Psychological and Educational Interventions Among Cancer Patients: A Systematic Review to Analyze the Role of Immersive Virtual Reality for Improving Patients' Well-Being

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Abstract. Previous studies show that the lack of information about cancer-related topics (e.g., diagnosis, treatments) and the impact of treatment toxicity on patients' life, may undermine cancer patients' psychological well-being. Psycho-educational interventions are therefore implemented to support the oncological population. This systematic review aims to explore the state of art and effectiveness of psychological and educational interventions implemented using Virtual Reality and designed for pediatric and adult cancer patients. The review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (PRISMA), and it was registered with the PROSPERO international prospective register of systematic reviews (registration number CRD42022308402). Twenty studies were included in the review. Our findings show that psychological interventions predominantly use emotion-focused strategies (i.e., distraction) to reduce patients' emotional distress; educational studies prefer, on the contrary, cognitive-behavioral strategies (i.e., exposure) to restructure patients' beliefs, increasing their understanding of the procedure, and reducing situational anxiety. VR could be a promising and effective tool for supporting cancer patients' needs. However, since most of these VR interventions assign the patient a passive role in coping with his or her diagnosis, future research should develop psychological and educational VR interventions that have the primary goal of rendering people with a cancer diagnosis active characters in their psychological well-being, supporting in this way patients' empowerment.

Keywords: Virtual Reality · Cancer · Psychological intervention · Educational intervention · Systematic review · Emotion regulation · Well-being

1 Introduction

Cancer is a life-threatening disease that leads patients to experience emotional distress [1, 2]. The impact of cancer treatments on patients' functionality and appearance adds an extra source of stress in patients' lives [3], contributing to a further decline in their

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mental health [4]. These combined factors undermine patients' well-being (e.g., [5–7]), threaten their compliance [8, 9], endanger treatment outcomes [10], and increase their risk of mortality [11–13]. Additionally, the lack of information about cancer experience and treatment side effects may jeopardize to a greater extent patients' mental health [14], representing one of the unmet needs of this clinical population [15, 16]. Therefore, to support patients' mental health [17], educational (e.g., [18, 19]) and psychological interventions (e.g., [20–22]) are implemented. Psychological interventions buffer patients' emotional distress and reduce negative mood states using emotional, cognitive, or behavioral strategies [23]. Educational interventions are, on the other hand, based on the premise that exposure to care-related information provides coping assistance to patients, by offering answers to their search for information. This process restructures how the cognitive assessment of events is perceived (e.g., being stressful) and, consequently, reduces the associated situational anxiety [24].

Over the last decades, thanks to technological advancement and to the possibility to have affordable devices, health care has witnessed a switch, passing from in-person interventions to therapies that use technological devices. Thus, it is not surprising that the usage of virtual reality (VR) in the medical field has gradually increased [25, 26]. Recent studies have shown that VR is not only broadly used in treating mental health problems [27], but that it is also effective in health care [28]. VR allows the user to navigate and interact in real-time with a 3D environment [29], making it possible for patients to experience situations that would otherwise be impractical or difficult to access [30]. These characteristics are particularly pertinent in the oncological setting, where treatment toxicity (e.g., pain, fatigue, nausea) impairs physical functioning [31, 32] and leads to hospitalizations [33], rendering it complicated for cancer patients to attend in-person therapies or educational training. VR appears as a possible solution to overcome the barriers that oncological treatments create: thanks to VR patients can face situations, as well as receive interventions, without leaving their room, with the quality of an in vivo experience [30], and feeling present in the situation [34]. VR is a particularly suitable tool also for its capability to visually show realistic scenarios to users, through an experiential form of imagery [35]. This quality, combined with a well-structured narrative [36], is very helpful when patients have difficulties picturing the situations they are told to imagine [35], for example when staff explains how the surgical procedure will be performed or how radiotherapy works. Therefore, VR may assist nurses and surgeons in visually showing to patients the steps of the oncological procedure, avoiding misinterpretations, and reducing procedural anxiety [18]. Misunderstandings about treatment benefits and harms can, in fact, lead patients to regret the decision taken and the treatment accepted [37]: when patients do not fully understand the implications of the procedure or have incomplete information about outcomes are more susceptible to regret [38], risking to make poorly informed decisions about their oncological journey. The uncertainty in a negative situation makes the situation more unpleasant [39], potentially causing distress and poor health outcomes [40]. For this reason, being able to overcome this problem would be extremely valuable for patients' well-being. VR is already used in oncological settings. However, its major application is planning or simulating surgeries (e.g., resection of the tumor mass), as well as training residents or medical specialists to implement oncological procedures (e.g., surgery, radiotherapy, etc.) (e.g., [41–46]).

Since VR has the potential to support cancer patients' well-being, this systematic review aims to explore the state of the art of psychological and educational interventions among adult and pediatric cancer patients. It seems, in fact, essential to create an accessible understanding of how VR is used in the psycho-oncological setting, and which are its possible future uses. Hence, our research questions are:

RQ1: Which are the current educational and psychological interventions for cancer patients that use VR for their implementation?
RQ2: Which is the effectiveness of such VR interventions?

Interventions will be considered effective when there is a statistically significant improvement in the measures of interest for the intervention group compared to the control group.

2 Methods

A systematic review of scientific literature has been performed to identify studies that report the employment of psychological and educational VR intervention on cancer patients. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [47], and the study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) in 2022 (CRD42022308402). The detailed protocol is available upon request.

2.1 Data Sources and Search Strategy

Data sources were collected on the 14th of January 2022 through a selective computer search in the following databases: PubMed, PsycINFO, and Web of Science (Web of Knowledge). The current systematic review wants to offer a broad panoramic of the current literature: for this reason, we did not define a beginning year of publication for the articles to be included. Each database was searched independently, according to a specific iteration research string:

(Virtual Reality) AND ("Cancer" OR "Oncology" OR "Chemotherapy" OR "Cancer treatment" OR "Cancer care" OR "Cancer support").

