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Original Paper

Digital Biomarkers of Symptom Burden Self-Reported by Perioperative Patients Undergoing Pancreatic Surgery: Prospective Longitudinal Study

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Abstract

Background: Cancer treatments can cause a variety of symptoms that impair quality of life and functioning but are frequently missed by clinicians. Smartphone and wearable sensors may capture behavioral and physiological changes indicative of symptom burden, enabling passive and remote real-time monitoring of fluctuating symptoms

Objective: The aim of this study was to examine whether smartphone and Fitbit data could be used to estimate daily symptom burden before and after pancreatic surgery.

Methods: A total of 44 patients scheduled for pancreatic surgery participated in this prospective longitudinal study and provided sufficient sensor and self-reported symptom data for analyses. Participants collected smartphone sensor and Fitbit data and completed daily symptom ratings starting at least two weeks before surgery, throughout their inpatient recovery, and for up to 60 days after postoperative discharge. Day-level behavioral features reflecting mobility and activity patterns, sleep, screen time, heart rate, and communication were extracted from raw smartphone and Fitbit data and used to classify the next day as high or low symptom burden, adjusted for each individual's typical level of reported symptoms. In addition to the overall symptom burden, we examined pain, fatigue, and diarrhea specifically.

Results: Models using light gradient boosting machine (LightGBM) were able to correctly predict whether the next day would be a high symptom day with 73.5% accuracy, surpassing baseline models. The most important sensor features for discriminating high symptom days were related to physical activity bouts, sleep, heart rate, and location. LightGBM models predicting next-day diarrhea (79.0% accuracy), fatigue (75.8% accuracy), and pain (79.6% accuracy) performed similarly.

Conclusions: Results suggest that digital biomarkers may be useful in predicting patient-reported symptom burden before and after cancer surgery. Although model performance in this small sample may not be adequate for clinical implementation, findings support the feasibility of collecting mobile sensor data from older patients who are acutely ill as well as the potential clinical value of mobile sensing for passive monitoring of patients with cancer and suggest that data from devices that many patients

already own and use may be useful in detecting worsening perioperative symptoms and triggering just-in-time symptom management interventions.

KEYWORDS

Introduction

Cancer treatments such as chemotherapy and surgery cause a variety of symptoms and side effects that can impair subjective quality of life and functioning. Across a variety of cancer types, fatigue, pain, nausea, and other physical symptoms are highly prevalent and often severe [1,2], and many patients experience multiple symptoms simultaneously [3]. Patients who report more significant symptoms tend to exhibit worse performance status and functional ability [4,5]. Unfortunately, symptoms remain undetected by clinicians up to half of the time [6,7], limiting opportunities for timely and effective clinical management and resulting in undue patient suffering and functional impairment.

Remotely monitoring symptoms *between* hospital or clinic visits may improve our ability to capture severe or bothersome symptoms when they begin to emerge [8]. Smartphones, now owned by 81% of adults and increasing proportions of older adults, those living in rural areas, and all racial groups, offer new opportunities for remote symptom monitoring [9]. Systems leveraging smartphones for real-time patient-reported outcome (PRO) assessment during outpatient chemotherapy have been demonstrated to be feasible [10,11] and to reduce chemotherapy-related morbidity [12]. Although daily PRO symptom data are valuable, long-term assessment of PROs (eg, over months or years of chemotherapy) is burdensome. Indeed, previous work suggests that patients become significantly less compliant at recording symptoms over time [13], with patient compliance dropping to below 50% after 1 month in one longitudinal study [14]. Developing a remote symptom monitoring system that is less reliant on patient compliance may enable longitudinal symptom tracking and management throughout cancer treatment and even after treatment is completed, when symptoms persist for many survivors.

Smartphones are equipped with a rich array of sensors capable of measuring many behavioral and contextual variables, including mobility, location, ambient light and noise, and social interactions [15]. Most users keep their smartphones within arm's reach at all times and spend over 4 hours per day interacting with the device [16]. Thus, smartphones can gather digital traces as individuals go about their daily routines. From these raw digital data, meaningful behavioral features such as number of unique locations visited, number of outgoing calls placed, and average level of ambient noise detected during the night can be calculated to provide information about behavior patterns in real-world contexts [17].

Smartwatches and other wearable commercial activity monitors are also becoming more widely used, with about 1 in 5 adults using a wearable device [9]. Wearable devices contain sensors such as accelerometers and photoplethysmography which can provide continuous information about activity, sleep, and physiology (eg, heart rate). Together, these mobile sensing technologies enable objective assessment of behavioral patterns that may reflect worsening health status, including severe or increasing symptoms. Moreover, this high-density, multimodal, and objective data collection can be completed with minimal burden to patients; this feature makes this approach highly scalable and appropriate for remotely monitoring patients, even older patients and those who are acutely ill and even over long periods. Given evidence that physical activity and sleep behaviors as well as heart rate have prognostic value in oncology, technology that enables passive quantification of these metrics holds considerable promise for clinical cancer research [18-20].

Applying machine learning classification to smartphone sensor data has been shown to accurately discriminate depressed from nondepressed individuals [21], to recognize depressive and manic episodes in patients with bipolar disorder [22-24], to predict mental health indicators in schizophrenia [25], and to detect binge drinking and other substance use [26]. These methods can also shed light on *which* behavioral features are most useful for detecting or predicting mental health states or risky behaviors. Work applying this approach to passively detect physical health status in patients with cancer is more limited, but results from 14 recent small studies suggest that wearable and smartphone sensor data are related to symptom burden, quality of life, and other clinical oncology outcomes [27].

The perioperative context is an especially critical time for remote patient monitoring, as complications after cancer surgery are common and can escalate into re-admissions that may be preventable if detected and managed earlier. Results from similar studies of patients undergoing surgical oncology procedures found that accelerometer data were useful for quantifying differences in postoperative recovery [28] and for predicting re-admission risk [29]. In this study, we aimed to examine whether smartphone and wearable sensors can be useful in detecting overall patient-reported symptom burden as well as 3 specific physical symptoms (fatigue, pain, and diarrhea) among patients undergoing pancreatic cancer surgery, a complex but potentially curative procedure with postoperative morbidity rates as high as 40% [30].

Methods

Participants

Potential study participants were identified for the study by their surgical oncology care team. Men and women aged 18 years or older who were scheduled for pancreatic surgery at a large academic cancer center were eligible and were enrolled at their

preoperative clinic visit. Of 72 eligible and approached patients, 60 consented to participate in this study. Surgery was canceled for 4 patients, and 2 withdrew from the study prior to surgery due to poor health or feeling overwhelmed. An additional 10 had insufficient sensor data for analyses based on data cleaning thresholds (described in detail later), leaving 44 participants in our analytic sample (mean age 65.7 years, range 40-82; 41% [18/44] female; 93% [41/44] white). Most patients were undergoing surgery (75% [33/44] robotic, 16% [7/44] open, 9% [4/44] laparoscopic) for pancreatic cancer (36/44, 82%), with the remainder undergoing surgery for benign conditions (eg, pancreatic cysts). Participants were enrolled from January to September 2017.

Study Procedure

Study assessments began prior to surgery and continued during inpatient recovery after surgery (mean 7-day stay, range 2-22) and for 60 days after postoperative discharge. A total of 13/44 patients (30%) were re-admitted to the hospital at some point during the 60 days. At their preoperative visit, participants were provided with an Android smartphone with the AWARE app installed [31]. AWARE was used to passively collect smartphone sensor data, including movement and approximate location of the phone, device use, metadata about call and SMS events, and ambient light and noise levels. AWARE was also used to collect patient-reported symptom ratings each morning; participants rated the severity of 10 physical and psychological symptoms (pain, fatigue, sleep disturbance, trouble concentrating/remembering things, feeling sad or down, feeling anxious or worried, shortness of breath, numbness or tingling, nausea, diarrhea or constipation) on a scale from 0 (not present) to 10 (as bad as you can imagine). These symptoms were selected because they reflect common core symptoms during oncology treatment [32] and the symptom severity rating format was adapted from the MD Anderson Symptom Inventory [33]. AWARE stored this information on the device and transmitted deidentified data to a secure server over a secure network connection when the device was connected to Wi-Fi. Participants were asked to keep the phone charged and with them at all times and to use the phone for communication as much as possible.

Participants were also given a Fitbit Charge 2 device to wear for the duration of the study, which they were invited to keep after study completion. The Fitbit collected data about activity, sleep, and heart rate. The Fitbit Charge 2 has been shown to measure activity and sleep parameters with acceptable accuracy in older free-living adults [34].

After study completion, participants returned the mobile phones to the study team and received a compensation of US $150. The University of Pittsburgh institutional review board approved all study procedures.

Data Processing and Analytic Approach

Patient-Reported Symptoms

To compute daily symptom burden scores, we summed all 10 symptom ratings to create a composite reflecting total daily symptom burden (mean 15, range 0-97). We then calculated the mean daily symptom burden for each individual patient and then subtracted individual means from each of that patient's

daily symptom burden scores and categorized the resulting residual into average or below average (residual of daily score – individual mean ≤ 0) or high (residual of daily score – individual mean > 0). This approach allowed us to classify each day as a high or low symptom burden day, adjusting for each individual's typical level of reported symptoms. Approximately 35.99% (487/1353) of all days were classified as high symptom days (proportion of high symptom days for individual patients ranged from ranged from 0% [0/11] to 80% [8/10]). As the data set was imbalanced, we used the support vector machine synthetic minority over-sampling technique (SVM SMOTE) to resample the minority class. We also examined 3 specific physical symptoms (pain, fatigue, and diarrhea because these were the most common in our sample) using a similar approach.

Passive Smartphone and Wearable Sensor Data

We computed day-level (24 hours from midnight to midnight) behavioral features from both AWARE and Fitbit data using our Reproducible Analysis Pipeline for Data Streams (RAPIDS) [35]. Accelerometer, activity recognition, application, battery, call, conversation, light, location, SMS text message, and screen features were extracted from AWARE data. Heart rate, step, and sleep features were extracted from Fitbit data. For sleep, features were extracted for any sleep episodes that ended on that day to capture both overnight main sleep and naps. In total, we extracted 213 features from smartphone and Fitbit data; feature descriptions can be found in RAPIDS documentation [35,36]. We also included 3 additional features judged to be important for symptom prediction: (1) days since surgery, because symptoms tended to considerably increase immediately after surgery and then decline over time; (2) most recent symptom burden score, given that high symptom burden scores today tended to predict high symptom burden tomorrow; and (3) participant's average symptom burden score up to current time point, given the substantial between-participant variability in the range of symptom severities reported. Because symptom ratings were completed each morning, sensor data were used to predict the next day's symptom burden class.

