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A Novel Palliative Care Approach Using Virtual Reality for Improving Various Symptoms of Terminal Cancer Patients: A Preliminary Prospective, Multicenter Study

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Abstract

Background: Some terminal cancer patients wish to ''go to a memorable place'' or ''return home.'' However, owing to various symptom burdens and physical dysfunction, these wishes are difficult for them to realize.
Objective: The aim of the study is to verify whether simulated travel using virtual reality (VR travel) is efficacious in improving symptoms in terminal cancer patients.
Design: This is a prospective, multicenter, single-arm study.
Setting/Subjects: Twenty participants with terminal cancer were recruited from two palliative care wards; data were collected from November 2017 to April 2018.
Measurements: The VR software Google Earth VR® was used. The primary endpoint was the change in the Edmonton Symptom Assessment System scores for each symptom before and after VR travel.
Results: The average age of the participants was 72.3 (standard deviation [SD] = 11.9) years. Significant improvements were observed for pain (2.35, SD = 2.25 vs. 1.15, SD = 2.03, $p = 0.005$), tiredness (2.90, SD = 2.71 vs. 1.35, SD = 1.90, $p = 0.004$), drowsiness (2.70, SD = 2.87 vs. 1.35, SD = 2.30, $p = 0.012$), shortness of breath (1.74, SD = 2.73 vs. 0.35, SD = 0.99, $p = 0.022$), depression (2.45, SD = 2.63 vs. 0.40, SD = 0.82, $p = 0.001$), anxiety (2.60, SD = 2.64 vs. 0.80, SD = 1.51, $p < 0.001$), and well-being (4.50, SD = 2.78 vs. 2.20, SD = 1.99, $p < 0.001$; pre- vs. post-VR travel score, respectively). No participants complained of serious side effects.
Conclusions: This preliminary study suggests that VR travel can be efficacious and safe for terminal cancer patients for improving symptom burden.

Keywords: mental time travel; palliative care; quality of life; terminal cancer patients; virtual reality

Introduction

Terminal cancer patients have various wishes at the end of their lives. Some of them are ''I want to go to a memorable place I have visited'' or ''I want to return home.'' However, given the burden of their various symptoms and physical dysfunction, it is difficult for them to realize these wishes.

Virtual reality (VR) is a computer-generated, simulated experience through the senses and perception. The immersive virtual environment can be similar to the real world, while also creating an experience impossible in ordinary reality. Recent studies have explored the use of VR in medical treatment. Rus-Calafell et al.[1] reported therapeutic effects on psychosis observed through treatments using VR. Ortiz-Catalan et al.[2] presented reductions in refractory phantom

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limb pain. There have not been studies on VR treatment for terminal cancer patients. Therefore, this study aimed to verify whether VR is efficacious in improving symptoms among terminal cancer patients.

Materials and Methods

Study design

This study is a prospective, multicenter, single-arm study conducted with the approval of the institutional review board of participating institutions (Registration No. UMIN000029893). Data from 20 participants, who provided their written informed consent, were collected from November 2017 to April 2018.

Terminal cancer patients were recruited from two palliative care wards. Participants had to be at least 20 years old. The following exclusion criteria were set: visual and hearing impairment, inability to answer a questionnaire owing to severe cognitive impairment, absolute inability to sit, and severe paralysis of an upper limb. We introduced this study to patients who met the eligibility criteria consecutively.

Simulated travel session using VR and evaluation of symptoms, emotional reaction, and side effects

The participants experienced one VR travel session that lasted 30 minutes in principle, but the session time was extended or shortened according to participants' wishes. The VR headset HTC VIVE and the free VR software Google Earth VR® were used. The detailed procedure is shown in Appendix 1. Figure 1 shows the VR travel session of one participant. The participants themselves operated the software, in principle, but a medical staff assisted as necessary.

Shortly before and immediately after VR travel, participants' symptoms were evaluated using the Edmonton Symptom Assessment System (ESAS) Japanese version.[3] We also used an 11-point Numerical Rating Scale (NRS) ranging from 0 (symptom absent or best) to 10 (worst possible) for the assessments of dizziness and headache, and an 11-point NRS ranging from 0 (none) to 10 (very much) for the assessments of participants' level of fun, happiness, and pre-VR travel expectations/post-VR travel satisfaction shortly before and immediately after VR travel. Regarding pre-VR travel expectations, participants were asked, ''How much do you expect from the VR experience?'' Regarding post-VR travel satisfaction, participants were asked, ''How satisfied were you with the VR experience?'' Participants themselves answered the ESAS and NRSs. The study representative attended all VR travels to standardize the method as much as possible. Communication among medical staff, participants, and participants' family members was not particularly restricted. Medical staff answered questions spontaneously asked by participants, for example, ''Where is this?'' during VR travel; however, they did not introduce or explain the location such as by saying ''This scene is amazing'' before or during VR travel.