To make this study repeatable in the future, detailed results are available in Table 1. The selection of these strings was made in the attempt to capture an extensive range of features regarding VR interventions and cancer patients. This systematic review focused on immersive VR, which comprehends technologies in which users wear head-mounted displays and are surrounded by enclosed virtual environments [48]. In other words, virtual environments are immersive when the user experiences a sense "of being there": the person feels in the virtual environment even if they are physically situated in another place [34]. Citations were retrieved independently for each iterative search crossing all databases. A complete list of citations and abstracts for each database was exported and imported into Rayyan [49] for the title and abstract screening.

Table 1. Detailed search strategy

Detailed search strategy

Virtual reality AND	PubMed	PsycINFO	Web of Science	
Cancer	754	123	1078	
Oncology	611	45	227	
Chemotherapy	233	20	84	
Cancer treatment	503	70	262	
Cancer care	186	43	207	
Cancer support	273	30	226	
Sub Total	2560	331	2084	
Total				4975
Duplicates removal				3073
Identified studies for Abstract and Title screen				1902

2.2 Study Selection and Inclusion Criteria

Two reviewers (M.S. and C.M.) independently screened all non-duplicate titles and abstracts, searching for eligible articles. The same reviewers retrieved, and analyzed the full text for all relevant articles, resolving discrepancies by consensus. G.R. was designated as the third reviewer to arbitrate potential differences in agreement.

Participants

We included patients (both pediatric and adult) diagnosed by a practitioner with cancer (all cancer diagnoses and stages were included). Both female and male participants were included. Patients with metastases or undergoing palliative care were included, too. We did not include studies focused on caregivers of cancer patients, oncological professionals (e.g., nurses, surgeons, etc.), or with a mixed sample of participants (i.e., studies that also included cancer patients, but that were not limited to them). In addition to this, we did not include interventions implemented on patients with benign neoplasms, or who have not received a cancer diagnosis yet (e.g., waiting for the biopsy result).

Interventions
We focused on interventions tailored both for cancer treatments (e.g., chemotherapy) and procedures (e.g., subcutaneous port access). We included studies that considered behavioral, emotional, educational, and cognitive interventions (e.g., cognitive restructuring), including those that targeted cancer fatigue and cancer pain. Studies that focused only on the assessment of psychological (e.g., anxiety) or educational (e.g., health literacy) dimensions were not included in the systematic review, but we did include interventions that aimed to improve those features. We did not include studies that focused on neuropsychological functions (e.g., sleep, attention, memory, etc.), and treatments' side effects (e.g., lymphedema, memory impairment, etc.). We excluded studies that were developed to improve surgeons' skills or training, focused on detecting or removing the tumor mass (e.g., computer-assisted surgery, VR to plan post-surgery reconstruction, VR to plan tumor resection, etc.), cancer screening interventions or medical procedures to diagnose cancers (e.g., biopsy).

Methodological Characteristics of the Studies
We included both cross-sectional studies and studies with repeated measures. We included randomized controlled trials, but randomization was not a requirement since it can be difficult to implement within social science intervention research (e.g., ethical reasons) [50]. We did not include qualitative studies. We excluded non-English published studies, studies that used animals, and articles in which the full text was not available. We also excluded the following types of manuscripts: reviews, meeting abstracts, conference proceedings, notes, case reports, letters to the editor, research protocols, patents, editorials, books or chapters, and other editorial materials. We excluded studies that did not use validated measures, and studies that used only some of the items of the validated measure (i.e., when the items used do not allow to calculate the total score or a subscale of the validated measure). In the case of studies with a pediatric population, we only included papers that also provided a self-report measure of the minor. We only included studies that presented a control group of healthy subjects or cancer patients, or studies with repeated measures of the same group of participants (e.g., within-subject design). The included studies needed to compare the experimental condition with a group of participants undergoing the same type of intervention, a different type of intervention, non-intervention, or standard care to point out the effectiveness of the VR condition (Fig. 1).

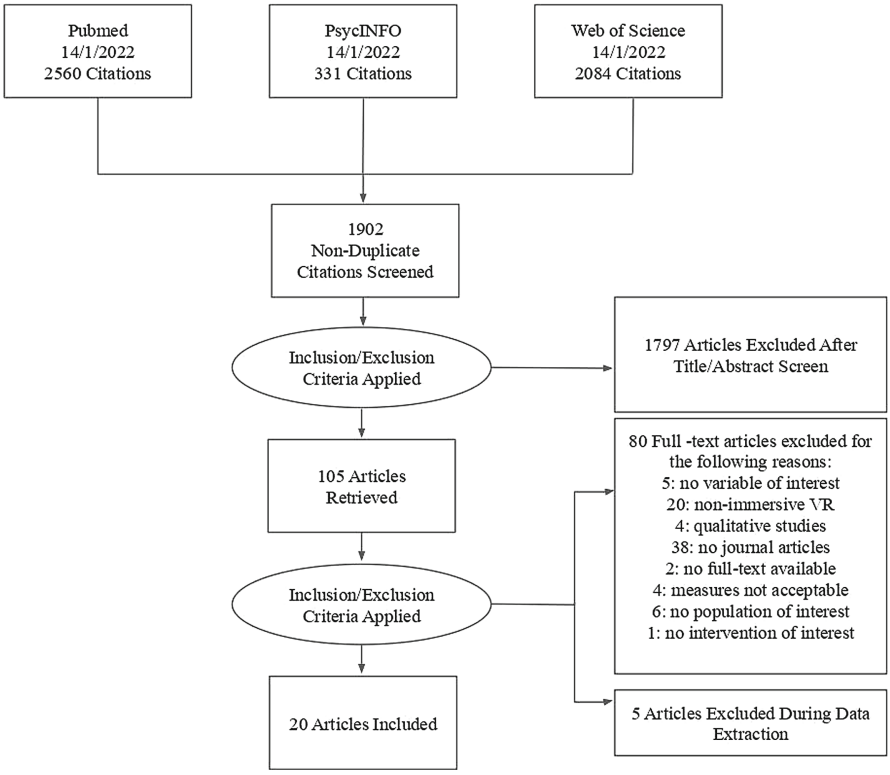

Fig. 1. Flow chart of the systematic review. The figure illustrates the search strategy of the systematic review conducted under PRISMA guidelines

2.3 Risk of Bias Assessment

To assess the risk of bias, the reviewers used the Downs and Black checklist [51]. This checklist provided an overall quality index and four subscales of quality assessment: reporting, external quality, internal validity bias, and internal validity confounding. After assigning the scores to each of the 27 items (answers are scored 0 or 1, except for one item that scored 0–2), a total score was provided. Scores could be "excellent" (24–28 points), "good" (19–23 points), "fair" (14–18 points), or "poor" (14 points or less) [51]. Two reviewers (M.S. and C.M.) independently evaluated the studies for risk of bias, and disagreements were resolved through consensus or the help of the third reviewer (G.R.).