We dropped sensor and symptom data from the date of surgery (as devices were with caregivers while patients were in the operating room) and from days that the patient was hospitalized (both after surgery and during any subsequent re-admissions, as we anticipated behavioral patterns to differ systematically in the hospital and we are most interested in detecting symptoms when patients are not in a health care setting).

To clean data, we first excluded days with less than 20 hours of sensor data and participants with fewer than 5 days of sensor data. We then dropped features missing more than 30% of values (days) or with 0 variance as well as days missing more than 30% of values (features). We merged sensor data with high/low symptom labels, then again filtered out participants with less than 5 days of valid labeled sensor feature data. After data cleaning, we had 1353 (mean 30.75, range 5-67 per patient) days of sensor data including 142 features from 44 patients.

On average, participants were missing 7.25% of data values (range 0%-19.08%). For each participant, we imputed continuous missing data as follows: (1) missing features in the training set (ie, subset of data used to train the model) were

replaced with the average of the 2 closest days; (2) missing features in the test set (ie, subset of data used to evaluate model performance) were replaced with the last valid day's feature from the training set; and (3) if a participant is missing a specific feature, replace it with the average from the rest of the participants' data. We imputed categorical missing data as follows: (1) missing features were replaced with the mode of that participant's training data; (2) if a participant is missing a specific feature, replace it with the mode of the remaining participants' training data.

Categorical features were converted into integer representation via one-hot encoding. Because the scale of features will not influence the results of tree-based algorithms (eg, light gradient boosting machine [LightGBM]), we normalized numerical features with either min–max, z-score, or scikit-learn package's robust scaler for the rest of the models. A total of 75 features were selected via mutual information.

We evaluated a number of different binary classifiers, including logistic regression, k-nearest neighbors, support vector machine, random forest, gradient boosting, extreme gradient boosting, and LightGBM. Model performance (ability of the model to generate predicted binary class labels [0 vs 1] that match true class labels) was compared with several baselines: majority class, random weighted classifier, and decision tree using days since surgery, most recent score, and average score (ie, the 3

nonsensor features used in our models). We used nested cross-validation. Three-fold cross-validation was considered for the inner loop to tune hyperparameters and leave-one-day-out cross-validation was considered for the outer loop to evaluate performance and calculate accuracy, precision, recall, F1, and area under the receiver operating characteristic curve (AUC) across all folds. Because our ultimate goal is real-time clinical implementation of these algorithms, we trained models only on past data from that participant as well as data from other participants (ie, data collected after the test day were not included in the training set for that fold). The code for feature extraction and analysis is available online [37].

Results

Models using LightGBM performed best for the population model. We used 0 as the random seed, 200 as the number of boosted trees, and 128 as the maximum tree leaves. The learning rate was chosen from {0.008, 0.01, 0.012} and the subsample ratio of columns when constructing each tree was chosen from {0.68, 0.7, 0.72}. Using this approach, models using smartphone and wearable feature data were able to correctly predict whether the next day would be a high symptom day with 73.5% accuracy (0.611 recall for the high symptom class and 0.772 AUC). This model surpassed the accuracy and performance of all 3 baseline models (Table 1).

Table 1. Performance of population models classifying next-day symptom class.[a]

Method	Accuracy (%)	Precision0 (%)	Recall0 (%)	F10 (%)	Precision1 (%)	Recall1 (%)	F11 (%)	Macro F1[b] (%)	AUC (%)
Baseline1: majority class	64.5	64.5	100.0	78.4	0.0	0.0	0.0	39.2	50.0
Baseline2: random weighted classifier	54.1	64.4	64.4	64.4	35.5	35.5	35.5	50.0	50.0
Baseline3: decision tree with nonsensor features	67.5	75.5	73.3	74.4	54.0	57.0	55.5	64.9	65.1
LightGBM	73.5	78.9	80.4	79.7	63.2	61.1	62.2	70.9	77.2

[a]0=average or lower than average symptom burden; 1=higher than average symptom burden.

[b]Macro F1 score refers to the average of the 2 F1 scores.

The most important features included the most recent symptom burden score, days since surgery, average symptom burden score, duration of active and exertional activity bouts, minimum heart rate, number of unique activities, time spent at the most frequent location, maximum ambient lux, total duration of time awake and asleep, and total duration of the heart rate in cardio zone (70%-84% of the participant's maximum heart rate) and peak zone (85%-100% of the participant's maximum heart rate; Figure 1). In this plot, features with many instances in red with SHAP (SHapley Additive exPlanations) [38] value greater than 0 had a positive relationship with symptom burden (eg, longer median duration of nonexertional episodes related to high symptom burden), whereas those in blue had an inverse association (eg, shorter total duration of active bouts related to high symptom burden).

We also generated population models for diarrhea, fatigue, and pain, respectively. All steps are the same as above except for the target values. Instead of calculating the labels based on the summation of all 10 symptom ratings, diarrhea score or fatigue score or pain score is applied directly.

Like the overall symptom burden results, LightGBM models outperformed all 3 baseline models and predicted next-day diarrhea with 79.0% accuracy (AUC 83.41%), next-day fatigue with 75.8% accuracy (AUC 80.29%), and next-day pain with 79.6% accuracy (AUC 83.48%; Table 2). Location features are very important for diarrhea prediction, while step features and sleep features are very important for fatigue prediction and pain prediction, respectively. The most recent symptom burden score, days since surgery, and average symptom burden score are the most important features for all symptoms.

Figure 1. Density scatter plot showing SHapley Additive exPlanation (SHAP) values for each feature, reflecting how much impact each feature has on model output. Features with many instances in red with SHAP values greater than 0 are positively associated with symptom burden, while those with many blue instances are inversely associated with symptom burden.
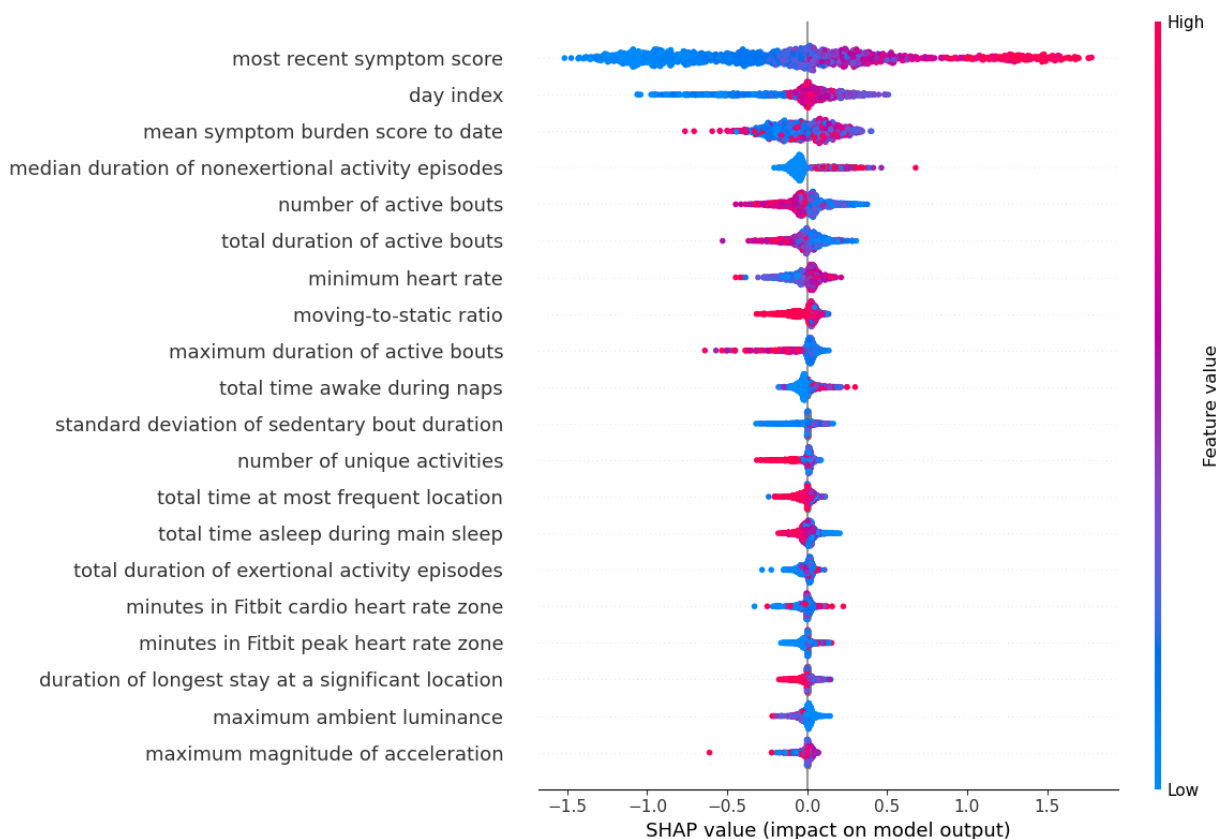

Table 2. Performance of population models classifying next-day diarrhea or fatigue or pain symptom class (1=higher than average) from wearable and smartphone sensors.

