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Virtual Reality Use for Stress Reduction and Patient Comfort During Chemotherapy

Abstract: Background. For many years virtual reality (VR) has been used to support therapy in many clinical contexts. This study aimed to investigate the effectiveness of VR as an intervention to reduce distress and increase patient comfort during chemotherapy.

Participants and Procedure. Twenty-six adult patients of the Haematology Clinic participated in the between-group design study. The experimental group used a VR application during three chemotherapy sessions, while the control group underwent treatment as usual. Participants' task in VR was to locate and destroy cancer cells using drug particles emitted from a virtual weapon. Several self-report measures were used, measuring attitudes towards the chemotherapy session, experiences during the session, items related to using visualization techniques, and questions related to evaluating the VR application.

Results. We found a significant difference between groups regarding the experience of the session. Participants in the experimental group reported more sense of control over the treatment process, higher levels of physical comfort, and relaxation. We discuss the implications of these results in various contexts, including gender differences, age, and time between chemotherapy sessions.

Conclusions. Virtual Reality applications can effectively influence the experience of the chemotherapy session positively. Its use can also affect the psychological aspects of a patient's treatment process.

Keywords: *chemotherapy, oncology patient care, stress reduction, virtual reality, psychological wellbeing*

INTRODUCTION

Virtual reality (VR) has been used for over 20 years to support therapy in many clinical contexts. VR can be defined as an immersive medium where patients wear head-mounted displays, look around, and participate in an interactive, computer-generated environment (VE). Benefits resulting from the use of VR are particularly well documented in pain therapy. A meta-analysis of 14 experimental studies (where VR was compared with a control group) showed an average pain reduction effect of d=0.9, which means that 82% of participants from the distraction group had higher pain reduction than the mean of the control group (Kenney & Milling, 2016). Multiple studies have focused on different psychological factors that influenced the effectiveness of analgesic distraction (Triberti et al., 2014).

The existing research indicates the possibility of using VR to reduce the subjectively perceived duration of a chemotherapy session (Chirico, D'Aiuto, et al., 2016; Schneider et al., 2011). In previous similar research, persons undergoing chemotherapy assessed its duration as 11 minutes shorter than in reality. However, VR did not influence the reduction of intensity concerning the side effects of chemotherapy (Schneider & Hood, 2007).

VR was used to reduce stress in oncological patients and to improve their quality of life (Espinoza et al., 2012). The effective application of VR in the psychoeducation of patients undergoing radiotherapy was described by Marquess et al. (2017). The patients showed a lower level of

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anxiety and higher satisfaction from the radiotherapy session after using VR. Similar results regarding anxiety reduction were observed after using VR distraction during chemotherapy in women with breast cancer (Schneider et al., 2003). The examined patients evaluated VR as easy to use during a chemotherapy session and did not observe any adverse side effects of this technology. All tested persons declared their willingness to use VR again during subsequent chemotherapy sessions. In another study using VR on a similar group (i.e., women with breast cancer undergoing chemotherapy), fatigue reduction after chemotherapy and stress connected with chemotherapy's side effects were also observed (Schneider et al., 2004). Similar results were obtained by Andrea Chirico et al. (2020), who found that VR is a useful intervention for improving mood states and alleviating anxiety in breast cancer patients during chemotherapy.

Reductions in stress, pain, and anxiety were also observed during VR distraction in children who were oncological patients (Gershon et al., 2003; Nilsson et al., 2009; Schneider & Workman, 1999; Wolitzky et al., 2005). Other studies have shown that even a single session of VR reduces pain and anxiety in breast cancer patients (Bani Mohammad & Ahmad, 2019). Also, a review of the research on the use of VR in oncological patients concluded that the existing data indicate the possibility of using this technology to improve the emotional condition of patients (Chirico, Lucidi, et al., 2016).

These VR applications are based on an attention distraction mechanism—they make a specific medical situation less unpleasant or a procedure less painful and stressful. This type of technique influences patients only during the session itself, not providing them with any psychological tools that may improve the quality of their life between sessions. However, other alternative ways exist to use VR in a clinical context. Shiri et al. (2013) conducted a study on a sample of children with chronic headaches. In the study, they designed a VR system to reinforce patients with pain-free virtual images once they achieved an adequate state of relaxation. Results showed that the VR system improved daily functioning and quality of life and decreased pain ratings. In another study, Botella et al. (2013) showed that fibromyalgia patients combined cognitive behavioural therapy with a VR environment that sought to develop relaxation and mindfulness skills, a significant reduction in pain and depression, and an increase in positive affect. Another VR mechanism alternative to distraction can increase the feeling of control, using VR-supported visualization. VR studies indicate active coping strategies influence pain reduction (Gutiérrez-Martínez et al., 2011; Loreto-Quijada et al., 2014). Work in this direction was conducted in the context of pain perception, and its application may also benefit the chemotherapy process.

Guided imagery is a technique in psychological work used frequently in many clinical problems, including for patients with chronic pain (Lewandowski et al., 2005) and oncological patients (King, 2010). Roffe et al. (2005) reviewed six randomized clinical trials which used guided imagery. They found that there are sufficient arguments to apply this method to improving mental comfort in oncological patients—despite the lack of convincing evidence confirming the effectiveness of the guided imagery technique in reducing the intensity of the symptoms themselves or the side effects of the therapy. However, in three analyzed trials, improvement of the emotional attitude of patients towards the chemotherapy sessions was observed.

VR can be beneficial for persons who, because of a lesser ability to create clear mental images, cannot use these techniques. VR technology was already used successfully to increase the subjective feeling of control over pain (but in contexts other than cancer pain).

A randomized crossover trial with 50 cancer patients during chemotherapy compared the effects of Virtual Reality (VR) and Guided Imagery (GI) interventions. VR intervention showed significant improvements in mood across all sub-scales compared to GI. Additionally, VR had positive effects on biophysical parameters (Ioannou et al., 2022).

Additional supportive methods of helping patients are also recommended by the American Cancer Society. For people with cancer, this is extremely important because the disease causes negative mood states, anxiety, and fatigue, and treatment often has side effects like nausea and vomiting (Chirico et al., 2020; Grassi et al., 2015; Oyama et al., 2000), which could lead to a decline in quality of life (Mills et al., 2005).

Since VR is an engaging medium affecting many senses, it may help patients create clearer scenarios in their mental imagery based on what they experienced earlier in VR. The application at the centre of this study was developed to increase the subjective feeling of control over the treatment process—thus giving the patients a virtual experience of destroying cancer cells using virtual medication/drug particles.

In our study, we attempted to test an intervention to increase the emotional impact on the treatment process and to reduce negative emotions associated with treatment. We tried to identify areas that might benefit from VR application when treating cancer patients rather than testing specific hypotheses.

METHODS

Design

Between-subjects experimental design was used in this study. People suffering from different types of cancer participated in the study (see supplement materials Table A1 and A2). The experimental group was immersed in virtual reality for 15 to 20 minutes during three chemotherapy sessions. The control group underwent three sessions of the standard chemotherapy procedure. Due to ethical reasons spontaneous use of distraction was not restricted. Patients were reading books or using their phones during chemotherapy sessions. Participants in both groups were asked to answer several questions before and after the chemotherapy sessions. The experimental and

control groups were non-concurrently recruited. The data collection for the control group was conducted immediately after the completion of data for the experimental group. We did not want to deprive the control group participants who might be interested in VR of the opportunity to use it during chemotherapy sessions. The knowledge that other patients were allowed to use VR could affect the evaluation of their experience.

Participants

The study sample comprised 26 adult patients of the Department of Hematology, Blood Cancer, and Bone Marrow Transplantation at Clinical Hospital No. 1 (blinded for the review). Participants were selected based on their chemotherapy treatment duration. Only patients who planned to have at least three additional sessions were approached. Also, only patients for whom this was not their first chemotherapy session were recruited. The experimental (VR) and control groups comprised 26 adults (M_{age}= 49.58, *SD* = 16.27), including 15 females and 11 males. The experimental (VR) group was comprised of 13 adults (M_{age}= 55.39, *SD* = 10.78), including 6 females and 7 males. The control group was also comprised of 13 adults (M_{age}= 43.77, *SD* = 19.02), including 9 females and 4 males. The age distribution shows that most participants were middle-aged (Supplementary material, Fig. S1). The supplementary material shows a list of diseases and treatments in experimental and control groups (Table S2 and S3).

Materials and Equipment

Hardware

Participants experienced the VR intervention via Samsung Galaxy S8 and Samsung Gear VR head-mounted displays (refresh rate - 60 Hz or above; field of view - 101°; resolution - 2560 × 1440 px QHD). Participants heard a stereo sound from the head-mounted displays' audio output. The head-mounted displays provided head tracking, enabling participants to look around in the virtual environment. Participants navigated the game using Samsung Gear VR controllers.