Data on the participants' age, gender, primary cancer site, Eastern Cooperative Oncology Group (ECOG) Performance Status, presence or absence of an upper limb paralysis, difficulty in taking a sitting position, regular use of opioid drugs, and the use of psychotropic drugs were collected through a review of their medical records.

Primary and secondary endpoints

The primary endpoint was the change in ESAS score for each symptom before and after VR travel. Secondary endpoints were the correlations between the experience types (participants who went to memorable places or participants who went to a place they had wanted to go to but never visited) and the effects on ESAS symptom scores.

Statistical analyses

A paired *t*-test was conducted for the comparison of ESAS and NRSs before and after VR travel. The cutoff values reported in Yamaguchi et al.[4] were used for detecting moderate/severe symptoms on the ESAS: pain ≥3, tiredness ≥4, drowsiness ≥5, nausea ≥2, lack of appetite ≥3, shortness of breath ≥3, depression ≥3, anxiety ≥3, and well-being ≥4. The Wilcoxon signed-rank test was conducted for the comparisons

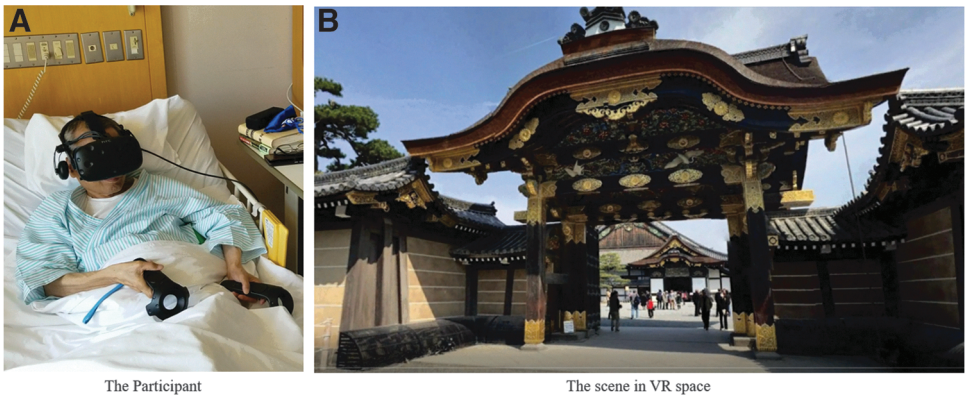

FIG. 1. A participant experiencing VR and an image of the scene that he is experiencing in VR space. **(A)** A participant experiencing VR travel. **(B)** Screenshot of the image in VR space that the participant is experiencing. In this instance, the participant enjoyed VR travel to a famous shrine in Japan where he had his wedding. The VR headset HTC VIVE and the free VR software Google Earth VR® were used. The scenes observed by the participants in VR space were built with 360° photographs, so that the participants could look forward, left, right, above, below, and behind in a seamless manner that evoked realism. VR, virtual reality.

Table 1. Participants' Demographics ($N=20$)

Variables	*Mean (SD)*
Age, years	72.3 ± 11.9
	n *(%)*
Gender	
Male	14 (70.0)
Female	6 (30.0)
ECOG PS	
0	0 (0)
1	0 (0)
2	2 (10.0)
3	14 (70.0)
4	4 (20.0)
Primary cancer site	
Pancreas	3 (15.0)
Uterus	2 (10.0)
Lung	2 (10.0)
Head and neck	2 (10.0)
Prostate gland	2 (10.0)
Kidney	2 (10.0)
Biliary duct	2 (10.0)
Other	5 (23.6)
Paralysis of an upper limb	3 (15.0)
Difficulty of taking a sitting position	3 (15.0)
Regular use of opioid drugs	8 (40.0)
Use of psychotropic drugs	5 (25.0)

ECOG PS, Eastern Cooperative Oncology Group Performance Status; SD, standard deviation.

by experience type. The required sample size was set to detect an effect size of 0.80 in score on depression and anxiety between pre- and post-VR travel scores and using a sample size calculator for a paired *t*-test. We assumed a 0.05 level of statistical probability and a power of 0.80. After calculation, the minimum sample size was determined to be 15. Statistical analyses were performed using Bell Curve (Social Survey Research Information Co., Ltd., Tokyo, Japan). Two-tailed *p*-values <0.05 were considered significant.