Target (symptom) and method	Accuracy (%)	Precision0 (%)	Recall0 (%)	F10 (%)	Precision1 (%)	Recall1 (%)	F11 (%)	Macro F1 (%)	AUC (%)
Diarrhea									
Baseline1: majority class	67.4	67.4	100.0	80.5	0.0	0.0	0.0	40.3	50.0
Baseline2: random weighted classifier	56.0	67.4	67.4	67.4	32.5	32.5	32.5	49.9	49.9
Baseline3: decision tree with nonsensor features	73.2	82.0	77.2	79.5	57.9	64.9	61.2	70.3	71.0
LightGBM	79.0	85.0	83.7	84.3	67.3	69.4	68.3	76.3	83.4
Fatigue									
Baseline1: majority class	64.7	64.7	100.0	78.6	0.0	0.0	0.0	39.3	50.0
Baseline2: random weighted classifier	54.3	64.7	64.7	64.7	35.3	35.3	35.3	50.0	50.0
Baseline3: decision tree with nonsensor features	67.0	75.9	71.8	73.8	53.0	58.2	55.4	64.6	65.0
LightGBM	75.8	81.2	81.5	81.4	65.9	65.5	65.7	73.5	80.3
Pain									
Baseline1: majority class	70.4	70.4	100.0	82.7	0.0	0.0	0.0	41.3	50.0
Baseline2: random weighted classifier	58.4	70.5	70.4	70.4	29.6	29.6	29.6	50.0	50.0
Baseline3: decision tree with nonsensor features	74.4	82.4	81.0	81.7	56.5	58.8	57.6	69.7	69.9
LightGBM	79.6	85.7	85.3	85.5	65.4	66.0	65.7	75.6	83.5

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Discussion

The purpose of this prospective longitudinal study was to evaluate passive smartphone and wearable sensor features as predictors of symptom burden in perioperative patients undergoing pancreatic surgery. Results suggest that machine learning models developed using mobile sensor data were more accurate than non–sensor-based baseline models in predicting whether the next-day patient-reported overall symptom burden would be higher than average for that patient. The most important features for symptom prediction included features related to physical activity, heart rate, and location. Models also accurately predicted next-day diarrhea, fatigue, and pain, although the most important features in each model differed across specific symptoms.

This work contributes to a small but growing literature investigating associations between consumer mobile sensors and clinical outcomes in oncology [27]. Similar to studies of patients undergoing chemotherapy [39] and hematopoietic cell transplant [40], features related to physical activity were most strongly related to fluctuations in physical symptom severity. Feature importance revealed that these were not simple features such as daily step counts but rather features reflecting patterns of activity and included measurements from both wearable Fitbit devices (eg, number, total duration, and maximum duration of active bouts) and smartphones (eg, duration of nonexertional episodes from phone accelerometer, number of unique activities recognized). Heart rate and sleep features were also important, suggesting that future work in this area should consider using wearable devices that enable collection of 24-hour behavioral and physiological data and examination of circadian rest-activity rhythms previously linked to outcomes in patients with cancer [41].

Because wearable and smartphone sensor data can be collected continuously as patients go about their daily lives, requiring minimal effort or attention from patients or their caregivers, mobile sensing offers an opportunity for long-term remote patient monitoring over months or years of cancer treatment and survivorship. This study supports the feasibility of collecting mobile sensor data, even from patients who are seriously ill during times of acute sickness and recovery. Despite undergoing invasive surgery and (for most patients) grappling with one of the deadliest cancer diagnoses, over 80% of participants had sufficient sensor data for analyses. This is also noteworthy given that the average age of patients was over 65 and that, as these data were collected in 2017, participants varied considerably in their comfort and familiarity with mobile technology.

Although models trained on past mobile sensor data outperformed baseline models, model performance still may not be adequate for clinical implementation. For example, recall of the high overall symptom burden class (when timely clinical action would be needed) was only 61%, meaning nearly 40%

of high symptom days would be missed by our model. This may be due in part to the relatively small sample and data set, the use of study-provided (rather than personal) smartphones, or the powerful effect of major abdominal surgery and prolonged hospitalization on patient symptom profiles as well as behavior. Future studies with larger samples that collect data using their own personal devices over a period with less dramatic shifts in symptoms and behavior may yield better model performance. In future studies with larger data sets more robust to class imbalance, setting a higher threshold for severe symptoms requiring care provider attention or intervention may also result in more clinically useful models. Regardless, mobile sensor data may be a useful complement to patient-reported symptom data, allowing for a more personalized and adaptive delivery of symptom ratings when behavioral fluctuations are detected, reducing patient burden and improving early capture of worsening side effects and symptoms. Predictive models based on sensor and patient-reported data could also be used to deliver symptom self-management instructions to patients, an approach demonstrated to benefit patients undergoing pancreatic cancer surgery [42].

Given the small data set, we focused on building population models that used data from all other participants, which also may have constrained model performance. Because each participant had on average only 30 rows of data, individual models were unstable, but with more training data could be useful in learning patterns based on each participant's behavior and its relationship to symptoms and developing more accurate predictions. Developing models based on similar subgroups of participants (based on demographic, clinical, or behavioral factors) could be a useful approach for future work and could yield superior results to a single population model.

Strengths of the study include longitudinal sensor data collection over a wide perioperative window, from presurgery to 60 days after discharge following pancreatic surgery. We considered a wide range of features from both wearable and smartphone sensors and examined prediction of next-day overall symptom burden as well as next-day pain, fatigue, and diarrhea specifically. Our models were also trained on past data only so that we could evaluate how well models could perform if implemented in real-world clinical settings.

This study suggests that digital biomarkers may be useful in predicting patient-reported symptom burden during cancer treatment. In an ongoing study, we are following up on this work by collecting 3 months of smartphone and wearable sensor data as well as daily symptom reports from a large sample of patients undergoing outpatient chemotherapy. With a larger outpatient sample using their own smartphones, we hope to improve upon the models developed here and to use real-time next-day symptom predictions to deliver more timely and personalized symptom management support.

Acknowledgments

Conflicts of Interest

MH receives an unrestricted education grant from Intuitive Surgical. All other authors declare no conflicts of interest.

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Abbreviations

AUC: area under the ROC curve
LightGBM: light gradient boosting machine
PRO: patient-reported outcome
RAPIDS: Reproducible Analysis Pipeline for Data Streams
ROC: receiver operating characteristic
SHAP: SHapley Additive exPlanations
SVM SMOTE: support vector machine synthetic minority over-sampling technique

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Review

The Value of Web-Based Patient Education Materials on Transarterial Chemoembolization: Systematic Review

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Abstract

Background: Thousands of web searches are performed related to transarterial chemoembolization (TACE), given its palliative role in the treatment of liver cancer.

Objective: This study aims to assess the reliability, quality, completeness, readability, understandability, and actionability of websites that provide information on TACE for patients.

Methods: The five most popular keywords pertaining to TACE were searched on Google, Yahoo, and Bing. General website characteristics and the presence of Health On the Net Foundation code certification were documented. Website assessment was performed using the following scores: DISCERN, Journal of the American Medical Association, Flesch-Kincaid Grade Level, Flesch Reading Ease Score, and the Patient Education Materials Assessment Tool. A novel TACE content score was generated to evaluate website completeness.

Results: The search yielded 3750 websites. In total, 81 website entities belonging to 78 website domains met the inclusion criteria. A medical disclaimer was not provided on 28% (22/78) of website domains. Health On the Net code certification was present on 12% (9/78) of website domains. Authorship was absent on 88% (71/81) of websites, and sources were absent on 83% (67/81) of websites. The date of publication or of the last update was not listed on 58% (47/81) of websites. The median DISCERN score was 47.0 (IQR 40.5-54.0). The median TACE content score was 35 (IQR 27-43). The median readability grade level was in the 11th grade. Overall, 61% (49/81) and 16% (13/81) of websites were deemed understandable and actionable, respectively. Not-for-profit websites fared significantly better on the Journal of the American Medical Association, DISCERN, and TACE content scores.

Conclusions: The content referring to TACE that is currently available on the web is unreliable, incomplete, difficult to read, understandable but not actionable, and characterized by low overall quality. Websites need to revise their content to optimally educate consumers and support shared decision-making.

Trial Registration: PROSPERO International Prospective Register of Systematic Reviews CRD42020202747; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020202747

KEYWORDS

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Introduction

Background

The World Wide Web has greatly facilitated access to medical knowledge for consumers. Nowadays, 6 to 7 of 10 internet users browse the web in search of health-related answers [1,2]. In fact, consumers are four times more likely to turn to the internet first rather than to a physician [3]. Although most users still believe that physicians are the most trustworthy information source, more than half shape their health-related decisions based on information they obtain from the web and may consequently decide against visiting a medical professional [1-4]. However, the quality of websites is often questionable. Websites may contain distracting information and incomprehensible content and may not meet the standards to facilitate medical decision-making [5-9].

Health literacy (defined as the ability to read, understand, and act on health-related information) is a major determinant of the way people process the information they obtain from the web [10,11]. Older people or those with a low educational level tend to have poor health literacy; practice ineffective ways of web searching; and are more vulnerable to physical, emotional, or financial harm caused by inaccurate information [12-14]. As approximately 36% of adults in the United States lack adequate health literacy, the need for reliable and comprehensible websites has become more critical [11,15].

Patients may be skeptical and nervous when they are referred for a procedure they are unfamiliar with and may lack the capacity to fully process the educational materials they are provided [16]. This holds true for interventional radiology (IR) procedures that, despite their multiple applications and benefits, are not widely known to the general public. Although minimally invasive procedures are generally preferred among patients, there is still a considerable lack of awareness of procedures performed by interventional radiologists [17,18].

One of the most widely used procedures in the armamentarium of interventional oncology is transarterial chemoembolization (TACE), which is recommended as the standard of care for select cases of primary or metastatic liver tumors [19]. Web-based content referring to TACE can be found on a wide range of websites (eg, scientific journals, patient blogs, and commercial websites), most of which target medical professionals rather than the average reader. The availability of high-quality, consumer-friendly websites is essential to ascertain that patients can accurately self-educate and make informed decisions. Improved patient education may also have clinical benefits, as it has been linked to more favorable outcomes, such as lower rates of postchemoembolization pain [20].

Studies evaluating websites that provide patient information on IR procedures have been published previously. McEnteggart et al [21] assessed the readability of websites discussing 7 IR procedures (central venous catheter placement, vertebroplasty, varicocele embolization, deep vein thrombosis treatment, transjugular intrahepatic portosystemic shunt, uterine artery embolization, and peripheral artery angioplasty) and found their readability to be below the recommended grade level. Murray et al [22], Alderson et al [23], and Lee et al [24] evaluated the quality and readability of websites referring to uterine artery, varicocele, and pelvic vein embolization, respectively. Website quality was found to be fair, and readability was suboptimal. However, to date, no study has evaluated web-based patient education resources referring to TACE.