2.4 Data Extraction

Two reviewers (M.S. and C.M.) independently extracted the following data: type of population, duration of the VR intervention, type of VR intervention, construct assessed, the content of the VR intervention, delivery modality, study design, and effectiveness compared to the control group.

3 Results

Of 4975 studies retrieved from PubMed, PsycINFO, and Web of Science, 1902 were non-duplicate. After screening all non-duplicate titles and abstracts, the full text of 105 articles was retrieved, and the studies were analyzed for the specific inclusion criteria. Of 105 studies, 25 were identified as suitable for our review. However, during the extraction process, we decided to exclude five additional studies. Reasons for removal were lack of clarity of the VR procedure and device used (n = 2), lack of immersion of the VR environment (n = 1), lack of clarity about the participants' clinical diagnosis (n = 1), and absence of specific outcomes for the VR intervention (n = 1). Therefore, in the end, twenty studies were included in the review. Detailed information about study characteristics, including the target population, duration, and type of the VR intervention, assessed construct, content of the intervention, delivery modality, study design, and outcome measures are presented in Table 2. For the aim of this systematic review, only the results that contained psychological variables (e.g., anxiety, depression, well-being, etc.) were presented and reported in Table 2. Since only a few of the studies included physiological measures, we did not include these kinds of variables in the results and the table either.

3.1 Study Characteristics

The studies took place in eleven countries: one study took place in Japan [52], one in Spain [53], one in France [54], one in Jordan [55], one in Iran [56], and another in Canada [57]. Two studies took place in China [58, 59], Italy [60, 61], Turkey [62, 63] and Australia [64, 65]. Lastly, six studies took place in the United States [66–71]. There was a variation in sample size between the studies, ranging from 11 [67] to 126 participants [53]. Papers were published within the past 23 years (1999–2022), with over fifteen studies published in the past 3 years [52–66]. About the study design, ten studies were randomized controlled trials (RCT) [53, 55–59, 62–64, 71], two were characterized by a within-subjects design (i.e., repeated measures) [61, 65], four were crossover studies [66, 68–70], one was an observational study [54], one a prospective single-arm study

[52], one an externally controlled trial [60], and one an interrupted time series study [67].

Sample Characteristics

The mean ages of participants ranged from 10 [59] to 72 years [52]. Participants of the studies were both adults [52–55, 58, 60, 61, 66, 68–70] and children/adolescents [56, 57, 59, 62–65, 67, 71]. Only one study [68] specifically focused on older cancer patients of at least 50 years. Most studies were conducted with female and male samples: only five studies were conducted only with female participants [54, 55, 60, 68, 69]. Of all studies, two [52, 61] recruited patients undergoing palliative care, and three focused on patients who were about to start their treatment (e.g., surgery) [53, 58, 65]. Most studies focused on patients on active treatments (e.g., chemotherapy) [54–56, 60, 64, 66–70], and patients undergoing oncological procedures (e.g., access to the venous port) [57, 59, 62, 63, 71]. In terms of diagnosis, nearly all studies enrolled patients with different cancers. Six studies enrolled only a specific oncological population, focusing on people with cervical [54], breast [55, 60, 68, 69], and colon cancer [53].

Characteristics of VR Interventions

The duration of the VR interventions was variable, going from 4–7 min in Tennant et al. [65], to eight sessions of 30-min each, once a week for 2 months in the study by Sharifpour, Manshaee, and Sajjadian [56]. Nearly all studies were psychological interventions (n = 17). These interventions shared the same underlying psychological strategy known as distraction. Distraction was implemented through different scenarios (e.g., naturalistic, games, etc.): some of them were interactive (e.g., [57]), and others were not (e.g., [59]). In general, interventions were tailored to participants' age. Some VR interventions simulated pleasant activities or exposed the person to a relaxing virtual environment. This is the case of Niki and colleagues [52], in whose study the adult patients simulated a trip, visiting a memorable place (e.g., a shrine in Japan where one of the participants had his wedding) or a destination (e.g., a city) that they wanted to explore, but that had never the occasion to. A similar approach was used by Tennant and colleagues [64], who proposed to their young participants a trip to Australian national parks, zoos, or global city tourist spots. The study of Wolitzky and colleagues [71] also offered as a distraction a visit to a zoo. In particular, in this scenario children went to the Zoo Atlanta, and virtually explored the gorilla habitat. Varnier and colleagues [54] used as a distraction a virtual dive with a whale swimming in a peaceful environment. The authors invited the patient to slow down their breathing following the moves of the whale's tale. This type of distraction was tailored for adult participants. Sharifpour and colleagues [56] opted for a VR video showing the young participants a stroll along the beach and a journey to the depth of the oceans. In the study by Semerci, Akgün Kostak, Eren, and Avci [63], always tailored for children, the authors opted for a roller coaster that speeded up and then slowed down in the forest accompanied by slow music. In other scenarios, the type of distraction