Software

Description of the Game. The game was created for this study to support patients during chemotherapy sessions. The game is not publicly available. The VR game *My Battle VR* consists of 14 levels and a virtual menu—the area where the player goes after completion of each level and can observe their progress in the game. In the menu area, there is an avatar with a schematically marked lymphatic system.

After moving to a given location (i.e., level) of the game, the player's task is to locate and destroy cancerous cells using medicine particles shot from a virtual handheld launcher. In the virtual space, there are anywhere from a dozen to several dozen healthy and cancerous cells. These cells move in various directions all over the area. In addition, new cells appear from time to time (Figure 1).

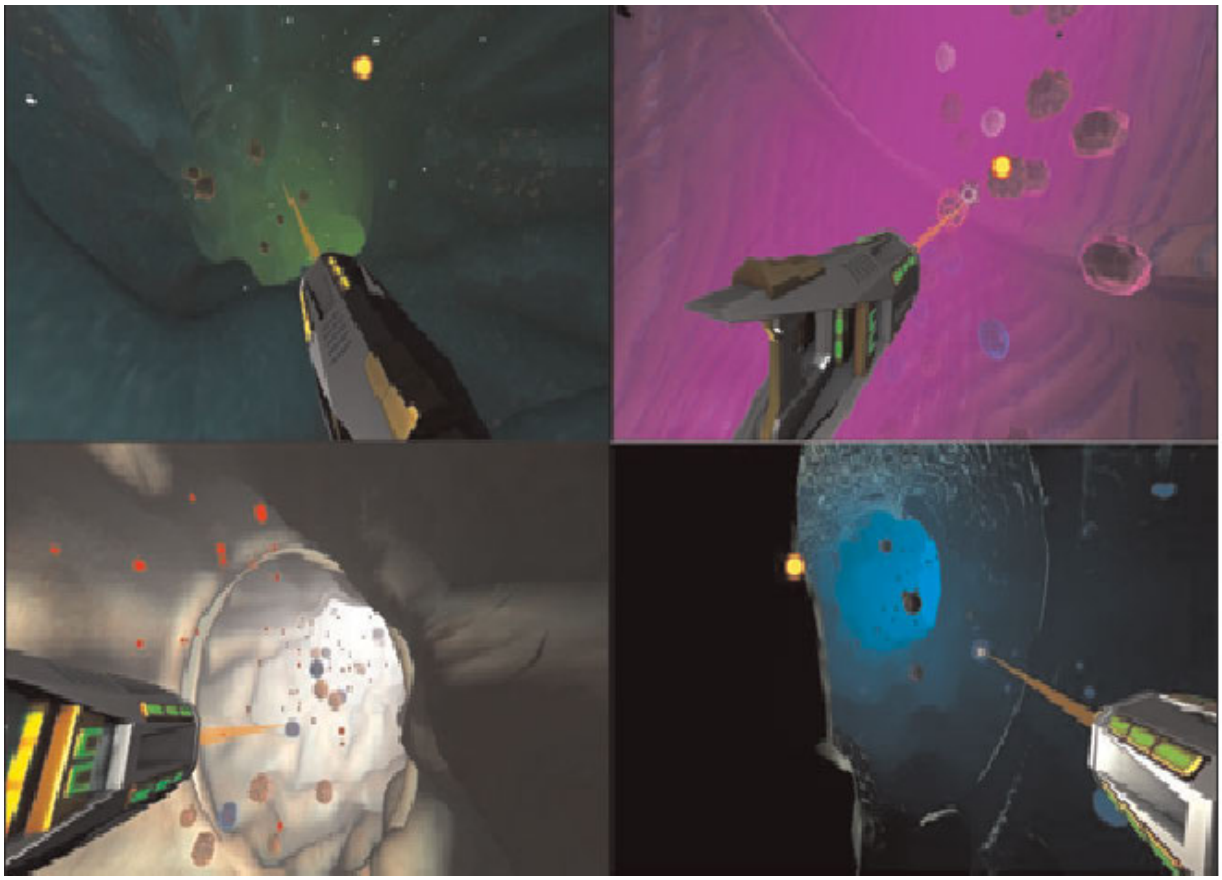

Figure 1. Screenshots of Four Sample My Battle VR Levels

Adjusting the game's difficulty level consisted of changing how precise aiming had to be to hit the target. The difficulty level is adjusted dynamically to the player's skills, increasing when the player destroys a sufficient number of cells during a defined period or decreasing if they do not reach the specified threshold. The game was designed in such a way as to occupy attention while maintaining a calm pace of the play—the purpose of which is to reduce the player's stress in connection with the conducted chemotherapy session.

Measures

Initial Questionnaire

The participants answered questions about age and gender. Additionally, the treating physician supplemented this information with the type of disease, medication used, and dosage.

Attitude Toward the Session

Participants responded to the following statement: Awareness of impending medication administration elicited (a) negative versus positive attitudes, (b) lack of versus strong motivation for treatment, and (c) anxiety versus calmness. Participants provided a score on each range using an 11-point scale from −5 to 5.

Experience of the Session

Participants answered questions about how they experienced the administration of the medication by responding to the statement: During the administration of the drug, I felt (a) nothing depends on me versus a lot depends on me, (b) physically unwell and uncomfortable versus physically well and comfortable, and (c) tense versus relaxed. Participants provided a score on each range using an 11-point scale from −5 to 5.

Sense of Influence

The next question asked participants to rate their impact during the past month on the treatment process: no impact versus very strong impact. Participants provided a score on an 11-point scale from −5 to 5.

Visualization

The next question verified whether the participants tried to visualize fighting the cancer cells in between the drug administrations. Participants were not given any specific instructions or advice to perform visualizations. First, they answered whether they had visualized fighting cancer cells since the last session (answer yes or no), and only then did we assess the frequency of these visualizations. Participants provided a score on an 11-point scale from −5 (*never*) to 5 (*several times a day*). Only extreme values of the scale had verbal labels.

Evaluation of VR Application

Additionally, participants in the experimental group answered the question of whether the VR application used (a) allows relaxation versus stimulation, (b) is boring versus interesting, and (c) whether they would like to use the application again in the future (*yes*, *no*, or *don't know*). Participants provided a score for the first two questions on an 11-point scale from −5 to 5.

Procedure

This study was conducted at the Department of Hematology, Blood Cancer and Bone Marrow Transplantation at Clinical Hospital No. 1 (blinded in Wrocław review). Before participating in the study, the participants were aware of its general purpose. They were informed that the study was about reducing stress and increasing subjective feelings of control over the treatment process during chemotherapy sessions. After consenting to the study, the participants were given detailed instructions. The study received the approval of the Bioethics Committee at the Medical University (blinded in Wrocław review) (2018; Approval No. KB – 281), and all participants provided informed consent.

Participants in the experimental group were told that, during the subsequent three drug administration sessions, they would play a VR game specially designed for them for approximately 15 minutes. Before the start of the study, the participants were familiarized with the instructions for the game and had time to learn how to use the interface. Participants could also stop the game at any time without giving a reason. Before starting the drug administration, participants completed an initial questionnaire and answered questions about their attitudes toward the session. After each drug administration session, participants responded to questions about how they felt during the session, their feeling of influence over their treatment, visualization frequency since their last visit, and questions related to the evaluation of the VR application. In the control group, participants were asked during the standard drug administration procedure to answer the same questions as those in the experimental group except for questions related to the VR application.

Statistics

Statistical data processing was performed in JASP 0.16.4.0 and Python 3.7.0 with pandas (correlations), scipy.stats (hypotheses testing), sklearn (linear regression), and pingouin (ancova) libraries. Table 1 shows the following descriptive statistics: attitude toward the session, experience of the session, sense of influence, and frequency of visualizations. Most variables did not have a normal distribution; thus, non-parametric tests (i.e., Mann–Whitney *U* test, chi-squared test, Spearman's correlation coefficient, and linear regression) were used for statistical analyses. Also, in most cases, distributions had a different shape; therefore, any significant Mann-Whitney U test results should be interpreted as differences in the distributions of the two groups and not as differences in medians.

Anonymized data is available on request.

The descriptive statistics of the variables describing the evaluation of the VR game were then calculated (see Table 2). Distribution of the variables deviated significantly from normality.