Objective

The aim of this study is to evaluate the reliability, quality, readability, and completeness (using a novel content score) of websites that provide patient information about TACE.

Methods

Overview

A protocol delineating the objectives of the study, the outcomes of interest, and assessment criteria was registered with the International Prospective Register of Systematic Reviews (identification number CRD42020202747). This systematic review was performed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [25].

Study Design

A keyword analytic tool named *Keywords Everywhere* was used to identify the most common keywords pertaining to TACE that are used in web searches globally [26]. The five keywords that were isolated, followed by their respective search volume (average number of searches performed per month over the last 12 months), were as follows: *tace* (40,500), *tace procedure* (6600), *chemoembolization* (2400), *tace in hcc* (1300), and *transarterial chemoembolization* (1300).

The three most popular search engines based on global traffic rankings were selected: Google, Yahoo, and Bing [27]. The website search was performed on May 24, 2020. Web browser cookies and search history were erased so that the search was not influenced by the reviewer's prior searches. Geolocation was turned off before the search to eliminate any geographical bias. The first 250 results of the five keyword searches on each of the three search engines were downloaded on a Microsoft Excel spreadsheet. Duplicate websites were initially eliminated by the *Remove duplicates* tab in the Excel sheet. As URL addresses with minor alterations (eg, *http* vs *https*) can redirect to the same website, all the remaining website links were opened by one reviewer (GAS), who manually removed the rest of the duplicates. Inaccessible websites or websites with password-restricted access were excluded.

After removal of duplicate and inaccessible links, websites were excluded if they were (1) not in English, (2) irrelevant, (3) discussing TACE using less than 300 words (similar to the study by Hirsch et al [28]), (4) clearly addressing a scientific audience (eg, journal articles, medical newsletters, and treatment guidelines), (5) containing only medical education materials (eg, lecture slides and e-books), (6) providing only discharge instructions, (7) containing only audiovisual material (video), and (8) describing personal experiences of patients (eg, blogs, diaries, and commentaries). Websites discussing TACE with drug-eluting beads or embolization therapy for liver cancer were

considered relevant. Eligible websites that directed to a PDF file were also included.

Webpages that belonged to the same domain and served as a succession of one another were evaluated as a website entity. Webpages that belonged to the same domain but served as an independent and stand-alone resource were evaluated separately. Website screening and extraction of website characteristics were performed by one reviewer (GAS). Comprehensive website assessment was performed by 2 medical doctors (GAS and ATV). To limit bias, only one of the 2 reviewers had experience with TACE (GAS). Both reviewers worked independently on a predefined Excel spreadsheet. Discrepancies were resolved through discussion.

Website Characteristics

Websites were categorized based on website owners into four categories: nonacademic hospitals (eg, community health care institutions), academic hospitals (eg, university health care institutions), not-for-profit organizations (eg, governmental or nongovernmental organizations and medical societies), and for-profit organizations (eg, private medical groups and commercial companies). The website owner, country of origin, date of creation, and date of the last update were extracted. The presence of a privacy statement and medical disclaimer and the number of images, videos, and advertisements were documented. The word count of each website was measured via a web browser extension named *Word Counter Plus* [29]. Only the words in the main text contributed to the total word count, whereas the text on the margins of the webpage, the contact information, and the references were disregarded. Websites with supplemental video content were excluded from the word count analysis. However, information from the videos was considered when evaluating the content of a website.

Health On the Net Foundation Code

The Health On the Net (HON) Foundation Code of Conduct is a certification provided by a board of experts (HON Foundation) to websites containing objective and transparent medical information [30]. Websites should adhere to the following eight principles: (1) authority (content is written only by medical professionals), (2) complementarity (information supports and does not replace the physician-patient relationship), (3) confidentiality (readers' privacy is protected), (4) attribution (sources of information are provided), (5) justifiability (claims are balanced and objective), (6) transparency (contact details of authors are provided), (7) financial disclosure (sources of funding are provided), and (8) advertising (advertised and editorial content are clearly distinguished). A browser extension named *HONcode Toolbar* was used to identify the websites that carried the HON code badge [31].

Website Assessment Tools

Journal of the American Medical Association Score

The Journal of the American Medical Association (JAMA) score was generated to assess the reliability of health-related websites [32]. It comprises four benchmarks: (1) authorship (name, credentials, and affiliations of authors), (2) attribution (references and copyright), (3) currency (creation and review date), and (4) disclosure (ownership, sponsorship, advertising, underwriting, commercial funding arrangements or support, and conflict of interest). The total JAMA score ranges from 0 to 4. Points are awarded based on whether the subdivisions of each benchmark are addressed. Websites mentioning an editorial board for the entire website but not specifically for the TACE-related page were not given credits for authorship.

DISCERN Instrument

The DISCERN instrument has been widely used to evaluate the quality of written health information (Multimedia Appendix 1) [33]. It consists of 16 questions, each receiving points from 1 (definitive *no*) to 5 (definitive *yes*). Questions 1-8 assess the reliability of the material, questions 9-15 assess the quality of the content regarding treatment choices, and question 16 is a rating of the overall quality of the publication. To limit subjectivity between the 2 reviewers, the grading system for each question was standardized in advance, based on the DISCERN manual. The total DISCERN score spans between 16 and 80 and breaks down as excellent (68-80), good (55-67), fair (42-54), poor (29-41), and very poor (16-28).

TACE Content Score

To evaluate the completeness of the information provided by websites, a novel scoring system was created based on the 2017 Society of Interventional Radiology Quality Improvement guidelines [34] and on our expert opinion (Multimedia Appendix 2). Our TACE content score consists of 35 key points that fall under the following categories: (1) background, (2) indications, (3) contraindications, (4) benefits, (5) preoperative considerations, (6) procedure description, (7) postoperative considerations, (8) additional treatments, and (9) risks. The key points were selected based on what information is expected to be found in materials that provide information to patients. Technical aspects, such as nomenclature or size of chemoembolic agents, were not considered relevant for patients and were therefore not included in our scoring system. Each key point was awarded 2 points for full mention, 1 point for partial mention, and 0 points for no mention. Total TACE content scores are hinged between 0 and 70.

Flesch Reading Ease Score and Flesch-Kincaid Grade Level

The Flesch Reading Ease Score (FRES) and Flesch-Kincaid Grade Level (FKGL) are mathematical formulas that take into account the number of words per sentence and the number of syllables per word to quantify the readability of written materials [35]. The FRES measures the complexity of the text and corresponds to the writing style difficulty proposed by the US Department of Health and Human Sciences. The FKGL corresponds to the grade level that the reader must have to comprehend the text. Although the two scores consist of the same core metrics, they correlate inversely, so a website with a higher FRES would have a lower FKGL. Formulas such as the Gunning Fox Index that take into account the total number of complex words (ie, words that contain more than three syllables) were not preferred in our study, as many medical terms (including the word *chemoembolization*) contain more than three syllables. FRES and FKGL indexes were used instead,

as they are the most widely used and do not solely weigh polysyllabic words.

Text from each webpage was copied and pasted on a free web-based readability checker named *Readability Formulas* [36]. The selection of words for readability assessment was the same as the aforementioned selection of words for the calculation of word count. The two scores were calculated after text formatting (addition of full stops when absent, removal of references and hyperlinks, removal of bullets, and addition of commas when the listed items were single words). Websites with video content were excluded from readability analysis.

The average reading level of the US population is eighth grade; therefore, it has been suggested that website content should be written at the 6th grade level or lower [37].

Patient Education Materials Assessment Tool

The Patient Education Materials Assessment Tool (PEMAT) was developed by the Agency for Healthcare Research and Quality of the US Department of Health and Human Sciences to evaluate the understandability and actionability of patient education materials (printable or audiovisual) [38]. Understandability refers to the ability of the material to be understood by readers of varying levels of literacy, whereas actionability refers to the extent to which the material points out the potential actions that readers must take. Overall, PEMAT consists of 19 items measuring understandability and 7 items

measuring actionability. Each item is scored as 0 (*disagree*), 1 (*agree*), or NA (*not applicable*) when appropriate. The sum of all awarded points gets divided by the number of total possible points. The quotient multiplied by 100 gives the final PEMAT score for each subdivision. Materials with scores above 70% are considered adequately understandable and actionable [38].

Statistical Analysis

Medians and interquartile ranges were calculated for continuous variables, whereas frequencies and percentages were calculated for categorical variables. The chi-square test was used to compare categorical variables among the website categories. Continuous variables were compared among website categories using one-way analysis of variance and Kruskal-Wallis test. Correlation between continuous variables was examined using Pearson or Spearman rank correlation coefficients. Statistical significance was set at $P<.05$. Analyses were performed using SPSS software, version 20.0 (IBM Corporation).