was chosen by the participants among different options, according to their interests: Schneider, Prince-Paul, Allen, Silverman, and Talaba [69] allowed their participants to choose between a scuba diving experience, a walk into an art museum or a resolution of a mystery. Two studies by Schneider [68, 70], in addition to the scenarios mentioned above, also added the possibility to explore ancient worlds. These three studies were tailored for adult participants. Schneider [67] proposed different options when implementing the study on the pediatric population: the young patients could, in fact, choose between the experience of riding a magic carpet, solving a mystery, or staying in a haunted mansion. Moscato and colleagues [61] proposed two scenarios that adult participants could watch: the first one was a non-interactive virtual environment characterized by natural and relaxing scenarios (i.e., seascape, park, waterfall, London Bridge, mountain landscape). The second environment was an interactive scenario that consisted of a skill game where the user, surrounded by a calm underwater landscape, had to reproduce an ideogram that represented concepts like friendship, courage, or strength. Mohammed and Ahmad [55] offered as a distraction two scenarios from which adult participants could choose: deep sea diving or sitting on the beach while listening to the "Happy Place" track. Chirico and colleagues [60] opted for interaction with relaxing virtual environments: the participant explored an island, walked through a forest, observed different animals, climbed a mountain, and swam in the sea. Also this type of scenario was tailored to adult participants. Ashley Verzwyvelt, McNamara, Xu, and Stubbins [66] proposed to their adult participants nine different scenarios. They could explore tropical beaches, underwater oceans, take to the stars, discover over sixty different animals, command the weather, take control of the night, or create and shape their own world. Gerçeker and colleagues [62] offered to the children that took part in their study three different environments: swimming with marine animals underwater, riding a roller coaster, and exploring the forest through the eyes of woodland species. Some scenarios implemented the distraction through a game to play with or by watching a video without interacting with it. Hundert [57] and colleagues, for example, proposed as a distraction a game that consisted of aiming rainbow balls at sea creatures as they explored an underwater scenario in search of a treasure. In the study by Wong and colleagues [59], on the contrary, two animated videos of Minions were shown to the patients during the medical procedure to distract them. Both these types of distraction were tailored to children.

Three educational interventions were included in the systematic review. These studies focused on preparing pediatric or adult patients for therapy. In particular, Gao and colleagues [58] focused on radiation therapy, showing to the adult participants the entire radiotherapy process, from the accelerator functioning to the equipment used, while patients lay down on a couch. Tennant and colleagues [65] proposed a similar scenario by showing their young participants a 360° video displaying the radiotherapy procedure. Turrado and colleagues [53] focused on surgery instead. These authors proposed to their adult participants a scenario that revealed the various steps of admission to surgery, from the first interview with the surgeon to the operating room and postoperative recovery.

Regardless of whether they were psychological or educational, the focus of the included studies was mostly pain [52, 54–57, 59, 61–64, 66, 71] and anxiety [52–56, 58–62, 64, 65, 67–71]. Some studies also assessed depression [52, 53, 60, 61], anger [60, 64], fear [57, 58, 62], distress [57, 66, 71], as well as fatigue and tiredness [52, 60, 61, 68–70]. A few studies considered well-being [52, 61], positive mood [64], and other mood states such as tension, vigor, and confusion [60]. For more information about how the studies targeted each of the psychological dimensions, please see Table 2.

Effectiveness of VR Interventions

Four studies reported no significant differences between the VR and the control condition or between the pre-post VR intervention [57, 66, 67, 70]. Other four studies reported mixed results [58, 61, 68, 69], displaying significant improvements for some clinical dimensions but not for others. In particular, Gao and colleagues [58] reported significantly lower anxiety in the VR condition compared to the control group, but they did not find a significant reduction in the fear scores of the VR condition: the fear was lower but not significant. Schneider and colleagues [69] observed a similar trend in their study: a significant decrease in the fatigue scores was observed in the VR condition, but not in the anxiety, which was lower but not significant. Moscato and colleagues [61] reported a significant improvement in pain, depression, anxiety, and well-being scores assessed through the Edmonton Symptom Assessment System. However, no statistical difference was found in depression, anxiety, and pain scores when they used different assessment measures (i.e., Hospital Anxiety and Depression Scale and Brief Pain Inventory). Another study reported mixed results [54]: however, since the authors did not use inferential statistical analysis, it was not possible to describe the results in terms of statistical difference. What we can say is that these authors observed a greater decrease in anxiety in the control condition compared to the VR and a larger improvement in pain in the VR group. According to these findings, VR worked better in the management of pain than anxiety. Eleven studies showed a significant improvement in the VR condition compared to the controls or to the pre-VR assessment [52, 53, 55, 56, 59, 60, 62–65, 71]. Tennant and colleagues [65] showed a significant reduction of anxiety in their pediatric patients. However, this improvement did not last for long and increased again just before the beginning of the cancer treatment.

3.2 Methodological Quality of Studies

As shown in Table 3, the Downs and Black checklist [51] revealed that the methodological quality of studies was mixed. Most studies were classified as "fair" [52, 54, 56, 58, 60–62, 65, 66, 67, 69, 71] implying a medium risk of bias. One study [68] was classified as "poor" implying a high risk of bias, and seven other studies [53, 55, 57, 59, 63, 64, 70] were classified as "good", implying a mild risk of bias. None of the studies was classified as "excellent" with a poor risk of bias.

Table 2. Studies characteristics according to extraction parameters

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Authors(s) and Year	Population	Duration	Type of intervention	Construct of interest assessed*	Content of the intervention	Delivery modality	Study design	Outcome
Niki et al., 2019	Adults (M=72.3 years)	One session of 30 minutes. The session time was extended or shortened according to participants' wishes.	Psychological	Pain intensity, anxiety, tiredness, depression, well-being	VR travel session using Google Earth VR. Participants could freely decide where they wanted to go (memorable places or places that wanted to visit but had never).	Headset HTC VIVE (includes headphones).	Prospective single-arm study	There was an improvement in the variables of interest post-intervention. 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.
Hundert et al., 2022	Pediatric (8-18 years)	Same duration of the subcutaneous port access procedure.	Psychological	Pain intensity, fear, distress, pain catastrophizing	EG: Standard care (adhesive topical local anesthetic patches placed before the needle insertion) + VR intervention. The VR scenario consisted of a game that aimed rainbow balls at sea creatures, while participants explored an underwater environment in search of treasure. CG: Standard care + same video of the VR condition implemented through an iPad.	Samsung GearVR™ with Sony MDR 10R Headphones and MOGA PRO™ POWER controller.	RCT	Although not statistically significant, less pain and distress were seen in the VR group compared to the iPad group, while fear scores remained similar between study groups.
Wolitzky, Fivush, Zimand, Hodges, & Rothbaum, 2005	Pediatric (7-14 years)	Same duration of the subcutaneous port access procedure.	Psychological	Pain intensity, anxiety, distress	EG: an exploration of the gorilla habitat at Zoo Atlanta. CG: NO VR intervention. Children in the CG were allowed to play with the VR for a few minutes after the end of the procedure and assessment.	Computer connected to a joystick and a head-mounted display. Participants also wore headphones.	RCT	During the procedure, there was a significant difference between groups on pain and a trend for the retrospective distress rating of the procedure. The children in the EG did not experience as much pain and anxiety and tended to be less distressed than the CG.
Tennant et al., 2021	Pediatric (6–18 years)	4–7 minutes, depending on treatment location	Educational	Anxiety	360 videos recording of actual treatment procedures. Participants viewed two virtual simulation experiences that corresponded to their upcoming procedure: VR CT Simulation [VR CT] and VR Radiation Therapy [VR RAD].	Samsung Gear VR® and Oculus Go® Facebook Technologies	Within-subjects, repeated measures	Significant reductions in child pre-radiation therapy (RT) anxiety levels were observed following the VR CT intervention compared to the baseline measures. On the day of RT commencement, following multiple exposures to VR RAD, children's anxiety showed an increase at follow-up from levels at post-VR CT.
Semerci, Akgün Kostak, Eren, & Avci, 2021	Pediatric (7-18 years)	8 minutes	Psychological	Pain intensity	EG: the VR scenario consisted of a roller coaster that speeds up and slows down in the forest, accompanied by slow music. CG: Standard care (parent's presence during the procedure without local anesthetic patches) + no VR treatment.	Piranha™ VR system. Headphones included.	RCT	There was a significant difference between the EG and the CG: the mean pain score of the children in the CG was significantly higher than that in the EG. The difference observed was quite large and clinically meaningful, with a large effect size reported.