Results

The participants' demographics are shown in Table 1. Eighteen (90%) participants had an ECOG performance status ≥3. The results of VR travel are shown in Table 2. Significant improvements were observed for pain, tiredness, drowsiness, shortness of breath, depression, anxiety, and well-being, as well as fun and happiness. Among them, the greatest effect size was shown for depression. The number of participants whose symptoms were classified as moderate/severe decreased in all symptoms after VR travel.

No participants complained of serious side effects from VR travel. Although there were a few participants who reported increased ESAS scores after VR travel (Table 3), none reported moderate/severe symptoms. The analysis results by experience type are shown in Table 4. Fifteen (75%) participants went to memorable places. Significant improvements were observed for pain, tiredness, drowsiness, lack of appetite, shortness of breath, depression, anxiety, well-being, fun, happiness, and pre-VR travel expectation/post-VR travel satisfaction in the participants who ''went to memorable places.'' However, there were no significant improvements in

Table 2. Symptoms, Emotional Reaction, and the Frequency of Moderate/Severe Side Effects Pre- and Postvirtual Reality Travel

	Score				*Moderate/severe symptoms according to ESAS*	
Outcome variables	*Before VR travel, mean (SD, range)*	*After VR travel, mean (SD, range)*	p	*Cohen's* d	*Before VR travel,* n *(%)*	*After VR travel,* n *(%)*
Symptoms (ESAS)						
Pain	2.35 (2.25, 0–6)	1.15 (2.03, 0–6)	0.005	0.574	10 (50.0)	3 (15.0)
Tiredness	2.90 (2.71, 0–9)	1.35 (1.90, 0–7)	0.004	0.679	6 (30.0)	2 (10.0)
Drowsiness	2.70 (2.87, 0–9)	1.35 (2.30, 0–8)	0.012	0.533	6 (30.0)	3 (15.0)
Nausea	0.10 (0.31, 0–1)	0.05 (0.22, 0–1)	0.577	0.191	0 (0)	0 (0)
Lack of appetite	2.85 (3.66, 0–9)	1.60 (2.60, 0–8)	0.063	0.404	7 (35.0)	5 (25.0)
Shortness of breath	1.74 (2.73, 0–8)	0.35 (0.99, 0–4)	0.022	0.684	4 (20.0)	1 (5.0)
Depression	2.45 (2.63, 0–8)	0.40 (0.82, 0–3)	0.001	1.081	10 (50.0)	1 (5.0)
Anxiety	2.60 (2.64, 0–8)	0.80 (1.51, 0–6)	<0.001	0.858	9 (45.0)	2 (10.0)
Well-being	4.50 (2.78, 0–10)	2.20 (1.99, 0–8)	<0.001	0.976	12 (60.0)	3 (15.0)
Other side effects						
Dizziness	0.25 (0.79, 0–3)	0.15 (0.37, 0–1)	0.428	0.167	—	—
Headache	0.10 (0.31, 0–1)	0.00 (0.00, 0–0)	0.163	0.471	—	—
Emotional reaction						
Fun	4.30 (3.28, 0–10)	7.30 (2.74, 2–10)	<0.001	1.019	—	—
Happiness	4.55 (2.95, 0–10)	7.05 (2.44, 2–10)	<0.001	0.949	—	—
Pre-VR travel expectation/post-VR travel satisfaction	5.90 (2.67, 1–10)	7.35 (2.08, 3–10)	0.005	0.621	—	—

ESAS, Edmonton Symptom Assessment System; VR, virtual reality.

Table 3. Details of Participants Whose Edmonton Symptom Assessment System Score Increased After Virtual Reality Travel

	n (%)	*ESAS score change (pre-VR travel → post-VR travel)*	*Reason for the increase in ESAS score*	*How easily do you get motion sickness?*	*VR travel session time (minutes)*
Tiredness	1 (5.0)	2 → 3	Tiredness of arms due to continuous operation	Never	35
Drowsiness	1 (5.0)	1 → 2	Unknown	Never	40
Nausea	1 (5.0)	0 → 1	Length of experience	Somewhat easy	60
Dizziness	1 (5.0)	0 → 1	Ease of getting motion sickness	Somewhat easy	15

participants who ''went to a place they had wanted to go to but never visited.''