Table 1. Descriptive statistics - Attitude toward the session, Experience on the session, Agency between sessions, Frequency of visualizations

	Session 1		**Session 2**		**Session 3**	
	VR	**Non- VR**	**VR**	**Non- VR**	**VR**	**Non- VR**
Attitude toward the session						
negative-positive						
Mean	1.69	2.00	3.23	2.15	2.69	2.15
SD	3.73	2.94	2.68	2.91	3.12	2.30
Mdn	4.00	3.00	5.00	3.00	4.00	3.00
Range	-5-5	-5-5	-3-5	-5-5	-5-5	-3-5
treatment motivation						
Mean	3.92	4.17	4.00	3.92	3.69	3.58
SD	1.75	1.47	1.68	0.95	1.89	1.51
Mdn	5.00	5.00	5.00	4.00	5.00	4.00
Range	0-5	0-5	0-5	3-5	0-5	0-5
Anxiety						
Mean	2.46	1.92	3.69	2.85	3.39	1.85
SD	3.10	3.25	1.97	2.76	2.43	3.11
Mdn	4.00	3.00	4.00	4.00	5.00	3.00
Range	-4-5	-4-5	-2-5	-3-5	-2-5	-5-5
Experience of the session						
Agency						
Mean	1.69	2.23	3.39	3.00	3.69	2.39
SD	2.29	2.20	1.76	1.58	1.60	1.94
Mdn	2.00	3.00	4.00	3.00	4.00	3.00
Range	-3-4	-3-5	0-5	0-5	0-5	-1-5
physical comfort						
Mean	3.54	1.54	3.08	2.54	3.39	2.15
SD	1.61	2.93	2.87	2.54	2.33	1.82
Mdn	4.00	3.00	4.00	3.00	5.00	3.00
Range	0-5	-5-5	-5-5	-3-5	-2-5	-1-5
Relaxation						
Mean	3.08	2.00	3.92	2.08	3.46	1.15
SD	2.60	2.35	1.44	2.99	2.40	2.88
Mdn	4.00	2.00	4.00	3.00	5.00	2.00
Range	-4-5	-3-5	0-5	-5-5	-2-5	-5-5
Agency between sessions						
Mean	2.69	2.85	3.39	2.92	3.54	2.92
SD	1.70	1.63	1.81	1.61	1.81	1.66
Mdn	3.00	3.00	4.00	3.00	4.00	3.00
Range	0-5	-1-5	-1-5	0-5	0-5	0-5
Frequency of visualizations						
Mean	1.10	2.17	2.50	2.50	2.20	3.00
SD	2.77	1.72	2.54	1.52	2.70	1.41
Mdn	2.00	2.00	3.50	2.00	3.00	3.00
Range	-5-4	0-5	-4-5	1-5	-4-5	1-5

Table 2. Descriptive statistics – Evaluation of VR application

	Session 1	Session 2	Session 3
	boring vs. interesting		
Mean	3.85	4.08	3.92
SD	1.14	1.04	1.38
Mdn	4.00	4.00	4.00
Range	2-5	2-5	1-5
	stimulating vs. relaxing		
Mean	3.00	3.62	2.62
SD	2.61	1.19	3.23
Mdn	4.00	4.00	4.00
Range	-5-5	2-5	-5-5

RESULTS

Attitude Toward the Session

First, it was analyzed whether participants in the experimental and control groups differed in their attitudes toward the sessions. Participants answered questions regarding negative versus positive attitudes toward the session, lack of versus strong motivation for treatment, and anxiety versus calmness experienced at any given time. In the analysis, the 11-point response scale ranged from −5 to 5, where −5 represented the lowest extreme and five the highest extreme response.

The results revealed that there were no statistically significant differences between the experimental group and the control group in any of the studied variables in any of the three sessions of drug administration: the negative versus positive attitude toward Session 1 ($U = 83$, $p = .96$), toward Session 2 ($U = 59$, $p = .19$), and Session 3 ($U = 63$, $p = .27$); treatment motivation before Session 1 ($U = 78.5$, $p=1$), before Session 2 ($U = 68$, $p = .374$), and before Session 3 ($U = 67$, $p = .548$); anxiety before Session 1 ($U = 73.5$, $p = .58$), before Session 2 ($U = 67$, $p = .36$), and before Session 3 ($U = 55.5$, $p = .13$).

Experience of the Session

The next step of the statistical analysis was to examine whether participants in the experimental and control groups differed in how they felt during the medication administration sessions. Participants rated the level of agency, physical comfort, and relaxation. In the analysis, the 11-point response scale ranged from −5 to 5, where −5 represented the lowest extreme, and 5 described the highest extreme response.

First, the level of the agency was compared. Only in the third session, the difference in agency between the experimental and control group was observed; however, it was only marginally significant (U=47.0, p = .05; see Table 3).

Table 3. Mann-Whitney U Test for Agency, Physical Comfort and Relaxation in experimental and control group

		Session1	Session2	Session3
Agency				
U		94.50	69.50	47.00
p		0.62	0.45	0.052
Effect size		0.12	-0.18	-0.44
95% CI for Rank-Biserial	Lower	-0.32	-0.56	-0.73
Correlation	Upper	0.52	0.27	-0.03
Physical Comfort				
U		44.50	66.50	47.50
p		0.04*	0.36	0.055
Effect size		-0.47	-0.21	-0.44
95% CI for Rank-Biserial	Lower	-0.75	-0.58	-0.73
Correlation	Upper	0.06	0.23	-0.02
Relaxation				
U		56.50	46.00	39.50
p		0.15	0.04*	0.02*
Effect size		-0.33	-0.46	-0.53
95% CI for Rank-Biserial	Lower	-0.66	-0.74	-0.78
Correlation	Upper	0.11	-0.04	-0.14

*p < 0.05

Another indicator of the experience of the session was the rating of physical comfort. Analyses showed a clear difference between groups only during the first chemotherapy session (U=44.5, p<.05). The strength of the effect of the VR game on the comfort felt while taking the drug was medium. A similar difference was also found during the third session, but this result was not statistically significant (U=47.5, p=.06; see Table 3).

The final indicator of the session experience is the level of relaxation. Statistical analysis showed an apparent effect of the VR game on feeling more relaxed in subsequent chemotherapy sessions. The Mann–Whitney U test showed a significantly higher sense of relaxation in the experimental group in the second (U=46; p<0.05) and third (U=39.5; p<0.05) measurements. The strength of the effect of the VR game on mood during the session was medium during the second measurement and high during the third measurement (Table 3).

Agency Between Sessions

The further statistical analysis examined whether there was a difference between groups in their agency in the last month. Differences in individual measures were found to be statistically insignificant (Session 1: U = 0.86, p = .96; Session 2: U = 66.5, p = .36; Session 3: U = 64.5, p = .30).

Visualization

The final step in comparing groups was whether the participants tried to visualize fighting off the cancer cells during the time between drug administrations. A chi-squared test showed that the difference at the second chemotherapy session between groups was statistically significant, with significantly more participants in the experimental group using visualization than those in the control group (χ^2=4.29,df=1,p= .04; see Supplementary material, Fig. S4).

Analyzing the level of increments of the studied variables between sessions, statistically significant differences were revealed in the frequency of visualization between women in the experimental group and women in the control group (Sessions 1–2: U = 14, p = .05; Sessions 2–3: U = 25, p = .41; Sessions 1–3: U = 12, p = .03). Despite the non-significant increments in the variables between Sessions 2 and 3, the increments counted from Session 1 to 2 and overall from Session 1 to 3 are significant. That is, the frequency of visualizations significantly increased in the group of women using VR, although the effect is only apparent when comparing the distributions for each group. It should be noted that the variable's value is ignored when interpreting the increments. Thus, the result means that the tendency of women in the experimental group to increase the frequency of visualization was significantly higher than that of the women in the control group. Distributions of in-between sessions increase of frequency of visualizations by gender and study group can be found in the supplement (Supplementary material, Fig. S5).

Gender Differences

In further statistical analysis, we tested whether there were gender differences in the effectiveness of VR interaction during chemotherapy sessions. The results revealed that male participants' experience of the session in the experimental group was different from those in the control group. Statistically significant differences were observed comparing the variables of physical comfort (Session 3: U = 4, p = .03) and relaxation (Session 2: U = 4, p =.02; Session 3: U = 3.5, p = .02). Men experienced greater physical comfort (during the 3rd session) and greater relaxation (during the 2nd and 3rd sessions) in the VR group compared to the control group.

Similarly, the variable frequency of visualizations between sessions revealed a difference in males between the experimental and control groups. Men who played the VR game were more likely to visualize fighting cancer cells between Sessions 1 and 2 (U = 5, p = .05). Distributions of physical comfort, relaxation and frequency of visualizations by gender and study group during three chemotherapy sessions can be found in the supplement (Supplementary material, Fig. S6, S7 and S8). Comparison of all examined variables between sessions in both study groups and for men and women can be found in the supplementary material.

Correlation with age

The variable that could have influenced the relationships studied was age. Correlations between age, study group, and measured variables were observed, especially during Session 2. This is the session during which the strongest correlations between all studied variables were observed. The direction and significance of differences between groups were tested using linear regression. When examining the attitude towards Session 2, the research group revealed no statistically significant differences, while age proved to be a significant variable. It turned out that, regardless of group membership, the older the participants were, the more positive their attitude towards the session was (R^2=.24, p=.01) and the more calmness they experienced (R^2=.22, p=.02) (Supplementary material, Fig. S11).