(*continued*)

Table 2. (*continued*)

Table 2. Studies characteristics according to extraction parameters

Authors(s) and Year	Population	Duration	Type of intervention	Construct of interest assessed*	Content of the intervention	Delivery modality	Study design	Outcome
Schneider, & Workman, 1999	Pediatric (10-17 years)	Same duration of the chemotherapy treatment	Psychological	Anxiety	The VR environment consisted of commercially available scenarios: Magic Carpet®, Sherlock Holmes Mystery®, and Seventh Guest® (a haunted mansion). The VR intervention was implemented only throughout the second chemotherapy (3 chemotherapies in total).	Virtual i-O brand headset connected to a personal computer.	Interrupted time series	Participants showed high levels of anxiety during the initial chemotherapy treatment that decreased during subsequent treatments. However, anxiety levels were not influenced by the VR intervention.
Sharifpour, Manshaee, & Sajjadian, 2021	Pediatric (14–18 years)	8 sessions of VRT (virtual reality therapy), each 30-min long, once a week for 2 months	Psychological	Pain intensity, pain-related anxiety or fear responses in individuals with chronic pain, pain catastrophizing, pain self-efficacy	EG: A VR film was watched offline by the patients using AAA VR Cinema. It showed a stroll along the beach and a journey to the depths of the ocean. CG: No VRT. Participants were put on a waiting list.	Samsung Gear VR headset. Auditory stimuli were included but not played using headphones.	RCT	There was a significant difference in pain scores between the EG and the CG. Moreover, the effect of the treatment remained constant during the first and second follow-up periods.
Ashley Verzwyvelt, McNamara, Xu, & Stubbins, 2021	Adult (26-84 years)	5-15-minutes intervals throughout their infusion (as tolerated). Mean usage: 53.3 minutes	Psychological	Distress, pain intensity	VR room: Nature Treks software. Patients were able to choose between 9 different interactive natural environments: they could explore tropical beaches, underwater oceans, take to the stars, discover over 60 different animals, command the weather, take control of the night or create and shape their own world. Control room: standard treatment room with no windows, equipped with a standard infusion chair, vital signs monitor, and television. Participants in this condition received standard care. Green therapy room: the intervention placed the patient in a window-lined room. Participants could sit facing the large wall of windows overlooking a rooftop garden and picturesque mural. Each of the participants received chemotherapy once in each room.	Oculus Quest Head Mounted Display (HMD), headphones were included.	Crossover design	No significant differences were shown in the changes of pain or distress before and after infusion between the control, Green Therapy, and Virtual Reality rooms.
Tennant et al., 2020	Pediatric (7–19 years)	10 minutes	Psychological	Positive mood, anxiety, anger, pain	EG: Participants viewed one of three immersive 360° virtual simulation experiences, including simulated trips to Australian national parks (i.e. 'Nature experience), Australian zoos (i.e. 'Animal experience), or global city tourist spots (i.e. 'Travel experience). EG: identical content of the VR group presented using the iPad (360° video).	Samsung Gear VR® first-generation mobile HMD. Headphones were included.	RCT	Patients benefited from both Immersive VR and novel iPad intervention with no statistically significant differences found between conditions on child outcomes. However, patients accessing Immersive VR consistently reported greater positive shifts in mood state and reductions in anxiety, anger, and pain when compared with iPad.

(*continued*)

Table 2. (*continued*)

Table 2. Studies characteristics according to extraction parameters

Authors(s) and Year	Population	Duration	Type of intervention	Construct of interest assessed*	Content of the intervention	Delivery modality	Study design	Outcome
Gao et al., 2020	Adult (18-75 years)	30 minutes	Educational	Anxiety, fear	EG: Advance face-to-face educational meeting to explain the purpose and content of the education before the simulation appointment. The VR program included RT-related content (i.e., RT process, RT equipment, linear accelerator functioning, demonstrations with the radiation beam during the treatment process, and RT positioning). The patient, while wearing VR glasses, was lying on a treatment couch to simulate the RT position. Explanation material was also provided in this condition. CG: Standard care (regular face-to-face education).	Based on the HTC VIVE system the authors developed a VRRT system (Virtual Reality Radiotherapy Simulator) implemented through the use of VR glasses.	RCT	Anxiety was significantly lower in the EG than in the CG. Fear was also reduced, even if the statistical difference was not significant. Comparing the two groups pre- and post-intervention, the EG had a significant decrease in anxiety and fear.
Gerçeker et al., 2021	Pediatric (6-17 years)	Same duration of the access to the venous port	Psychological	Pain intensity, fear, anxiety	EG: Standard care (children and parents were informed 1h before the procedure, and no pharmacological methods were used) + three VR applications: swimming with marine animals underwater (Ocean Rift), riding a roller coaster (Rilix VR), and exploring the forest through the eyes of woodland species. Children could choose the scenario to explore. CG: Standard care.	Samsung Gear Oculus headset	RCT	The study found a statistically significant difference between the EG and the CG in post-procedural pain, fear, and anxiety scores.
Schneider & Hood, 2007	Adult (32-78 years)	Same duration of the chemotherapy treatment (45–90 minutes)	Psychological	Anxiety, fatigue	VR intervention during one chemotherapy treatment and no intervention (standard care) during an alternate matched chemotherapy treatment (e.g., watching television, conversing with others, or reading). When in the VR intervention, participants could choose from four possible CD-ROM–based VR scenarios: deep sea diving (Oceans Below®), walking through an art museum (A World of Art®), exploring ancient worlds (Timelapse®), and solving a mystery (Titanic: Adventure Out of Time®): participants were free to change scenarios at any time.	i-Glasses® SVGA Head-Mounted Display, i-O Display Systems	Crossover design	Patients had an altered perception of time when using the VR, which validates the distracting capacity of the intervention. However, the analysis demonstrated no significant differences in symptom distress immediately or two days following chemotherapy treatments.