Results

Search Results

A total of 3750 websites were extracted from the three search engines. Overall, 86 URLs belonging to 78 unique website domains met the inclusion criteria (Multimedia Appendix 3). After grouping the URLs with split chemoembolization content, 81 website entities were evaluated (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram.
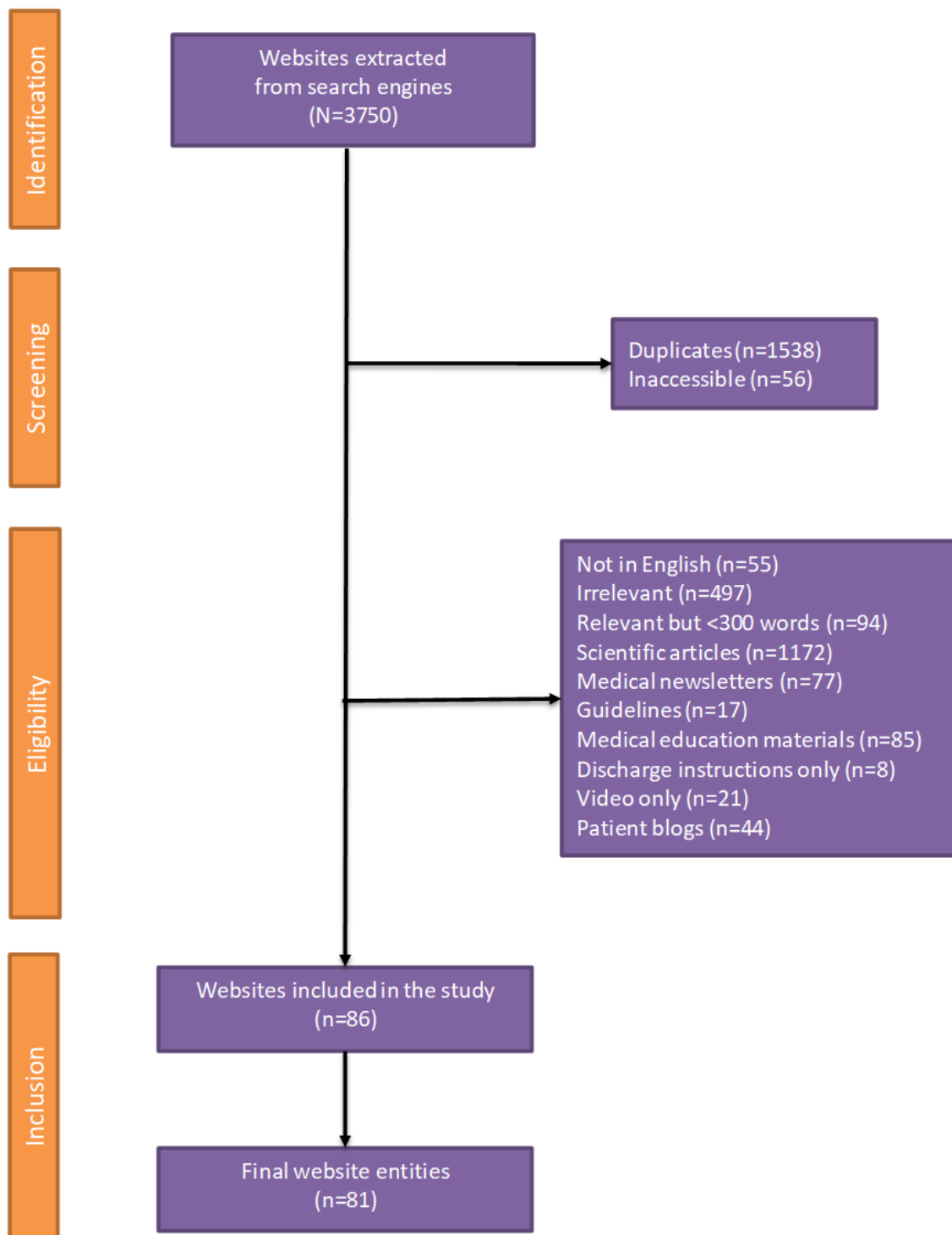
Website Characteristics

The included websites originated from 11 different countries, 62% (50/81) of which were from North America. Of the 81 websites, 15 (19%) belonged to nonacademic hospitals, 29 (36%) belonged to academic hospitals, 21 (26%) belonged to not-for-profit organizations, and 16 (20%) belonged to for-profit organizations.

A privacy statement was provided on 86% (70/78) of website domains. The presence of a privacy statement did not vary by website category. A medical disclaimer was present on 72% (56/78) of website domains. Not-for-profit websites were significantly associated with the presence of a medical disclaimer (χ^2_3=2.8; P=.005), whereas for-profit websites were significantly associated with the absence of a medical disclaimer (χ^2_3=3.7; P<.001).

No illustrations or videos were used on 56% (45/81) of the websites. Of 81 websites, 21 (26%) used only one image and 13 (16%) used more than one image, whereas supplemental videos were used in 5 (6%) websites. Advertisements were displayed on 6% (5/81) of the websites, most of which (4/5, 80%) were in the for-profit category.

The median word count was 765 words (IQR 518.3-1152.3; Table 1). Not-for-profit websites were associated with a significantly higher word count than nonacademic hospitals and for-profit websites (P=.04 and P=.01, respectively). There was a positive correlation between word count and total JAMA score (r_s=+0.463; P<.001), total DISCERN score (r_s=+0.786; P<.001), total TACE content score (r=+0.665; P<.001), and PEMAT actionability score (r_s=+0.548; P<.001).

Table 1. Assessment results per website category and overall.

Assessment tools	Nonacademic hospitals (n=15), median (IQR)	Academic hospitals (n=29), median (IQR)	Not-for-profit organizations (n=21), median (IQR)	For-profit organizations (n=16), median (IQR)	Total (N=81), median (IQR)
Word count	678 (435.3-873.8)	718 (501.5-1268.8)	1091 (792.5-1785.5)	544 (403.0-763.0)	765 (518.3-1152.3)
Journal of the American Medical Association	1.17 (0.83-1.17)	1.17 (0.83-1.50)	1.67 (1.33-2.25)	1.25 (0.83-1.67)	1.33 (0.83-1.75)
DISCERN	45.0 (37.0-52.0)	47.0 (37.5-54.0)	55.0 (49.0-62.0)	43.5 (34.0-46.0)	47.0 (40.5-54.0)
Transarterial chemoembolization content score	31.0 (29.0-43.0)	34.0 (26.5-41.5)	42.0 (35.0-46.0)	31.0 (23.3-33.8)	35.0 (27.0-43.0)
Flesch Reading Ease Score	43.1 (31.1-52.8)	47.9 (36.1-62.6)	48.9 (45.3-58.4)	41.9 (31.6-48.4)	47.0 (38.7-57.8)
Flesch-Kincaid Grade Level	11.2 (10.0-12.9)	10.8 (8.3-13.4)	10.6 (8.7-11.8)	11.9 (10.4-12.7)	11.2 (8.9-12.6)
PEMAT[a] understandability	0.75 (0.66-0.79)	0.77 (0.69-0.81)	0.77 (0.69-0.85)	0.69 (0.54-0.77)	0.75 (0.69-0.81)
PEMAT actionability	0.00 (0.00-0.40)	0.40 (0.00-0.60)	0.40 (0.00-0.70)	0.00 (0.00-0.40)	0.00 (0.00-0.60)

[a]PEMAT: Patient Education Materials Assessment Tool.

HON Code

The HON code certification was present on 12% (9/78) of the included website domains. Per category, there were 0% (0/14) HON-certified website domains in the nonacademic, 4% (1/28) in the academic, 24% (5/21) in the not-for-profit, and 20% (3/15) in the for-profit categories. No significant association was found between website categories and the presence of HON codes.

Websites with a HON code certification had higher total JAMA scores (P=.001) but did not have a significantly higher total DISCERN score, TACE content, FRES, FKGL, or PEMAT score.

JAMA Score

The median JAMA score was 1.33 (IQR 0.83-1.75; Table 1). Information about authorship was absent on 88% (71/81) of the websites (Table 2). Of 81 websites, 8 (10%) mentioned author qualifications, 7 (9%) of which were authored or coauthored

by a medical doctor. Sources of information were provided by 17% (14/81) of the websites (range 1-14 references). The date of publication of the latest update was mentioned in 42% (34/81) of websites. The median years since publication and update were 5.50 (IQR 2.25-9.75) and 1.50 (IQR 0.25-2.75), respectively. Only 11% (9/81) of the websites provided full disclosure.

Not-for-profit websites had significantly higher total JAMA scores than all other categories (P=.001 for nonacademic hospitals, P=.008 for academic hospitals, and P=.04 for for-profit organizations; Table 1). Not-for-profit websites were significantly associated with the presence of full disclosure and full attribution (P=.003 and P=.06, respectively).

There was a positive correlation between the total JAMA score and total DISCERN score (r_s=+0.579; P<.001), total TACE content score (r_s=+0.344; P=.002), FRES (r_s=+0.356; P=.002), and FKGL (r_s=−0.315; P=.006).

Table 2. Performance of websites on subdivisions of Journal of the American Medical Association benchmarks per category.

| Aspects of benchmark disclosed on the website	Nonacademic hospitals (n=15), n (%)	Academic hospitals (n=29), n (%)	Not-for-profit organizations (n=21), n (%)	For-profit organizations (n=16), n (%)	Total (N=81), n (%)
Authorship					
Name of author	0 (0)	2 (7)	4 (19)	3 (19)	9 (11)
Credentials of author	1 (7)	2 (7)	3 (14)	2 (13)	8 (10)
Affiliations of author	1 (7)	1 (3)	2 (10)	2 (13)	6 (7)
Adherence to all aspects of benchmark	0 (0)	1 (3)	1 (5)	2 (13)	4 (5)
Attribution					
References	0 (0)	2 (7)	8 (38)	4 (25)	14 (17)
Copyright information	15 (100)	28 (97)	18 (86)	15 (94)	76 (94)
Adherence to all aspects of benchmark	0 (0)	2 (7)	7 (33)	4 (25)	13 (16)
Currency					
Date created	3 (20)	7 (24)	9 (43)	2 (13)	21 (26)
Date updated	0 (0)	8 (28)	12 (57)	2 (13)	22 (27)
Adherence to all aspects of benchmark	0 (0)	5 (17)	3 (14)	1 (6)	9 (11)
Disclosure					
Site ownership	15 (100)	29 (100)	21 (100)	16 (100)	81 (100)
Sponsorship, advertising, underwriting, commercial funding arrangements, or support	7 (46.7)	11 (37.9)	11 (52)	7 (44)	36 (44)
Conflicts of interest	0 (0)	1 (3)	8 (38)	3 (19)	12 (15)
Adherence to all aspects of benchmark	0 (0)	0 (0)	6 (29)	3 (19)	9 (11)

DISCERN Score

The median DISCERN score was 47 (IQR 40.5-54.0), corresponding to fair quality (Table 1). No website had a total DISCERN score in the *excellent* range. The median score in the *Overall quality* section was 3.

The questions with the lowest scores were *No TACE* and *Sources*, whereas *How TACE works* and *Relevance to patients* were the questions with the highest scores (Figure 2). The median score in the *Bias and balance* section was 4. Mention of benefits did not receive a more favorable scoring compared with risks, and vice versa (mean rank 30.48 vs 32.29; *P*=.27). No additional resources for further reading were provided on 21% (17/81) of the websites. The median score in the *Shared decision making* section was 1.