Similar results were revealed when comparing variables examining the experience of Session 2. The level of the relaxation variable did not differ between groups, while age proved to be a variable that significantly influenced it. The situation is similar for the physical comfort variable, although the p-value is slightly above the statistical significance threshold (p=.056). Both variables revealed that, regardless of the group, the older the participants were, the more relaxed they were (R^2=.24, p=.01) and the more physical comfort they experienced during Session 2 (R^2=.16, p=.05) (Supplementary material, Fig. S12).

Evaluation of VR Application

The final stage of statistical analysis was to evaluate the VR application. The participants from the experimental group (N=13) rated the application on one 11-point scale

ranging from −5 (*stimulating*) to 5 (*allows relaxation*) and another 11-point scale ranging from −5 (*boring*) to 5 (*interesting*). At the end of the session, the experimental group participants answered: "Would you like to use this application again in the future?" There were three possible answers: *yes*, *no*, and *don't know*.

From the first measurement, participants indicated that the game was more likely to enable relaxation than stimulation. The average scores during the three sessions ranged from 2.62 to 3.62, where 5 meant complete relaxation. It is worth noting that one person during Session 1 and two during Session 3 found the app more stimulating than relaxing.

The results of evaluating the VR game on the boring–interesting scale were similar. The average scores during the three sessions were between 3.85 and 4.08, indicating that it aroused interest and curiosity among the participants (see Table 2). Of those who played the VR game, 84.6% wanted to continue using the application. After three sessions with the VR game, the score remained the same, indicating that the game met patients' needs during chemotherapy sessions.

DISCUSSION

This study aimed to investigate the possible uses of VR technology in supporting cancer patient care. The study analyzed both attitudes toward the drug administration session and experiences during the session and patient behaviours between drug administration sessions, such as visualizing cancer cell fighting.

The results revealed no differences in attitude toward the session between the experimental group and the control group. Participants did not differ in their negative versus positive attitudes, motivation for treatment, or anxiety in any of the three drug administration sessions. Differences in attitude alone were expected in Sessions 2 and 3, following prior experience with the VR game. However, due to the small sample size, this should not be interpreted as non-existence of such differences. The lack of observed differences in attitude could be explained by the fact that participants did not have enough experience with the game. Another reason could be the ceiling effect—the scores of the control participants in the session attitude questions were high and very high; hence, there was only a limited possibility of a further increase in these values.

However, the groups differed in the experience of sessions. During some sessions, participants in the experimental group felt more in control over the treatment process, experienced more physical comfort, and felt more relaxed than patients in the control group. These differences did not reach statistically significant values in every session, but they always indicated a more positive experience of the drug administration session in the experimental group. The results show the effectiveness potential of the VR application in making the drug administration session more comfortable for patients. The results also suggest that the experience of visualizing how cancer cells are destroyed during the VR game is extended to the time between sessions and results, in some cases in the more frequent use of the visualization technique. The results from this study are consistent with previous studies that have argued that VR intervention during treatment can reduce anxiety and stress while increasing satisfaction and improving the quality of life for people with cancer (Chirico et al., 2020; Chirico, Lucidi, et al., 2016; Espinoza et al., 2012; Marquess et al., 2017; Schneider et al., 2003).

Next, we discuss the use of visualization techniques. There was a between-group difference, with significantly more patients in the experimental group using visualization between the 1st and 2nd session than those in the control group. This result suggests that the developed VR intervention may be an effective support technique during cancer treatment. Previously published research indicated that the mental state of cancer patients is correlated with quality of life and the level of stress experienced. One of the most beneficial attitudes is the "fighting spirit" while one of the most maladaptive is helplessness/hopelessness (Akechi et al., 1998). However, the results indicate that between the 2nd and 3rd sessions, the groups did not differ in the use of visualization. It is possible that the novelty of VR was partly responsible for the effect, and thus it diminishes with repeated exposure. In our study, the feeling of agency differed between groups only at the time of the VR intervention and not at the last month's assessment. This may be because there were too few sessions, and the intervals between sessions were not fully controlled.

We observed different patterns of results in men and women. Men in the experimental group showed higher levels of physical comfort and relaxation than men in the control group. However, those differences were not significant in each session of drug administration. Additionally, men who played the VR game were more likely to visualize fighting cancer cells than those in the control group. The results indicate that VR application has a more positive effect on selected aspects of the session experience for men than for women. However, it is worth noting that the frequency of visualization in the group of women using VR significantly increased from session to session. The lack of such increases in male participants may be because, at the baseline, they used visualization more frequently than female participants. As a result, it was easier for the women to increase their visualization frequency after experiencing a VR game than it was for the men, who had already started with a high visualization frequency.

The results may be because the use of VR technology to combat illness is closer to the interests of male patients. Also, men may have less anxiety towards VR technology. Previous research has shown that males have less computer anxiety than females (Broos, 2005). On the other hand, women prefer relationships; perhaps peer-led visualizations would be even more effective for them. When analyzing the results, it should be taken into account that the number of participants in both groups was small, and the results obtained should form the basis for further research rather than drawing definite conclusions.

It is also worth noting that the strongest correlations between the study variables occurred during Session 2. These correlations were also more robust in the experimental group than in the control group—the correlations in Session 2 bound many variables together. We have followed the reasoning behind the factor analysis to give a rationale for the sudden increase of magnitudes of correlations (Fabrigar & Wegener, 2011). Factor analysis aims to discover a few latent factors that could "explain" the values of the entire set of measured variables. It assumes that a solid mutual correlation of a subset of variables manifests a common factor affecting them. We hypothesize that the explanatory factor accounting for a network of correlations appearing in the second session is the group assignment (VR or non-VR). There are two observations to support our claim. First, the network of correlations appeared only in the experimental group. Secondly, time gaps between Sessions 1 and 2 were significantly smaller on average than time gaps between Sessions 2 and 3, indicating that the effect of forgetting comes into play by weakening the influence of the VR sessions on correlations. This study cannot address this hypothesis alone because it requires a specific experiment design and controlling for the time gap variable. Still, it may be possible to grasp it rigorously at the meta-analysis level.

The last variable significantly influenced the attitude towards and experience of the drug administration session was the patient's age. It turned out that, regardless of group membership, the older the participants were, the more positive and relaxed they were toward the session. Similarly, when it came to experiencing the drug administration session, the older the participants were, the more relaxed they were and the more physical comfort they experienced. However, these results did not reach significance for all treatment sessions.

In part, the correlation with age may be due to the study groups' age distribution. The mean age in the experimental group was slightly higher ($M = 49.58$) than in the control group ($M = 43.77$). Moreover, the age distribution in the groups was different. In the control group, young people (20–29 years old) were the most numerous subgroup; in the experimental group, older people (over 50 years old) were the most numerous. The fact that the older participants were VR players may suggest that age is not the important variable here, but the VR intervention during the drug delivery session. However, our study does not provide a definitive conclusion on this issue, and further research is needed.

STUDY LIMITATIONS

The main limitation of the study conducted is the small number of participants. The limited group size does not allow us to confirm with certainty the results suggesting gender differences in response to VR gaming during chemotherapy sessions. The participants differed significantly in age in both groups, which may have influenced the results. The study also lacked a control group, with subjects experiencing regular VR rather than therapeutic VR. The addition of such a group would have made it possible to determine whether a mechanism related to the novelty effect and curiosity about the new technology is at work in the groups using VR, or whether the specially prepared application has a stress-reducing effect during chemotherapy sessions. Another limitation is the lack of randomization during the participants' recruitment. Furthermore, another group could be added – testing if VR content specific to cancer treatment is more effective than any other "pure distraction" VR content. It is also worthwhile in future studies to increase the number of chemotherapy sessions analyzed and to control the time lapse between them.

CONCLUSIONS

To summarize the results, it is worth noting that this study showed that the designed VR game greatly influenced the experience during chemotherapy sessions and increased the subjective sense of control over the treatment process. However, due to the exploratory nature of this study and the small sample size, the results reported here need to be interpreted with caution and used to formulate hypotheses for further confirmatory studies. During some sessions, individuals who used the VR application felt more relaxed and experienced greater physical comfort. In addition, they made more frequent attempts to visualize fighting cancer cells in between sessions. It also appeared that the VR application had a more positive impact on men's experiences than women's. It is worth noting that the attitude of patients toward the VR game was positive; they rated the game as interesting and generally enabling relaxation. The developed tool is simple and does not require special competence to use, which, on the one hand, makes it possible to conduct further studies with its use. On the other hand, this indicates its applicability and possible wide use in treating cancer patients.