(*continued*)

Table 2. (*continued*)

Table 2. Studies characteristics according to extraction parameters

Authors(s) and Year	Population	Duration	Type of intervention	Construct of interest assessed*	Content of the intervention	Delivery modality	Study design	Outcome
Chirico et al., 2020	Adult (18-70 years)	20 minutes	Psychological	Mood states (i.e., tension, depression, anger, vigor, fatigue, and confusion) and anxiety.	VR condition: participants used the VR for 20 minutes to experience the relaxing landscapes created on the Second Life® platform. In particular, they could explore an island, walk through a forest, observe different animals, climb a mountain, and swim in the sea. MT condition: an mp3 reader and headphones were provided to the patients, after 5 min from the start of the chemotherapy infusion. Patients listened to 20 min relaxing music, pre-taped by an expert music therapist. Control condition: standard care (patients were free to choose different activities during treatment, including conversation and reading).	Head-mounted glasses (VuzixWrap 1200 VR) with a head motion tracking system. A controller to interact with the virtual environment was also included.	Externally controlled trial	Both VR and MT were useful interventions for alleviating anxiety and for improving mood states in cancer patients during chemotherapy. Moreover, VR seems more effective than MT in relieving anxiety, depression, and fatigue.
Schneider, Prince-Paul, Allen, Silverman, & Talaba, 2004	Adult (18–55 years)	Same duration of the chemotherapy treatment (45–90 minutes)	Psychological	Anxiety, fatigue	Participants received the VR intervention during either their first or second chemotherapy treatment, and they were free to change scenarios if they wanted (deep sea diving, walking through an art museum, or solving a mystery). During the control condition, subjects received standard care (pre-treatment teaching, obtaining venous access, administering chemotherapy, providing homecare instructions, and administering antiemetic medications). Each of the participants experienced both conditions.	Sony PC Glasstron PLM-S700 headset. Headphones were included.	Crossover design	Significant decreases in fatigue occurred immediately following chemotherapy treatments when participants used the VR intervention. Anxiety scores were lower following the use of VR, but no significant differences were found.
Mohammad & Ahmad, 2019	Adult (18-70 years)	15 minutes	Psychological	Pain intensity, anxiety	EC: Morphine + VR intervention. Participants chose from two scenarios on a CD-ROM: deep sea diving "Ocean Rift," or sitting on the beach with the "Happy Place" track. CG: Morphine alone + no VR intervention.	Head-mounted display with headphones (model not specified).	RCT	The study findings showed that one session of the immersive VR plus morphine made a significant reduction in pain and anxiety self-reported scores, compared with morphine alone.
Varnier et al., 2021	Adult (43-67 years)	10 minutes. However, the VR intervention could be renewed if the procedure lasted longer.	Psychological	Pain intensity, anxiety	EG: VR intervention (Aqua 10 French Version) consisting of a virtual dive with a whale swimming in a peaceful environment. The patient was invited to slow down his breathing following the moves of the whale's tale. EG: Nitrous oxide (N2O) conscious sedation.	Goggles harboring a smartphone and earphones (no model specified).	Observational Study	The mean anxiety score was 2.9 before and 2.7 at the peak in the EG versus 4.1 and 1.6, respectively in the CG. The mean pain score was 1.0 before, 3.1 at the peak, and 0.4 after the procedure in the EG, vs 1.8, 2.0, and 0.6 respectively in the CG.

(*continued*)

Table 2. (*continued*)