Figure 2. Distribution of scores on each component of the DISCERN score. Scores range from 1 (definitive no, red) to 5 (definitive yes, dark green). TACE: transarterial chemoembolization.
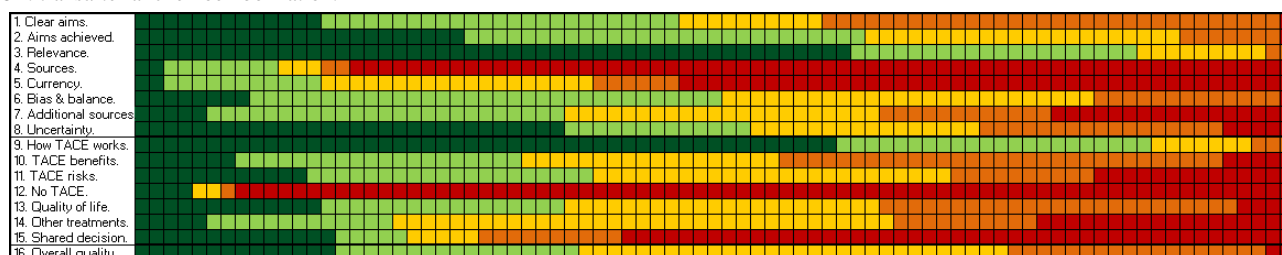
Not-for-profit websites had significantly higher total DISCERN scores than all other website categories (*P*=.006 for nonacademic hospitals, *P*=.03 for academic hospitals, and *P*<.001 for for-profit organizations; Table 1). They also scored higher in certain subdivisions (*Currency*, *Bias and balance*, *Reference to uncertainty*, and *Risks*) compared with all other categories (*P*<.05), and in *How TACE works* and in *Overall quality* compared with for-profit websites (*P*<.05).

Higher DISCERN scores were associated with higher TACE content scores (*r*=+0.701; *P*<.001).

TACE Content Score

The median TACE content score was 35 (IQR 27-43; Table 1). Of 81 websites, only 4 (5%) websites reached a completeness of ≥70%, whereas only 1 (1%) website reached 90% completeness.

Nearly all (78/81, 96%) websites mentioned the involvement of both chemotherapeutic and embolic agents in the procedure (Figure 3). Of 81 websites, 24 (30%) did not mention that the procedure is performed by an interventional radiologist; 45 (56%) websites failed to mention that the procedure involves exposure to x-rays along with injection of a contrast agent; 34 (42%) websites did not mention that TACE is offered when

tumors are not amenable to curative treatments; 36 (45%) websites did not mention the nonchemotherapeutic medications that patients receive perioperatively; and 54 (67%) websites did not mention that certain medications need to be held before the procedure. The most underrepresented section was *Contraindications*, as 37% (30/81) of the websites failed to mention a single contraindication.

Figure 3. Distribution of scores on each component of the transarterial chemoembolization–content score. Scores range from 0 (no mention, blue) to 2 (full mention, yellow). TACE: transarterial chemoembolization.
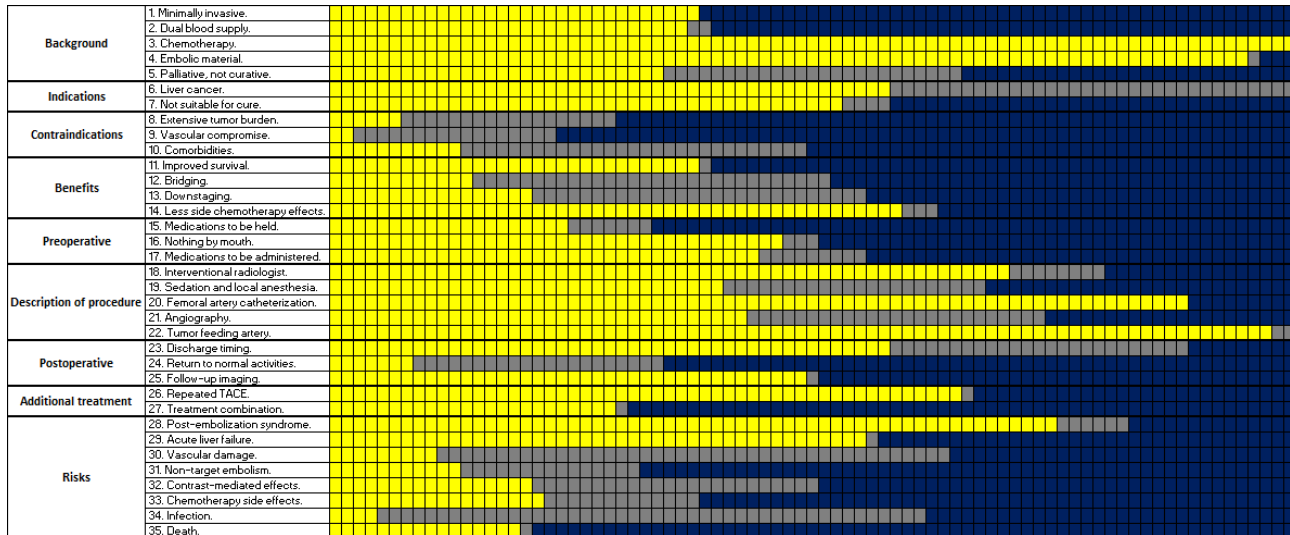
No benefits were mentioned on 5% (4/81) of the websites. Of 81 websites, 43 (53%) mentioned one or two benefits, whereas 34 (42%) websites mentioned two or more benefits. The most frequently mentioned benefit was "*less chemotherapy side effects*" (51/81, 63%), whereas the least commonly mentioned benefit was "*bridging to liver transplantation*" (42/81, 52%).

No risks were mentioned on 11% (9/81) of the websites. Of 81 websites, 14 (17%) mentioned one or two risks, whereas 58 (72%) mentioned three or more risks. The most commonly mentioned risks were "*postembolization syndrome*" (mentioned on 67/81, 83% of websites) and "*liver dysfunction*" (mentioned on 46/81, 57% of websites), whereas the least commonly mentioned risks were "*postoperative death*" (not mentioned on 64/81, 79% of websites) and "*nontarget embolism*" (not mentioned on 55/81, 68% of websites).

Not-for-profit websites had higher total TACE content scores than academic and for-profit websites (*P*=.04 and *P*=.001, respectively; Table 1). They also had significantly higher scores in *Risks* compared with all other categories (*P*=.01 for nonacademic hospitals, *P*<.001 for academic hospitals, and *P*<.001 for for-profit organizations) and in *Procedure description* compared with for-profit websites (*P*=.001). For-profit websites had a significantly lower score in *pre- and*

postprocedure considerations compared with academic (*P*=.04) and not-for-profit websites (*P*=.009). No statistically significant difference existed between website categories in terms of *background*, *indications*, *contraindications*, *benefits*, and *additional treatments*.

Flesch Reading Ease Score and Flesch-Kincaid Grade Level

The median FRES was 47.0 (IQR 38.7-57.8), and the median FKGL was 11.2 (IQR 8.9-12.6), corresponding to difficult degrees of readability (Table 1). Of the 76 websites, only 2 (3%) had a readability level of 7th grade, whereas 0 (0%) websites were within the recommended readability level of 6th grade or lower (Table 3). Moreover, 0 (0%) websites had an FRES corresponding to the *easy* or *very easy* readability level. Most websites (48/76, 63%) were deemed *difficult* or *very difficult* to read.

No significant difference was found in the FRES and FKGL between the website categories (Table 1). Websites with a higher FRES were associated with higher total DISCERN scores (*r*=+0.411; *P*<.001) and total TACE content scores (*r*=+0.250; *P*=.03). Websites with a lower FKGL were associated with higher total DISCERN scores (*r*=−0.392; *P*<.001) and total TACE content scores (*r*=−0.289; *P*=.01).

Table 3. Percentage of websites per each Flesch Reading Ease Scale category and corresponding Flesch-Kincaid Grade Level.

Flesch Reading Ease Scale	US Department of Health and Human Sciences writing style difficulty	Corresponding grade	Number of websites (n=76), n (%)	Corresponding Flesch-Kincaid Grade Level, median (IQR)
91-100	Very easy	5th	0 (0)	N/A[a]
81-90	Easy	6th	0 (0)	N/A
71-80	Fairly easy	7th	2 (3)	6.7 (6.4-7.0)
61-70	Standard	8th-9th	13 (17)	8.0 (7.4-8.5)
51-60	Fairly difficult	10th-12th	13 (17)	9.2 (8.8-10.6)
31-50	Difficult	College student	37 (49)	11.7 (11.0-12.6)
0-30	Very difficult	College graduate	11 (15)	15.1 (14.4-16.3)

[a]N/A: not applicable.

Patient Education Materials Assessment Tool

The median understandability score was 0.75 (IQR 0.69-0.81; Table 1). Of 81 websites, 49 (61%) scored higher than 70% on the understandability score; 11 (14%) websites had distracting content; and 17 (21%) websites used medical vocabulary without adequate explanation (Table 4). Of the 36 websites that used visual aids (images or videos), 17 (47%) were deemed useful and 18 (50%) displayed captions.

The median actionability score was 0.0 (IQR 0.0-0.6; Table 1). Of 81 websites, 13 (16%) websites scored higher than 70% on the actionability score; 42 (52%) websites scored zero; 39 (48%) websites provided at least one action that consumers should take with regards to TACE (eg, holding certain home medications before the procedure, refraining from certain activities after the procedure, and discussing their concerns with their doctor; Table 4).

There were no significant correlations between the website category and PEMAT performance (Table 1). There was a positive correlation between PEMAT understandability and total DISCERN scores (r_s=+0.271; P=.02). There was a positive correlation between PEMAT actionability and total DISCERN score (r_s=+0.336; P=.002) and total TACE content score (r_s=+0.376; P=.001). There was a positive correlation between PEMAT understandability or actionability scores and the FRES (r_s=+0.372, P=.001 and r_s=+0.704, P<.001, respectively) and a negative correlation between PEMAT understandability or actionability scores and the FKGL (r_s=−0.346, P=.002 and r_s=−0.695, P<.001, respectively).

Table 4. Patient Education Materials Assessment Tool for understandability and actionability and performance of websites per website category.