Discussion

As the first report of its kind in the world, this study found that VR travel resulted in significant improvements in symptom burden of terminal cancer patients, without causing serious side effects. Further, the effect was observed even in participants who reported symptoms that were worse than moderate.

Since this study was the first attempt to use VR for terminal cancer patients, we aimed to broadly observe how various symptoms were affected by it. The symptoms that demonstrated the greatest benefit were depression and anxiety. Thus, VR was found in this sample to have a particularly significant influence on mental health. Shah et al.[5] reported a VR-based stress management program among participants with mood disorders in psychiatric wards, which demonstrated that VR significantly lowered subjective stress, depression, and anxiety. Similarly, Pot-Kolder et al.[6] reported that VR cognitive-behavioral therapy reduced paranoia and anxiety in a sample of patients with psychoses. The results of this study are consistent with these reports.

In this study, the participants who went to a memorable place tended to experience more benefits from VR than did those who went to a place they had wanted to go to but never visited. Considering that there was no significant difference in ESAS scores and emotional reaction before VR travel between the two groups (Appendix 2), memories of the destination in VR travel might have a large influence. The retrieval of memories of one's past experiences, namely

Table 4. Symptoms, Emotional Reaction, and Side Effects by Classification of Virtual Reality Travel Type

	Memorable places visited previously (n = 15)				*Places desired to visit but never visited (n = 5)*			
	Median score (IQR)				*Median score (IQR)*			
	Before VR travel	*After VR travel*	p	*Cohen's* d	*Before VR travel*	*After VR travel*	p	*Cohen's* d
Symptoms (ESAS)								
Pain	3.00 (0–3)	0.00 (0–1)	0.018	0.832	1.00 (1–5)	1.00 (0–5)	0.317	0.080
Tiredness	3.00 (1.5–5)	1.00 (0–3)	0.006	0.804	1.00 (0–2)	0.00 (0–1)	0.180	0.343
Drowsiness	1.00 (0.5–5)	0.00 (0–1)	0.014	0.590	3.00 (1–3)	1.00 (0–3)	0.180	0.325
Nausea	0.00 (0–0)	0.00 (0–0)	0.593	0.224	0.00 (0–0)	0.00 (0–0)	—	—
Lack of appetite	2.00 (0–8)	0.00 (0–3)	0.043	0.505	0.00 (0–0)	0.00 (0–0)	—	—
Shortness of breath	0.50 (0–2)	0.00 (0–0)	0.028	0.681	0.00 (0–0)	0.00 (0–0)	0.317	0.707
Depression	3.00 (0–3.5)	0.00 (0–0)	0.008	1.237	1.00 (0–3)	0.00 (0–1)	0.317	0.686
Anxiety	2.00 (0–3.5)	0.00 (0–0.5)	0.008	0.788	3.00 (3–3)	1.00 (0–1)	0.109	1.313
Well-being	5.00 (3–7)	2.00 (1–3)	0.002	1.175	3.00 (1–5)	1.00 (0–3)	0.317	0.503
Other side effects								
Dizziness	0.00 (0–0)	0.00 (0–0)	0.317	0.239	0.00 (0–0)	0.00 (0–1)	>0.999	0
Headache	0.00 (0–0)	0.00 (0–0)	0.317	0.378	0.00 (0–0)	0.00 (0–0)	0.317	0.755
Emotional reaction								
Fun	5.00 (2–7.5)	8.00 (6–10)	0.003	0.915	4.00 (1–5)	7.00 (5–8)	0.068	1.591
Happiness	5.00 (2–6.5)	8.00 (6.5–8.5)	0.003	0.962	5.00 (5–5)	6.00 (5–8)	0.068	0.949
Pre-VR travel expectation/post-VR travel satisfaction	6.00 (5–8)	8.00 (6–9)	0.041	0.621	4.00 (3–5)	7.00 (5–8)	0.109	0.690

IQR, interquartile range.

episodic memories, involves the medial temporal lobe (MTL).[7] Ramirez et al.[8] suggested that the activation of hippocampal cells that are part of MTL is associated with a positive memory result in the suppression of depression-like behavior. Since the biological mechanism by which VR improves anxiety and depression has not yet been clarified, evaluating the activity of the hippocampus in the future may lead to elucidation of the mechanism. Further, our participants did not experience serious side effects from VR travel, in concordance with the results of Jones et al.[9] who reported no serious side effects during VR treatment for middle-aged patients with chronic pain.