Table 2. Studies characteristics according to extraction parameters

Authors(s) and Year	Population	Duration	Type of intervention	Construct of interest assessed*	Content of the intervention	Delivery modality	Study design	Outcome
Moscato et al., 2021	Adult (18-70 years)	The authors did not set a minimum or a maximum time of VR usage/ number of sessions: patients used the headset at home for 4 days in moments of psychophysical discomfort (e.g., pain and growing anxiety), whenever they wanted.	Psychological	Pain intensity, anxiety, tiredness, depression, well-being	The VR included both an IS and a NIS. The NIS consisted of immersive 360° videos with different natural and relaxing scenarios, such as a seascape, a park, a waterfall, the London Bridge, and a mountain landscape. The IS consisted of a basic skill game called "Yuma's World": the user, surrounded by a calm underwater environment, had to reproduce with the controller a displayed "Kanji" (i.e., an ideogram that represents concepts like friendship, courage, and strength). On day 1 the participants could only watch the NIS, to familiarize themselves with the VR. From day 2 on, participants were free to choose the type of scenario.	Mirage Solo VR Headset. A remote controller was included.	Within-subjects, repeated measures	Depression, anxiety (assessed with the HADS), and pain (assessed with the BPI) did not change significantly between days one and four. However, pain, depression, anxiety, and well-being (assessed with the ESAS) collected immediately after the VR sessions showed a significant improvement.
Schneider, Ellis, Coombs, Shonkwiler, & Folsom, 2003	Adult (50-77 years)	Same duration of the chemotherapy treatment	Psychological	Anxiety, fatigue	Participants were randomly assigned to receive the VR treatment during either their first or next chemotherapy treatment. VR condition: Participants chose from 3 CD-ROM-based scenarios (Oceans Below®, A World of Art®, or Titanic: Adventure Out of Time®); they were free to change the VR scenarios. Control condition: standard care (e.g., pre-treatment teaching, obtaining venous access, administration of antiemetic medication).	Sony PC Glasstron PLM- S700. The sense of touch is involved through the use of a computer mouse that allows for the manipulation of the image.	Crossover design	The results demonstrated a significant decrease in anxiety scores immediately following chemotherapy treatments when participants used VR. No significant changes were found in the fatigue values. There was a consistent trend toward improved symptoms on all measures 48 h following completion of chemotherapy.
Wong et al., 2021	Pediatric (6-17 years)	5 minutes before the PIC + total duration of the procedure	Psychological	Anxiety, pain intensity	EG: 2 animated videos from "Minions" were selected and shown to the participants (from 5 minutes before the PIC procedure started to its end) CG: Standard care (phlebotomists explained and performed PIC. The patients were comforted verbally but no VR intervention was implemented).	Google cardboard goggles were used.	RCT	Participants in the EG demonstrated a significantly greater reduction in pain and anxiety levels compared with the CG.
Turrado et al., 2021	Adult (26-94 years)	16-34 minutes	Educational	Anxiety, depression	EG: The participants were exposed to a realistic environment in which they could experience the various steps of their admission to surgery, from the first interview with the surgeon to admission into the surgical ward, the operating room, and the postoperative recovery room.	Bluebee™ Genuine VR 3D Glasses	RCT	After exposure to VR, anxiety and depression rating scales decreased significantly.

EG= Experimental Group, CG= Control Group, IC= Informed Consent, MT=Music Therapy, IS= Interactive Scenario, NIS=Non-Interactive Scenario

* We only reported some of the variables the studies assessed (i.e., self-reported psychological variables). For more details about the rest of the variables, please see the original papers.

Table 3. Risk of bias assessment using the Downs and Black checklist (1998)

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	Niki et al., 2019	Hundert et al., 2021	Wolitzky, Fivush, Zimand, Hodges & Rothbaum, 2005	Tennant et al., 2021	Semerci, Akgün Kostak, Eren, & Avci, 2021	Schneider & Workman, 1999	Sharifpour, Manshaee, & Sajjadian, 2021	Ashley Verzwyvelt, McNamara, Xu, & Stubbins, 2021	Tennat et al., 2020	Gao et al., 2020	Gerçeker et al., 2021	Schneider & Hood, 2007	Chirico et al., 2020	Schneider, Prince-Paul, Allen, Silverman, & Talaba, 2004	Mohammad & Ahmad, 2019	Varnier et al., 2021	Moscato et al., 2021	Schneider, Ellis, Coombs, Shonkwiler, & Folsom, 2003	Wong et al., 2021	Turrado et al., 2021
Question 1	1	1	1	1	1	1	1	0	1	1	1	1	0	1	1	1	1	1	1	1
Question 2	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Question 3	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Question 4	1	1	0	1	1	0	0	1	0	1	0	0	0	0	0	0	1	0	0	1
Question 5	0	0	0	0	0	0	0	0	0	0	0	1	1	0	1	1	1	0	1	0
Question 6	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1	1
Question 7	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	0	1	1
Question 8	1	1	0	1	0	0	0	0	0	0	0	0	1	1	1	1	0	1	1	1
Question 9	0	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	1
Question 10	1	1	0	0	1	0	1	0	1	1	1	0	1	1	0	1	0	0	1	1
Question 11	1	1	0	1	1	1	1	0	1	0	1	1	0	0	0	1	1	0	1	1
Question 12	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	0	1	1	0
Question 13	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1	1	1	1	1
Question 14	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0	0	0
Question 15	0	1	0	0	0	0	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Question 16	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Question 17	0	0	0	0	0	0	0	0	1	1	0	0	0	0	1	1	0	0	0	0
Question 18	0	0	0	1	1	0	1	1	1	1	0	1	1	0	1	1	0	0	1	1
Question 19	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Question 20	1	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	1	1	1	1
Question 21	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Question 22	1	1	1	1	1	1	1	1	1	1	0	1	1	1	0	1	1	1	1	1
Question 23	0	1	1	0	1	0	1	1	1	1	1	1	0	1	1	0	0	1	1	1
Question 24	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	0	0	0	1	0
Question 25	0	0	1	0	0	0	0	0	1	0	0	1	1	0	0	0	1	0	1	0
Question 26	0	1	1	1	1	1	0	1	1	0	1	1	1	1	1	1	1	0	1	1
Question 27	1	0	0	0	1	0	0	0	0	0	1	0	0	0	1	0	0	0	0	1
TOTAL SCORE	17	20	15	18	19	15	15	15	21	17	18	19	18	17	20	18	17	13	22	20

NOTE: 0 = No/Unable to determine, 1 = Yes. Only question 5 could be answered 0 = No, 1 = Partially, 2 = Yes, Cut-off total score: 24–28 points (excellent), 19–23 points (good), 14–18 points (fair), 14 points or less (poor)