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SUPPLEMENTARY MATERIAL

Table S1. List of Diseases and Treatments in Experimental Group

Disease	ICD-10	Medication	Dosage
Experimental group			
Chronic lymphocytic leukemia (CLL)	C91.1	RFC (MabThera,Fludarabine, Endoxan)	Rituximab 740mg, Darabin49mg, Endoxan 492mg
Multiple myeloma (MM)	C90.0	Darzalex,Bortezomib	Daratumumab 1280mg Bortezomib 2,6mg
Primary immunodeficiencies	D80	Immunoglobulin	Immunoglobulin 30g
Diffuse large B-cell lymphoma (DLBCL)	C83.3	R-CHOP (Rituximab,Doxorubicin, Endoxan, Vincristine, Encorton)	Rituximab 630mg, Darabin 84mg, Endoxan 1261mg, Vincristine2mg
Chronic lymphocytic leukemia (CLL)	C91.1	Fludarabine, Endoxan	Fludarabine 54,41mg, Endoxan 544,11mg
Multiple myeloma (MM)	C90.0	Darzalex, Bortezomib	Daratumumab 1072mg Bortezomib 2,21mg
Multiple myeloma (MM)	C90.0	Kyprolis	Carfilzomib 60mg
Multiple myeloma (MM)	C90.0	Darzalex, Bortezomib	Daratumumab 1648mg Bortezomib 2,9mg
Hypogamma-globulinaemia	D80.1	Immunoglobulin	Immunoglobulin 2 x 10g
Hodgkin lymphoma (HL)	C81	ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine)	Doxorubicin 46mg,Vinblastine 10mg, Detimedac 697mg,Bleomycin 15000mg
Multiple myeloma (MM)	C90.0	Darzalex, Bortezomib	Daratumumab 1700mg Bortezomib 2,9mg
Peripheral T-cell lymphoma, not classified (PTCL)	C84.4	CHOEP (CHOP + Etoposide)	Doxorubicin 86mg, Endoxan 1297mg, Vincristine2mg,Etoposide 173mg, Encorton 1000mg
Chronic lymphocytic leukemia (CLL)	C91.1	RFC (MabThera,Fludarabine, Endoxan)	Rituximab 1000mg,Endoxan 500mg, Fludarabine 50mg/d
Acute lymphoblastic leukaemia (ALL)	C91.0	RFC (MabThera, Fludarabine, Endoxan)	Rituximab 621mg,Endoxan 500mg, Fludarabine 50mg/d

Table S2. List of Diseases and Treatments in Control Group

Disease	ICD-10	Medication	Dosage
		Control group	
Nodal marginal zone lymphoma (NMZL)	C83.0	R-CHOP (Rituximab, Doxorubicin, Endoxan, Vincristine, Encorton)	Rituximab 740mg, Doxorubicin 98,7mg, Endoxan 1481mg, Vincristine2mg, Encorton 1000mg
Follicular Lymphoma (FL)	C82	R-CVP	Rituximab 1000mg ,Endoxan 1400mg, Vincristine2mg, Encorton 100mg
Hodgkin lymphoma (HL)	C81	BGD (Bendamustine, Gemcitabine, Dexamethasone)	Bendamustine166mg, Gemcitabine 1478mg, Dexamethasone 40mg
Hodgkin lymphoma (HL)	C81	ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine)	Doxorubicin 40mg, Vinblastine 10mg, Detimedac 604mg, Bleomycin 15000mg
Hodgkin lymphoma (HL)	C81	ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine)	Doxorubicin 38mg, Vinblastine 9mg, Detimedac 570mg,Bleomycin 15000mg
Hodgkin lymphoma (HL)	C81	ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine)	Doxorubicin 42mg, Vinblastine 10mg, Detimedac 641mg,Bleomycin 15000mg
Hodgkin lymphoma (HL)	C81	ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine)	Doxorubicin 39mg, Vinblastine 10mg, Detimedac 585mg,Bleomycin 15000mg
Hodgkin lymphoma (HL)	C81	ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine)	Doxorubicin 41mg, Vinblastine 10mg, Detimedac 556mg,Bleomycin 15000mg
Peripheral T-cell lymphoma, not classified (PTCL)	C84.4	Veperiol, Doxorubicin, Vincristine, Endoxan	Endoxan 1190mg,Vincristine2mg, Doxorubicin 79mg,Etoposide 159mg
Multiple myeloma (MM)	C90.0	Carfilzomib	Carfilzomib54 mg
Myelodysplastic syndromes (MDS)	D46	Vidaza	Azacitidine78mg
Hodgkin lymphoma (HL)	C81	ABVD (Doxorubicin, Bleomycin, Vinblastine, Dacarbazine)	Doxorubicin 47mg, Vinblastine 10mg, Detimedac 709mg, Bleomycin 15000mg

Figure S3. Age Distribution in the Experimental and Control Groups and Among Females and Males

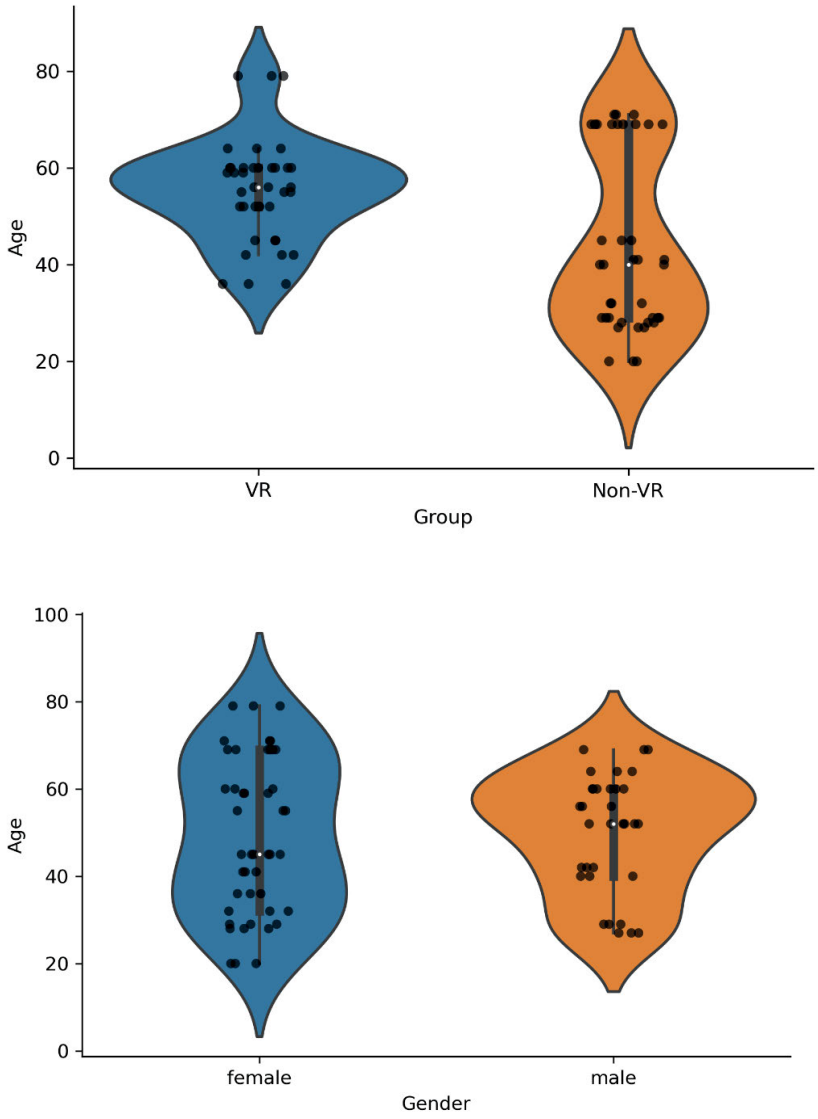


Figure S4. The Use of Visualization Fighting Off Cancer Cells During the Time Between Chemotherapy Sessions – Comparison Between Groups

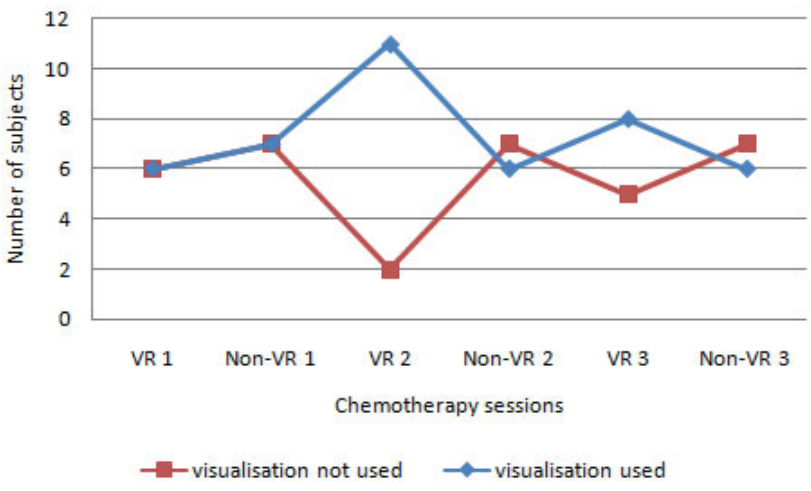


Figure S5. Distributions of In-Between Sessions Increase of Frequency of Visualizations by Gender and Study Group