There are several limitations to this study. First, there was no comparison group, and the influence of interpersonal bias could not be considered. Second, only transient effects could be investigated. It remains to be determined whether the effect observed by VR travel is a short-lived distraction, or if it is sustainable. Therefore, it is necessary to study the sustainability of the effect of a single intervention or periodic interventions as a next step. Third, statistical analysis for VR travel type was conducted for a small number of participants. Fourth, it is necessary to standardize VR travel session time and environmental conditions related to medical staff and participants' families attending the intervention. Thus, future studies should be conducted with larger, more diverse samples, include a comparison group, and use objectively evaluable methods to avoid bias.

Conclusions

This preliminary study suggests that VR travel can be efficacious and safe for improving symptom burden of terminal cancer patients. Further investigations on the mechanisms and sustainability of symptomatic improvement are needed to verify the possibility of palliative care using VR.

Author Disclosure Statement

No competing financial interests exist.

References

1. Rus-Calafell M, Garety P, Sason E, et al.: Virtual reality in the assessment and treatment of psychosis: A systematic review of its utility, acceptability and effectiveness. Psychol Med 2018;48:362–391.
2. Ortiz-Catalan M, Gudmundsdottir RA, Kristoffersen MB, et al.: Phantom motor execution facilitated by machine learning and augmented reality as treatment for phantom limb pain: A single group, clinical trial in patients with chronic intractable phantom limb pain. Lancet 2016;388:2885–2894.
3. Yokomichi N, Morita T, Nitto A, et al.: Validation of the Japanese Version of the Edmonton Symptom Assessment System-Revised. J Pain Symptom Manage 2015;50:718–723.
4. Yamaguchi T, Morita T, Nitto A, et al.: Establishing cutoff points for defining symptom severity using the Edmonton Symptom Assessment System-Revised Japanese version. J Pain Symptom Manage 2016;51:292–297.
5. Shah LBI, Torres S, Kannusamy P, et al.: Efficacy of the virtual reality-based stress management program on stress-related variables in people with mood disorders: The feasibility study. Arch Psychiatr Nurs 2015;29:6–13.
6. Pot-Kolder RMCA, Geraets CNW, Veling W, et al.: Virtual-reality-based cognitive behavioural therapy versus waiting list control for paranoid ideation and social avoidance in patients with psychotic disorders: A single-blind randomised controlled trial. Lancet Psychiatry 2018;5:217–226.
7. Milner B, Squire LR, Kandel ER: Cognitive neuroscience and the study of memory. Neuron 1998;20:445–468.
8. Ramirez S, Liu X, MacDonald CJ, et al.: Activating positive memory engrams suppresses depression-like behaviour. Nature 2015;522:335–339.
9. Jones T, Moore T, Choo J: The impact of virtual reality on chronic pain. PLoS One 2016;11:e016752.

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(*Appendix follows* →)

Appendix 1. Additional Methods Descriptions

Procedure of Virtual Reality Travel

First, we asked participants where they wanted to go, and then set the software so that participants could start their virtual reality (VR) travel from that point. Second, we explained the method of operation for the software to the participants. Third, the participants donned the VR headset.

Appendix A2. Symptoms, Emotional Reaction, and Side Effects by Classification of Virtual Reality Travel Type before Virtual Reality Travel

	Memorable places visited previously (n = 15)	*Places desired to visit but never visited (n = 5)*	
	Median score (IQR)		p
Symptoms (ESAS)			
Pain	3.00 (0–3)	1.00 (1–5)	0.788
Tiredness	3.00 (1.5–5)	1.00 (0–2)	0.103
Drowsiness	1.00 (0.5–5)	3.00 (1–3)	0.964
Nausea	0.00 (0–0)	0.00 (0–0)	0.450
Lack of appetite	2.00 (0–8)	0.00 (0–0)	0.092
Shortness of breath	0.50 (0–2)	0.00 (0–0)	0.443
Depression	3.00 (0–3.5)	1.00 (0–3)	0.325
Anxiety	2.00 (0–3.5)	3.00 (3–3)	0.476
Well-being	5.00 (3–7)	3.00 (1–5)	0.128
Other side effects			
Dizziness	0.00 (0–0)	0.00 (0–0)	0.503
Headache	0.00 (0–0)	0.00 (0–0)	0.450
Emotional reaction			
Fun	5.00 (2–7.5)	4.00 (1–5)	0.378
Happiness	5.00 (2–6.5)	5.00 (5–5)	>0.999

ESAS, Edmonton Symptom Assessment System; IQR, interquartile range.