4 Discussions

To the best of our knowledge, this is the first systematic review to offer a comprehensive panoramic of VR interventions implemented both with adult and pediatric cancer patients. Twenty studies were eligible for the review, and they included both educational and psychological VR interventions. The majority of these interventions showed complete or partial effectiveness of VR, demonstrating that this technology is an optimal delivering modality for psycho-educational interventions. Most studies we included in the systematic review carried out psychological interventions. The common thread between these interventions is the use of distraction as a strategy to reduce patients' distress during medical procedures and treatments. VR distraction has been identified as a promising emotion-focused method aiming at improving tolerance during medical procedures, mostly by reducing the distress and pain that patients experience [72]. According to Lazarus and Folkman's stress and coping model, when people acknowledge that there is nothing they can do to change a stressful situation, they tend to adopt emotion-focused coping strategies (e.g., distraction) to regulate their emotional response [73]: distraction diverts attention away from unpleasant stimuli toward intriguing ones, reducing tension and anxiety [70]. The mechanism behind the functioning of distraction is that human beings have the cognitive resources to process a limited pool of information: using the capacity for one activity limits their availability for another task, preventing other information from being processed and accessing consciousness [74]. VR is a tool of choice in achieving this goal thanks to the possibility of visually showing to the participant the distractor, and offering a sense of presence in the situation. When in the virtual environment, participants have the opportunity to interact with the distractor (e.g., playing the role of a character in the distracting virtual environment), or to just be receptive to the virtual world without interacting with it (e.g., watching a relaxing scuba dive in the ocean). In both cases the individual makes changes in their mental health in a passive way: VR distraction works due to the inability of our mind to manage so much information at the same time, not because the individual is actively involved in improving their own mental health (e.g., by learning how to cope with anxiety or self-regulate emotional distress). The perception of control over a patient's own change improves disease management, health status, and medication adherence [75], variables that are particularly important in cancer care. For this reason, further research should compare VR distraction with other coping strategies that engage patients in a more active way, in order to investigate which is the most effective and has long-term effects on patients' well-being. Problem-focused coping, for example, includes adaptive strategies that focus on reducing or eliminating stressors through the implementation of active behaviors [76]. In this context, problem-focused coping renders the individual actively engaged in the promotion of their mental health, and could be an important factor to develop interventions that make patients feel empowered. Another important element that emerges from this review is that educational tasks represented only a small part of the interventions implemented using VR. Even if the lack of information has been identified as an unmet need of the cancer population [15, 16], educational interventions are still limited. Results from this review show that VR educational interventions are effective both for children and adults and that they can reduce patients' emotional distress by

improving patients' knowledge and understanding. Johnson and colleagues [77] underline that patients themselves identify VR as an appropriate and important educational tool to include in cancer care for improving patients' understanding. Specifically, patients consider VR particularly effective in reducing anxiety thanks to the ability to recreate the spatial and acoustic aspects of cancer therapy. Educational studies generally exploit the cognitive-behavioral strategy known as exposure. Exposure-based techniques are broadly used in treating anxiety disorders: by confronting the feared stimuli and incorporating corrective information in the memory, exposure-based techniques decrease the distress experienced, disconfirming the dysfunctional associations [78]. In the educational studies we included, the authors used what we could define as an "informative exposure". Patients are exposed through VR to a simulation of the real experience they will face once the treatment will start: by doing that, they not only reduce the uncertainty associated with the procedure but also acquire the knowledge to predict the steps they will go through. This exposure process allows the patients to restructure their expectancies, reducing the anxiety experienced before the beginning of the treatment. In medical settings where the in vivo exposure (e.g., doing with the patients a tour of the surgical room) may be time-consuming and not always possible, the benefits of adopting VR are numerous. This technology creates an immersive experience, giving the patient the feeling of being in the treatment: the patient can wander around the virtual room and view the therapy from various perspectives. Using VR also decreases the risks (e.g., contamination) associated with physically going to a sterile operating room, radiotherapy vault, or chemotherapy chair, it decreases the amount of time needed in doing the same process in person, and the human and economic resources necessary to do that. VR exposure has recognized effectiveness, greater than in vivo exposure [79], and similar to the classical evidence-based interventions with no VR exposure [80]. By virtue of exposure effectiveness, and the importance that educational interventions have in rendering patients empowered and involved in their treatment, it is extremely important to include psycho-education in cancer care and the optimal tool to reach this goal is VR.

The studies included in this review are not without their limitations. First, only half of the studies included an assessment of the adverse events that may have taken place during the VR intervention. This appears as an extremely important element to incorporate in VR interventions due to the cybersickness (i.e., nausea, headache, and dizziness) that users may experience during or after VR immersion [81]. Secondly, the studies often did not include visual material (e.g., photos, screenshots, videos) to offer more insights into the VR environments used for the intervention. The absence of a clear understanding of how the scenario looks and its specific characteristics may affect the replicability of the results, and increase the risk of bias. A third limitation is the small sample size that characterized some of the studies. Although the difficulties that clinical researchers have in recruiting patients are well recognized, when the samples are very small it is hard to draw firm findings. Thus, to assess effectiveness in a variety of therapeutic contexts, and to make concrete and stable conclusions to refer to the population of interest, future large-scale research comparing VR to other technologies is needed. Lastly, an additional limitation to these studies is that confounders are often not made explicit nor taken into account during the analysis, increasing the risk of bias of the studies. This is especially true when VR interventions are implemented for the length

of the medical procedure because VR exposure is performed "as long as the procedure execution". Being implemented from a human being on another human being, a medical procedure rarely lasts the same amount of time for different people, leading participants to different exposures both to the VR and to the control condition. Therefore, it would be essential to keep this element into account both in the analysis and in the confounders' assessment in order to increase the methodological quality of these interventions.

In conclusion, VR seems to be a promising tool for supporting cancer patients' well-being. Two main focuses emerged from this systematic review: psychological interventions predominantly used emotion-focused strategies (i.e., distraction) to reduce patients' emotional distress, while educational studies employed cognitive-behavioral strategies (i.e., exposure) to restructure patients' beliefs towards oncological treatments and reduce their anxiety. However, if on the one hand educational VR interventions support cancer patients in actively acquiring skills for coping with their diagnosis, on the other hand, psychological VR interventions surprisingly do not, assigning a passive role to the patient. For a greater adherence to medical treatments and a meaningful enhancement of patients' psychological and physical well-being, psychological VR interventions need to switch their locus of control from an external to an internal focus, empowering patients. Psychological VR interventions have the potential to become the means to achieve patients' empowerment, assisting them in discovering and using their own intrinsic potential to master their cancer diagnosis. When patients receive a cancer diagnosis, they feel powerless and hopeless: psycho-oncological VR interventions need to fit into this point, accompanying the patient in regaining a perception of control over their life. This will allow the clinical research to have a real impact on the clinical practice and on patients' well-being. Therefore, future research should focus not only on improving the methodological quality of the studies but also on developing new interventions that can fulfill this essential and profound switch. It is the will of our team to develop VR experiences that embrace this change of mindset: starting from the results of this systematic review, we will harmonize psychological and educational tasks within the same VR intervention, with the aim of making the patient an active character of their own well-being [82].

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