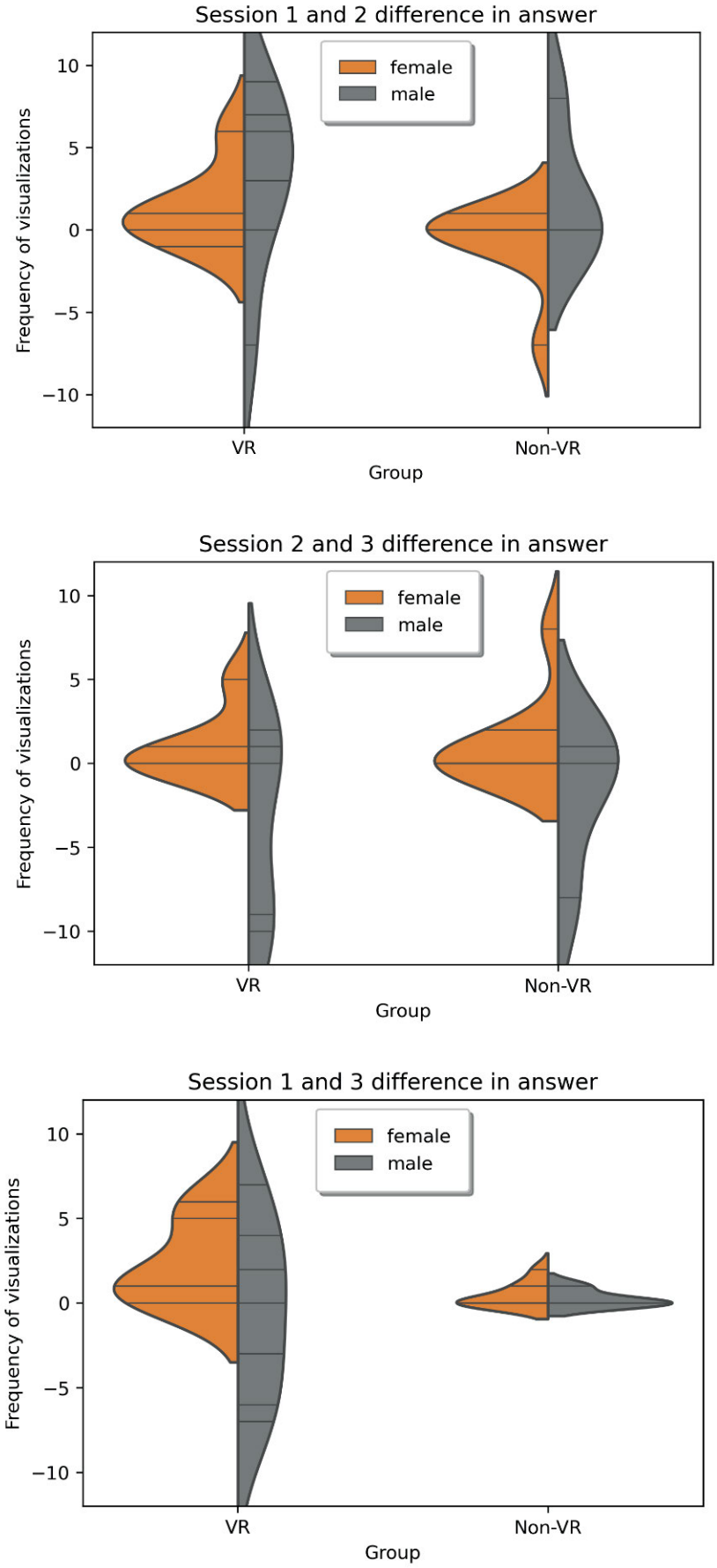


Figure S6. Distributions of Physical Comfort by Gender and Study Group During Three Chemotherapy Sessions

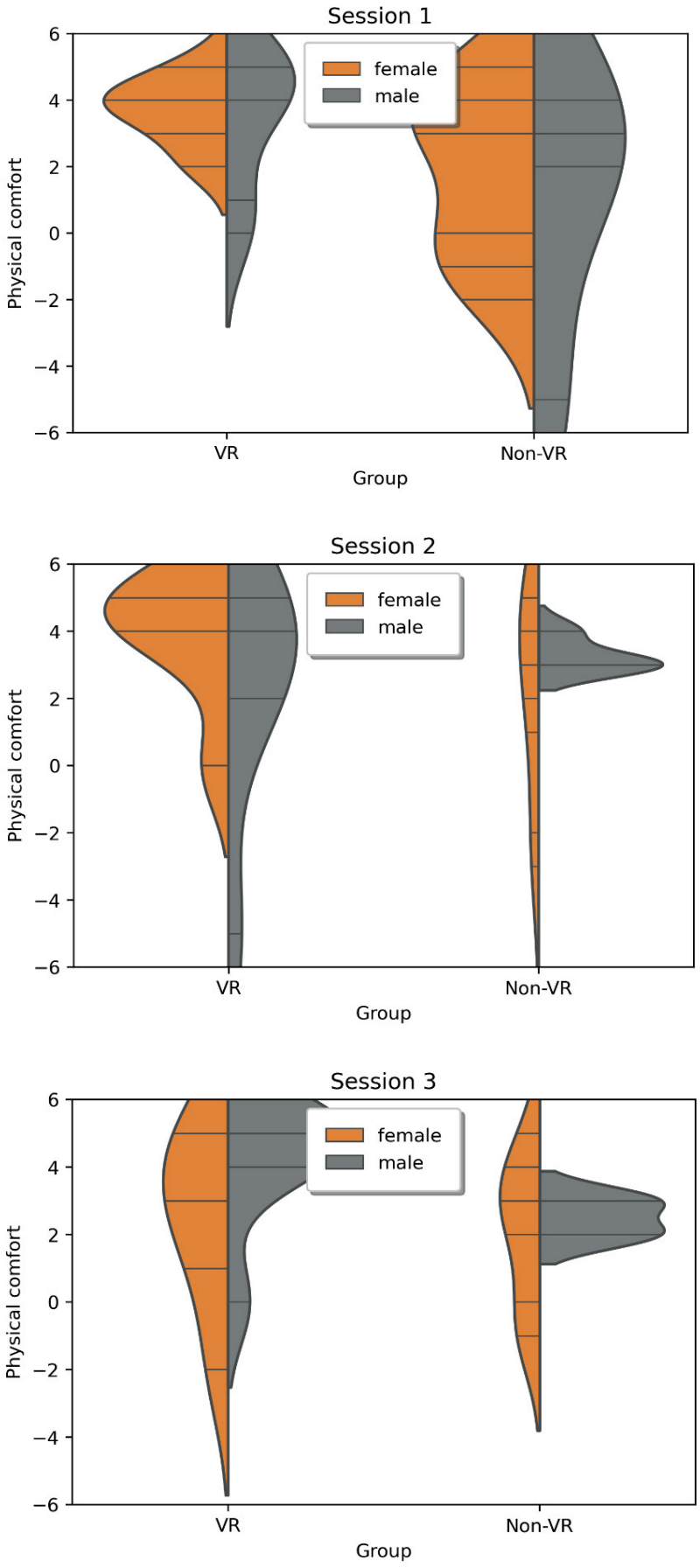


Figure S7. Distributions of Relaxation by Gender and Study Group During Three Chemotherapy Sessions

