeling calm, relaxed, and content. These findings support Stress Reduction Theory, which states that nature scenes contribute to the restoration of attention and improvement in mood (Golding et al., 2018). Results support the ability of virtual reality nature scenes to distract participants from their thoughts and surroundings, allowing for restoration of attention and improvement in cognitive functioning, which supports Attention Restoration Theory.

Previous literature has expressed concern regarding visually-induced motion sickness (VIMS), and virtual reality equipment could contribute or lead to cybersickness (Schneider et al., 2004; Lorenz et al., 2017). None of the study participants experienced unusual symptoms such as dizziness, nausea, vomiting, headache, or visual disturbances. As with any treatment, the intervention should be used with caution and safety parameters. Virtual reality should be discontinued if adverse reactions are experienced.

There are several limitations to this study. The number of participants is a limiting factor due to the difficulties in recruitment, COVID-19, and the restrictions that led to the inability to be involved in direct patient care areas. To expand the sample size for future studies, a randomized recruiting method for any potential participant within the population should be considered. The study did not include a control group with which to compare the outcomes. A control group would help to validate if VR is an effective intervention for chemotherapy patients. Levels of pain and anxiety were not measured on a longitudinal scale, so it is difficult to determine the impact of virtual reality over extended periods or multiple chemotherapy treatments. Distraction interventions are typically available as individualized experiences that generally require a quiet environment. Some of the factors that could have caused distractions for the participant during the intervention include background noises from medical equipment such as monitors, staff coming in and out of the room, televisions, and family members engaging with participants at the bedside during treatment.

A possible confounder to this study is that the principal investigator and study coordinator conducted the VR sessions and collected the outcome data from participants. Experimenter

bias could have been introduced through this process. A recommendation would be to have future sessions in which an unaffiliated person could assess the presence of this bias. Additionally, participants were aware of the study's purpose, which could have resulted in a biased effect.

DATA AVAILABILITY STATEMENT

The datasets generated and/or analyzed during the current study are not publicly available to protect patient confidentiality but are available from the corresponding author on reasonable request.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the INTEGRIS IRB. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KW was the Primary Investigator, and GS was the study coordinator for the presented research study. KW conceived of the presented idea, submitted the application for grant funding, managed all expenses, composed the protocol, created consent forms, prepared the assessment forms, performed computations, and verified the analytical methods for the research study. GS heavily investigated background literature and existing work to help formalize the theoretical foundation and provided critical feedback in the data analysis. KW and GS contributed jointly to the following; carrying out the study, sample preparation, data collection, interpretation of results, conducting the literature review, and drafting the manuscript.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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