Patient Education Materials Assessment Tool items	Nonacademic hospitals		Academic hospitals		Not-for-profit organizations		For-profit organizations		Total	
	n (%)	Total, n	n (%)	Total, n	n (%)	Total, n	n (%)	Total, n	n (%)	Total, n
Understandability										
Content										
The material makes its purpose completely evident.	14 (93)	15	29 (100)	29	20 (95)	21	16 (100)	16	79 (98)	81
The material does not include information or content that distracts from its purpose.	13 (87)	15	28 (97)	29	19 (91)	21	10 (63)	16	70 (86)	81
The material uses common, everyday language.	15 (100)	15	25 (86)	29	19 (91)	21	13 (81)	16	72 (90)	81
Medical terms are used only to familiarize the audience with the terms.	10 (67)	15	21 (72)	29	20 (95)	21	13 (81)	16	64 (79)	81
The material uses active voice.	8 (53)	15	19 (66)	29	9 (43)	21	7 (44)	16	43 (53)	81
Use of numbers										
Numbers appearing in the material are clear and easy to understand.	9 (100)	9	22 (100)	22	21 (100)	21	12 (100)	12	64 (100)	64
The material does not expect the user to perform calculations.	15 (100)	15	29 (100)	29	20 (95)	21	15 (94)	16	79 (98)	81
Organization										
The material breaks or *chunks* information into short sections.	15 (100)	15	26 (90)	29	20 (95)	21	14 (88)	16	75 (93)	81
The material's sections have informative headers.	15 (100)	15	26 (93)	29	21 (100)	21	12 (75)	16	74 (91)	81
The material presents information in a logical sequence.	14 (93)	15	23 (79)	29	19 (91)	21	8 (50)	16	64 (79)	81
The material provides a summary.	0 (0)	15	0 (0)	29	1 (5)	21	0 (0)	16	1 (1)	81
Layout and design										
The material uses visual cues to draw attention to key points.	13 (80)	15	21 (76)	29	16 (76)	21	9 (56)	16	59 (73)	81
Text on the screen is easy to read (*for audiovisual content*).	N/A[a]	N/A	1 (100)	1	N/A	N/A	2 (100)	2	3 (100)	3
The material allows the user to hear the words clearly (*for audiovisual content*).	1 (100)	1	1 (100)	1	N/A	N/A	1 (50)	2	3 (75)	4
Use of visual aids										
The material uses visual aids whenever they could make content more easily understood.	1 (7)	15	6 (21)	29	3 (14)	21	6 (38)	16	16 (20)	81
The material's visual aids reinforce rather than distract from the content.	1 (20)	5	6 (46)	13	4 (50)	8	6 (60)	10	17 (47)	36
The material's visual aids have clear titles or captions.	0 (0)	5	7 (54)	13	5 (63)	8	6 (60)	10	18 (50)	36
The material uses illustrations and photographs that are clear and uncluttered.	3 (60)	5	12 (92)	13	8 (100)	8	8 (80)	10	31 (86)	36
The material uses simple tables with short and clear row and column headings.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Actionability										
The material clearly identifies at least one action the user can take.	5 (33)	15	18 (62)	29	11 (52)	21	5 (31)	16	39 (48)	81
The material addresses the user directly when describing actions.	5 (33)	15	18 (62)	29	11 (52)	21	5 (31)	16	39 (48)	81

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Patient Education Materials Assessment Tool items	Nonacademic hospitals		Academic hospitals		Not-for-profit organizations		For-profit organizations		Total	
	n (%)	Total, n	n (%)	Total, n	n (%)	Total, n	n (%)	Total, n	n (%)	Total, n
The material breaks down any action into manageable, explicit steps.	1 (7)	15	11 (38)	29	7 (33)	21	2 (13)	16	21 (26)	81
The material provides a tangible tool whenever it could help the user take action.	0 (0)	15	6 (21)	29	5 (24)	21	2 (13)	16	13 (16)	81
The material provides simple instructions or examples of how to perform calculations.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
The material explains how to use charts, graphs, tables, or diagrams to take actions.	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
The material uses visual aids whenever they could make it easier to act on the instructions.	0 (0)	15	0 (0)	29	0 (0)	21	1 (6)	16	1 (1)	81

[a]N/A: not applicable.

Discussion

Principal Findings

TACE is a valuable treatment option for select cases of primary or metastatic liver tumors. As such, it will remain a reason for thousands of web searches by patients with liver cancer and their families. Despite the multitude of available websites, no previous study has explored the reliability, quality, readability, understandability, actionability, and completeness of websites providing consumer-directed information on TACE. Our systematic review demonstrates that these websites are generally unreliable and are characterized by fair quality, insufficient content, adequate understandability, and poor readability and actionability.

There is no consensus regarding the optimal method for rating health-related websites. To date, there has been considerable heterogeneity among studies in terms of search engines or keywords used, number of screened websites, inclusion criteria, parameters evaluated, and assessment tools. Some studies focus only on one parameter (eg, readability) [21,39-41], whereas others address quality and content as well [23,24,28,42-44]. Multiple quality and readability assessment tools exist, the selection of which relies on the discretion of the study group. On the contrary, the assessment of the content provided by websites is topic-specific and requires a scoring tool dedicated to the topic of interest.

Many studies have generated *topic-specific scores* to evaluate the accuracy and completeness of websites [28,42-44]. In this study, we generated a novel TACE-specific score that includes 35 key points, which we believe should be covered by any website that aspires to adequately educate patients on TACE. Our results showed that, on average, websites had 50% completeness, indicating a significant lack of content. Although the procedure was adequately described, certain benefits and risks were missed by many websites, and contraindications were largely neglected. One striking finding of our study is that almost 30% of websites failed to mention that the procedure was performed by an interventional radiologist. Of note, one website stated that the procedure was performed by *a technician*. Given the challenge of raising public awareness that IR has been

facing, not only in the general public but also in the oncology community, emphasizing the performing specialty is of utmost importance [18,45].

Another important finding of our study is the strikingly poor reporting of authorship, currency, and references in the included websites, irrespective of their category. Mention of these features is essential for any health-related website that aspires to provide credible information and gain the trust of readers [14]. Moreover, 28% (22/78) of websites did not provide a medical disclaimer. A medical disclaimer would remind readers that the accuracy of the content provided is not guaranteed and that direct patient-physician discussion is irreplaceable. A study of 512 participants showed that 60% of people believe that the information they find on the internet is the *same as or better than* the information provided by their doctors [46]. Therefore, a medical disclaimer would highlight that health decision-making cannot be shaped solely based on self-education and that consultation with a medical professional is essential. Ideally, disclaimers should be readily visible on the same page as the medical content, instead of an obscure spot at the bottom of a website, as in most websites we evaluated. Readers are very unlikely to specifically search for disclosure statements [47].

The lack of these reliability parameters is also reflected by the low percentage (9/78, 12%) of websites that carried the HON certification. As a simple identifier of website objectivity and transparency, the HON code badge directs internet users toward more reliable websites. Our results showed that websites carrying a HON badge had higher JAMA scores, which is expected because these 2 indices share certain similar parameters. However, the presence of HON certification was *not* associated with more favorable scores on the quality, completeness, and readability tools that we used. This proves that these websites may be trustworthy but may not adequately describe the health-related topic or may do so but in a way that is not reader friendly. Therefore, the HON badge should not be perceived as the sole identifier of high-quality websites.

There are dozens of readability formulas available for quantitative readability assessment [40]. Generally, their main presumption is that longer sentences and longer words are more difficult to read. Although this may hold true, it does not

consider the coherence of the text or the literal complexity of the words. For instance, a short word would be considered easy to read by the formulas, but it may be too sophisticated for the average reader. Moreover, readability results may vary based on word sampling, text formatting, and calculation tools [48].

To avoid a one-sided approach to readability, we chose to evaluate websites using PEMAT as an additional tool. PEMAT is not a formula-based readability index but a subjective scoring system dedicated to health-related materials. It evaluates the website holistically, taking into consideration not only the text but also the organization of the information, the effectiveness of the multimedia, and the presence of distracting content. These factors determine how likely the website is to engage readers and hold their attention.

The results from our readability assessment showed that the median readability level of the websites was at the 11th grade level, well above the recommended 6th grade threshold. This indicates that patients with low health literacy are at a disadvantage, as they would not be able to comprehend the web-based resources available for TACE. Although 61% (49/81) of websites were deemed understandable, 21% (17/81) of the websites used medical terms without adequate explanation, and 14% (11/81) of the websites had distracting content. Moreover, approximately half of the websites did not mention a single action that readers must take. Suggesting clear actions would enable readers to make informed decisions about their care and therefore improve their health literacy [49,50].

Websites with a higher word count scored better on the TACE content and PEMAT actionability scores. This is expected, as more words tend to provide more content and therefore more complete information. However, websites need to find the right *balance* between providing adequate content and maintaining optimal readability. Our results showed that websites with a higher word count were *not* significantly associated with higher PEMAT understandability scores. Therefore, longer texts need to provide comprehensible information without distracting the reader.

The websites we evaluated seemed to underestimate the value of multimedia, as 56% (45/81) of websites did not use a single illustration or video. Of the websites that provided visual aids, only half were considered to be reinforcing or adequately captioned. Visual aids deliver information in a way that is more familiar to some patients and do not require a high level of literacy [51]. Given that TACE is a procedure unfamiliar to the general public, the use of multimedia could be helpful in describing the process in a simplified manner. Spoken animation has been found to be the most efficient way of communicating complex health information to people with low health literacy and could prove useful in the context of TACE [52].

Not-for-profit websites were found to provide the most reliable, high-quality, and complete content compared with all other website categories, as reflected by the significantly higher scores in JAMA, DISCERN, and TACE- content scores. They also mentioned more risks and were deemed less biased. This is in line with other studies that have found more favorable quality scores on nonprofit websites [22,43,53-55]. Nonprofit organizations aspire to educate the public in an objective and balanced way without seeking direct financial benefits, as opposed to hospitals and companies. As such, they appear to be trustworthy sources of patient information.