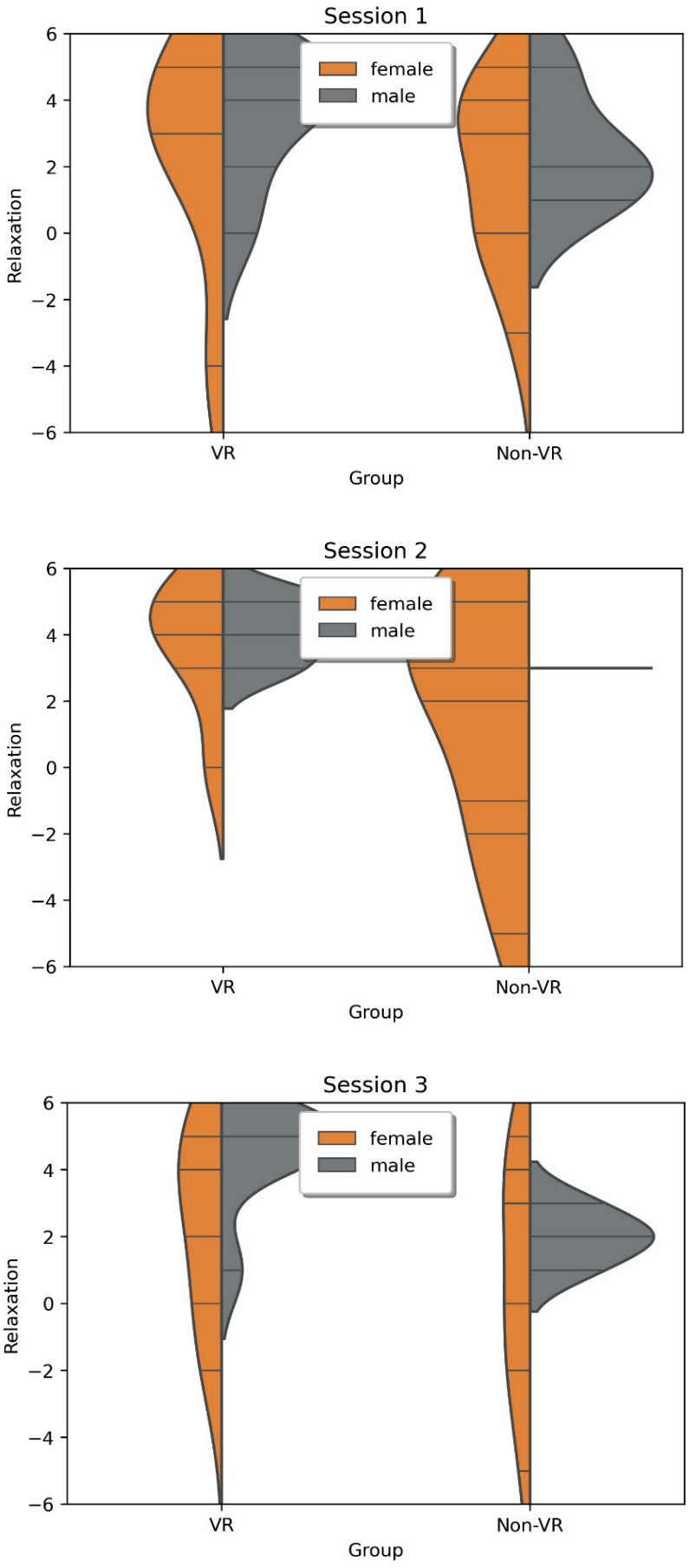
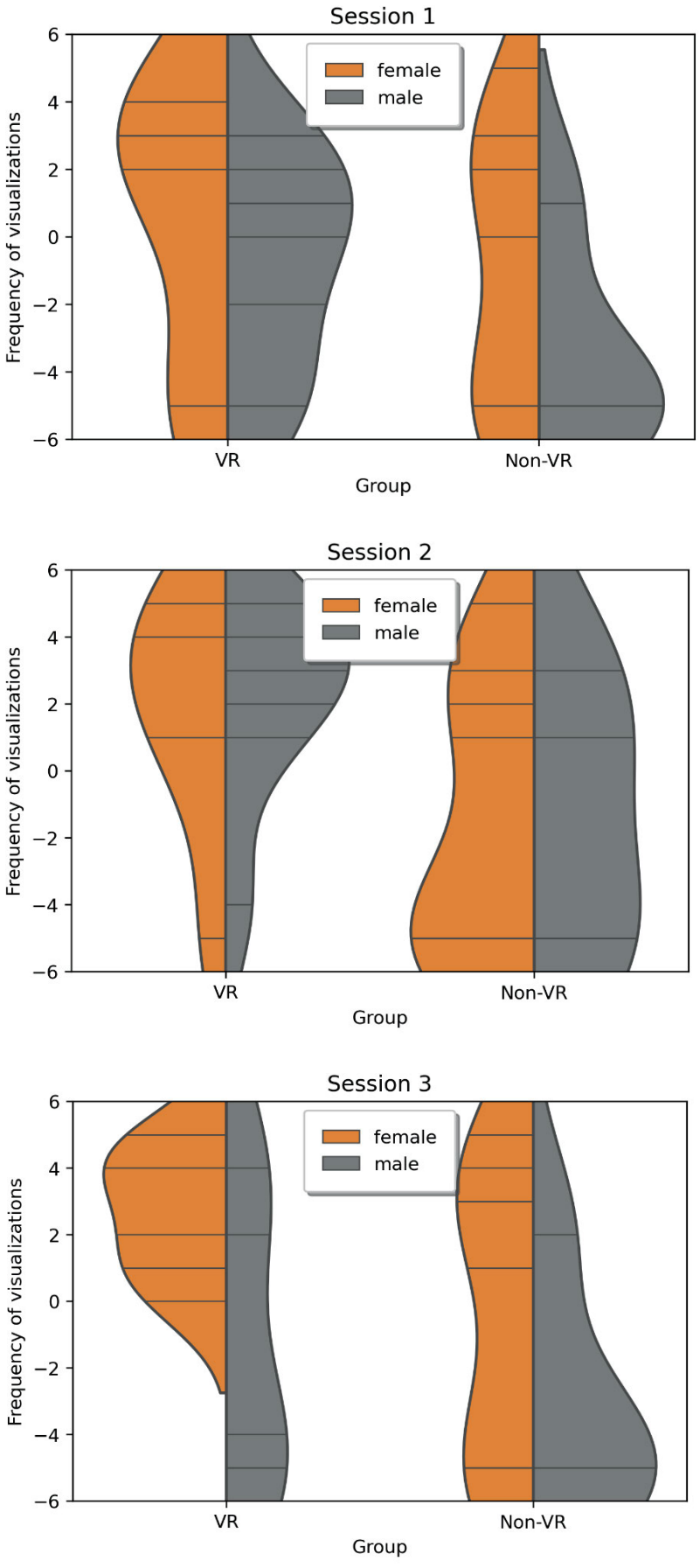


Figure S8. Distributions of Frequency of Visualizations by Gender and Study Group During Three Chemotherapy Sessions



Comparison of All Examined Variables Between Sessions in Both Study Groups and for Men and Women.

The results indicate that VR application had a more positive effect on selected aspects of experience of the session for men than for women. These results were confirmed by the analysis in which the differences of all examined variables were compared between Session 1 and Session 2 with and without the game and for men and women.

The aggregated difference between the measurements of all variables performed on i-th participant after Session 1 and Session 2 (see Fig. S9) is evaluated according to the formula:

$$d_i^{(1-2)} = 10 \cdot \frac{1}{M} \sum_{j=1}^{M} \left| x_{ij}^{(1)} - x_{ij}^{(2)} \right|$$

where $x_{ij}^{(1)}$ and $x_{ij}^{(2)}$ stand for the measurement of j-th variable performed on i-th participant during Sessions 1 and 2, respectively. Binary variables (yes/no) are encoded as 10 / 0 to unify the scale of all variables, most of which take values in the interval <−5, 5>. The sum of absolute differences is averaged out and multiplied by 10 so that the outcome $d_i^{(1-2)}$ could be interpreted as a percentage. For instance, the value $d_i^{(1-2)} = 100$ would indicate that all variables have extremely different values. Therefore, $d_i^{(1-2)}$ may be considered a measure of the overall difference between answers given by i-thpartici-pant during Sessions 1 and 2. The formula $d_i^{(2-3)}$ is analogous to the $d_i^{(1-2)}$, except that it concerns Sessions 2 and 3.

A similar analysis was conducted for the difference between all study variables between Sessions 2 and 3. The male distributions are very close to the distributions for the responses with the VR game, while the female distributions are very close to the distributions without the VR game. The effect holds regardless of session number. This means that the effects of gender and game may be difficult to distinguish in other statistical studies (see Fig. S9). This is an intentional procedure that manages to produce a reliable estimate of the distribution across the four groups with a relatively small number of participants. The results show that, with a large number of participants, it is worth considering dividing them into four separate groups: (a) female gamers, (b) male gamers, (c) female non-gamers, and (d) male non-gamers. Then independent tests can be used to verify the significance of between-group differences.

These results may have been caused by the difference in the time gap between Sessions 1 and 2 and between Sessions 2 and 3 in men and women. More time elapsed between treatment sessions in women (*Mdn* = 14 days, *M*= 13.2 days) than in men (*Mdn* = 6 days, *M* = 6.7 days). Time gap distribution among females and males in second and third session can be found in the supplement (Fig. S10).

Figure S9. Comparison of All Examined Variables Between Sessions in Both Study Groups and for Men and Women

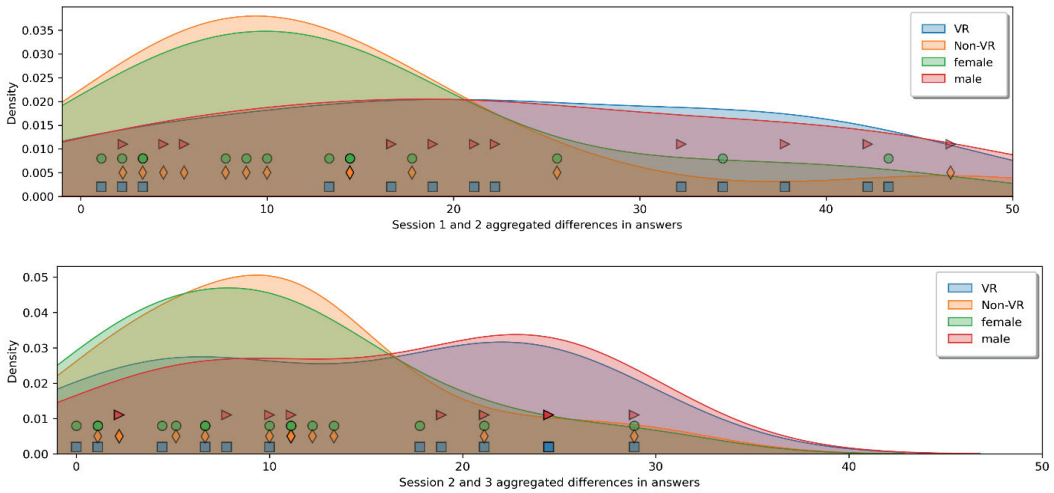


Figure S10. Time Gap Distribution Among Females and Males in Second and Third Session

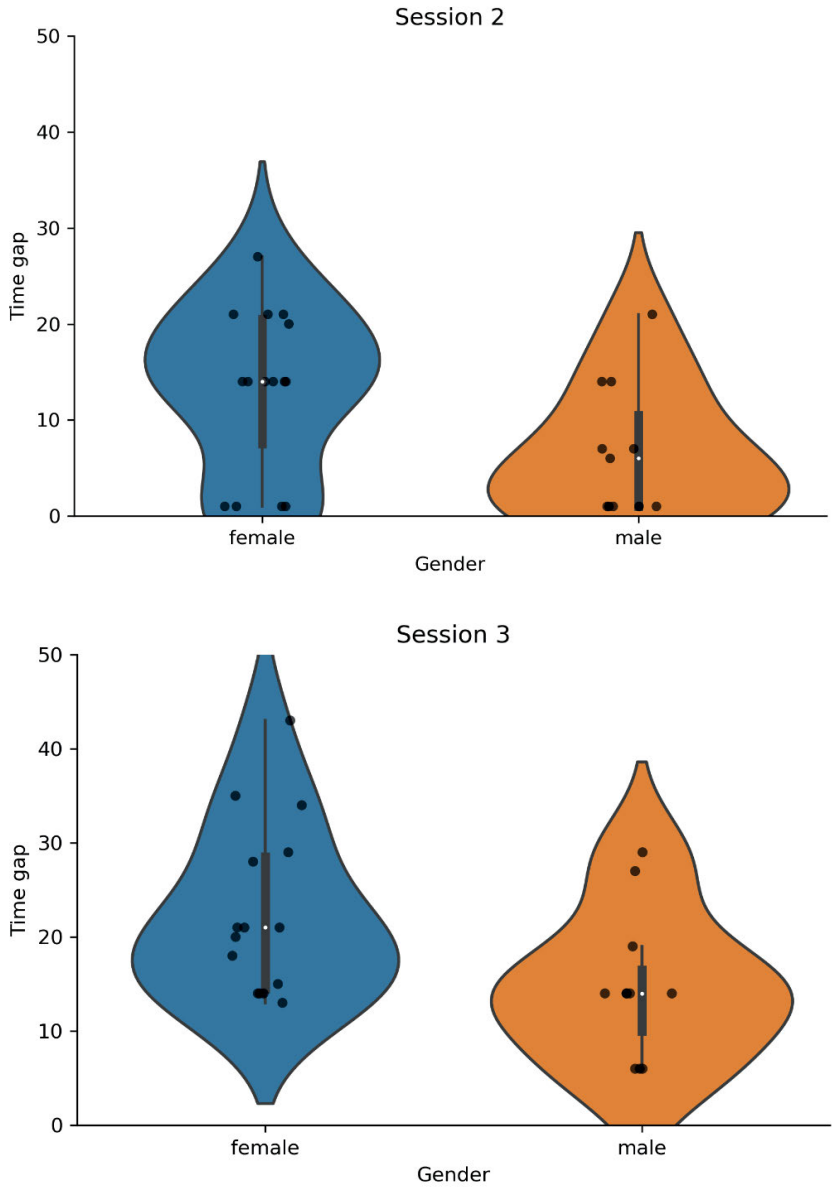


Figure S11. Linear Regression Analysis of Attitude Toward the Second Chemotherapy Session and Age in Both Study Groups.

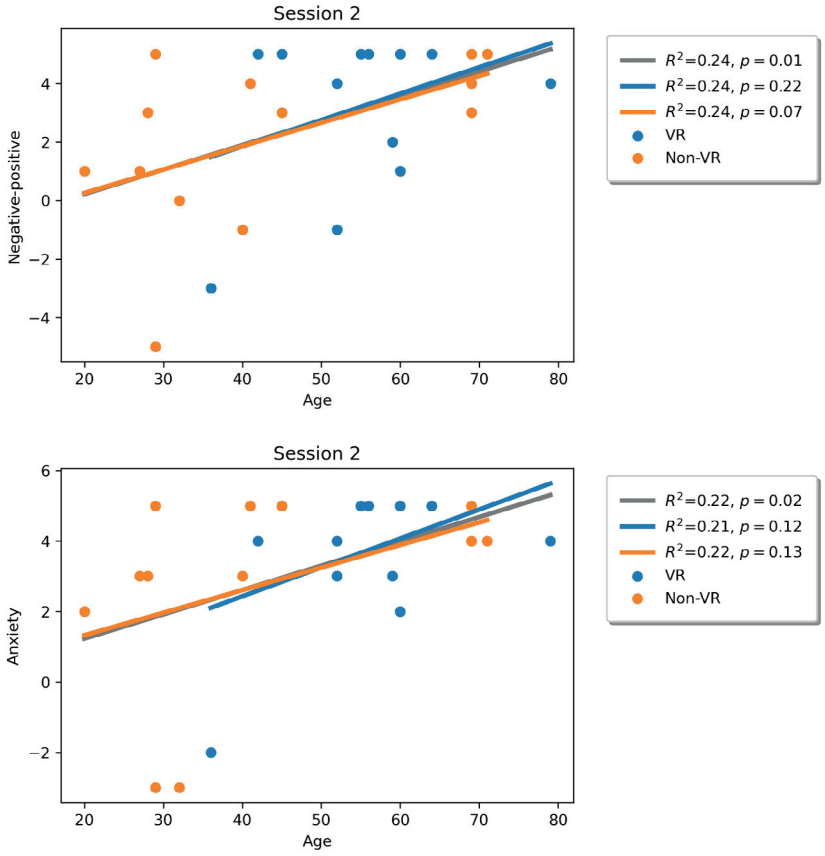
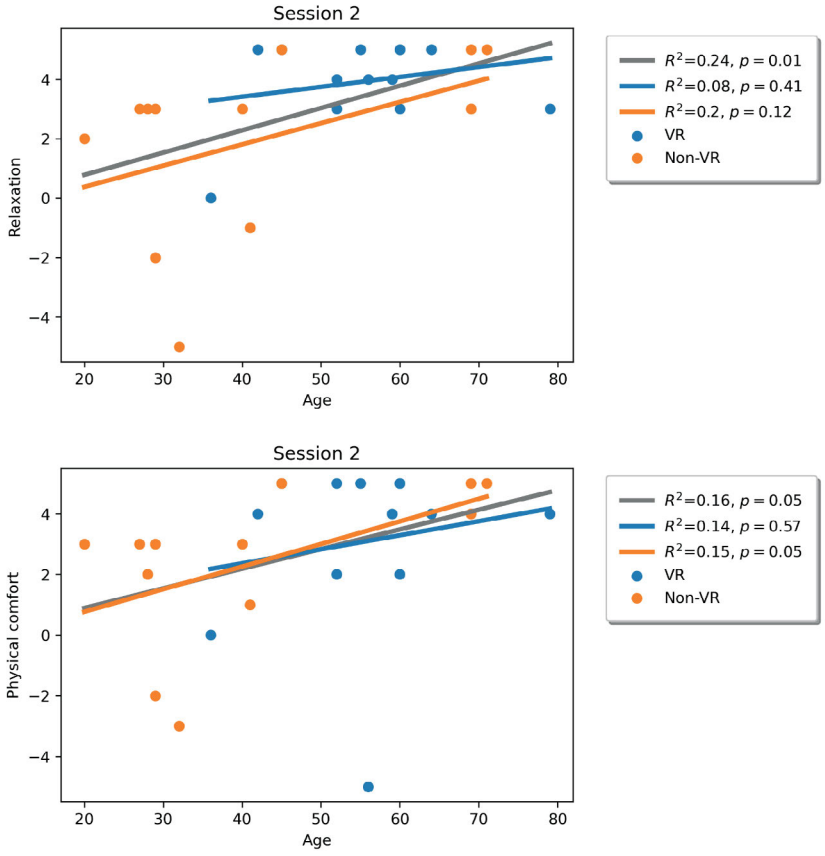


Figure S12. Linear Regression Analysis of Experience of the Second Chemotherapy Session and Age in Both Study Groups



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