Recommendations for Website Developers

When creating a website that aspires to provide health education, content creators need to consult medical professionals with expertise on the desired topic. The name and credentials of the author, the date of creation and of last update, and the references should by no means be neglected so that the reader is ascertained that the information is credible and reliable. A medical disclaimer should be considered an essential feature and should be clearly and distinctly located on the webpage.

There are multiple ways to enhance the learning process of website users. Illustrations and animated videos remarkably increase the understandability of the presented content and therefore should be more broadly used. Summary tables may draw attention to take-away points in a simplified way and aid in the decision-making process. Brief interactive quizzes at the end of the article could also consolidate the reader's knowledge. The presence of resources for additional reading is helpful in directing patients to other useful websites with pertinent information.

An average web user does not have the capacity to screen websites and proceed to those that address consumers. A useful addition to search engines would be to create a web browser extension that would provide a sign next to each health-related website (similar to the HON code badge), stating whether it is appropriate for consumer education. Another option for websites would be to either have two separate versions, one for consumers and one for professionals (eg, UpToDate [56] and Merck manual [57]), or provide plain-language summaries (eg, Cochrane evidence [58]). These suggestions would enable patients to be readily directed to websites that provide information in the lay language.

Limitations

Our study has several limitations. Quality assessment tools may introduce a subjective bias; however, a considerable attempt was made to standardize the grading process. Discrepancies were resolved by discussion, and no interrater variability was measured. No blinding existed between the reviewers and the website owner. Furthermore, a new scoring system for TACE has been suggested, which has not been validated by other studies. Website rank on the search engines was not documented, as websites may appear on different ranks depending on the search history and location of each user. Content provided by supplementary videos (when available) was considered; however, websites providing only video content and foreign-language websites were excluded. Studies assessing such websites could shed further light on the quality of existing resources. Finally, websites are dynamic and may have been updated by the time the quality assessment took place.

Conclusions

To our knowledge, this is the first study to evaluate web-based resources that provide information about TACE to patients. Our comprehensive assessment showed that the materials currently

available on the web are unreliable, difficult to read, easy to understand but difficult to act upon, and do not provide complete information about TACE. Websites were characterized by fair quality and did not meet the standards for shared decision-making. Website developers are encouraged to revise their content and provide transparent, complete, and readable resources so that patients can make informed and safe decisions. Certain suggestions are made that could help high-quality and reader-friendly websites become more accessible to consumers.

Acknowledgments

Conflicts of Interest

None declared.

Multimedia Appendix 1
DISCERN score.
[DOCX File , 14 KB - cancer_v7i2e25357_app1.docx]

Multimedia Appendix 2
Transarterial chemoembolization content score.
[DOCX File , 16 KB - cancer_v7i2e25357_app2.docx]

Multimedia Appendix 3
List of included websites.
[DOCX File , 28 KB - cancer_v7i2e25357_app3.docx]

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Abbreviations

FKGL: Flesch-Kincaid Grade Level
FRES: Flesch Reading Ease Score
HON: Health On the Net
IR: interventional radiology
JAMA: Journal of the American Medical Association
PEMAT: Patient Education Materials Assessment Tool
TACE: transarterial chemoembolization

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<u>Viewpoint</u>

Development of a Digital Patient Education Tool for Patients With Cancer During the COVID-19 Pandemic

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Abstract

Background: Due to the COVID-19 pandemic, a large portion of oncology consultations have been conducted remotely. The maladaptation or compromise of care could negatively impact oncology patients and their disease management.

Objective: We aimed to describe the development and implementation process of a web-based, animated patient education tool that supports oncology patients remotely in the context of fewer in-person interactions with health care providers.

Methods: The platform created presents multilingual oncology care instructions. Animations concerning cancer care and mental health during the COVID-19 pandemic as well as immunotherapy and chemotherapy guides were the major areas of focus and represented 6 final produced video guides.

Results: The videos were watched 1244 times in a period of 6 months. The most watched animation was the COVID-19 & Oncology guide (viewed 565 times), followed by the video concerning general treatment orientations (viewed 249 times) and the video titled "Chemotherapy" (viewed 205 times). Although viewers were equally distributed among the age groups, most were aged 25 to 34 years (342/1244, 27.5%) and were females (745/1244, 59.9%).

Conclusions: The implementation of a patient education platform can be designed to prepare patients and their caregivers for their treatment and thus improve outcomes and satisfaction by using a methodical and collaborative approach. Multimedia tools allow a portion of a patient's care to occur in a home setting, thereby freeing them from the need for hospital resources.

KEYWORDS

Introduction

Over the past few months, the drastic escalation of the COVID-19 pandemic has imposed unprecedented challenges to the global health care system. Oncology patients are among the most vulnerable populations. Compared to patients without cancer, oncology patients are at a higher risk of contracting (18% vs 0.29%), as well as developing (39% vs. 8%), severe complications of COVID-19 [1,2]. Liu et al [3] recently examined the use of telehealth in oncology during the pandemic and discussed health care services that can be provided through digital means. Indeed, telemedicine visits have been rapidly adopted to prevent disease transmission, and the uptake of digital tools that facilitate remote networking has increased significantly

[4,5]. However, despite the increasing value of telehealth and the development of vast educational resources, little has been implemented to address demands from the patients' perspective [6,7]. Most patient education platforms that are available attempt to explain, in simple terms, the technical and medical aspects of a certain condition while limiting the information regarding what patients wish to learn, such as information about their treatment or recovery process. Additionally, these resources have not been properly studied by academia and face difficulty in penetrating large scales of usage and feedback.

The development of digital education tools for oncology patients could fill an unmet need in the growing telehealth environment, thereby empowering patients and reducing anxiety [6]. An ideal patient education tool that addresses this demand should function in support of care by medical professionals and provide knowledge and instructions tailored to oncology patients during the COVID-19 pandemic. Additionally, the material presented should be based on updated medical information and be readily accessible and understandable.

The COVID-19 crisis has emphasized the demand for an organized, evidence-based, digital medical education tool that can satisfy patients' needs for knowledge. Although health information has become readily available on the internet, they are often ill adapted to the population's health literacy [8]. Furthermore, the lack of screening of published materials results in a heightened risk of misinformation [9]. Numerous studies have underlined the value of eHealth in the context of the pandemic and have provided evidence of the effectiveness of digital tools [7].

We propose an approach to the development of video guides for a web-based education platform for oncology patients that ensures that patients are equipped with adequate and accurate medical information. Similar strategies have been explored for the management of other diseases during the COVID-19 pandemic, such as the use of a storyboard-style, web-based education tool for patients undergoing otolaryngologic surgery [10]. The implementation of an oncology patient education tool that allows patients to provide feedback and communicate digitally could contribute toward overcoming challenges during this emotionally taxing period by alleviating anxiety and confusion, especially those among newly diagnosed oncology patients.

Methods

This is a descriptive study on the development process of a tool for addressing oncology patients' needs for educational information during the COVID-19 pandemic. The creation of this tool was conducted with a web-based platform via a collaborative process that united efforts from university, industry, and hospital departments. The platform was created to serve as an engaging access portal for patients to intuitively navigate information.

This study was conducted from April to August 2020, that is, after the pandemic became a well-established global threat that forced health care institutions to deliver patient education via novel procedural methods.

This study's procedures were performed in 4 major steps. The first step was topic selection. The topics covered in the education materials sought to directly target oncology patients' informational needs during the COVID-19 pandemic. Patients' informational needs were identified by consulting a cancer network consisting of patient advocates, nurses, physicians, and other health care professionals. Patients' opinions were also obtained either via one-on-one, in-person conversations or from written texts that were submitted to an anonymous, nonstandardized suggestion box located in the oncology center.

The second step was content development. Initially, a broad literature review was performed on medical databases such as UpToDate and PubMed. The topics searched were oncology and COVID-19, and this led to a list of determined topics to be mentioned. A summary of all relevant information was created, and a main document containing the content was developed. Afterward, this information was adapted into a video script and analyzed for language and cultural adjustments according to the target population.

The third step was video production. To aid patients' comprehension and connect with a diverse population, the delivery method chosen was animated videos with audio voice-overs that were spoken clearly. The videos were created by professionals via animation software and offered on our web-based platform [11]. Audio and text were presented in English and French, and subtitles in 20 languages were offered to accommodate for the various cultural backgrounds of the patient population.

The fourth step was implementation and feedback gathering. Implementation was carried out on the web-based platform and presented to patients by the oncology health care teams during consultations. Resources were explained to patients during their clinical visit in the same way as when they would be handed an information pamphlet. Patients were able to access the platform at any time, and feedback was obtained in order to identify patient needs. Patients were able to ask questions, communicate their concerns, and provide feedback directly on the platform or during their consultations. Multiple iterations were carried out based on feedback from health care professionals and patient representatives. Data analytics was performed, which allowed for assessments of acquisition, conversion, and behavior. These analytical data sets provided constant suggestions for improvements to find the balance between the standardization of content and the personalization of educational experiences to individual needs.

All data used were anonymous and summarized in a password-protected, web-based database. The data analysis was performed using Microsoft Office Excel software (licensed version 16.36).

Results

The creation of well-balanced, evidence-based patient education videos required a multidisciplinary team from different branches of health care and digital media that encompassed professionals such as physicians, nurses, psychologists, social workers, and

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graphic designers. This approach ensured the accuracy, validity, and efficiency of the medical information included in the script.

Based on the information obtained from health care professionals and oncology patients, the selected topics for the videos were related to cancer treatment options, good practices of self-care, and disease prevention for oncology patients during the COVID-19 pandemic. Animations concerning cancer care and mental health during the COVID-19 pandemic as well as immunotherapy and chemotherapy guides were the major areas of focus and represented 6 final produced video guides. A sample video guide that was developed during this process as well as 2 screenshots can be found in Multimedia Appendices 1 and 2.

The first guide addressed hospital treatments for oncology patients that have been maintained during the pandemic, which was the biggest demand from patients. The aim was to demonstrate treatment options for cancer care and procedures for hospital attendance and to provide general follow-up information. The second guide contained a general overview of the COVID-19 pandemic, the disease, its symptoms, general preventive measures, and treatment perspectives. The third guide was developed to address essential information on infection prevention and alert signs for oncology patients during the pandemic. Some of the topics mentioned in this video were related to SARS-CoV-2, handwashing techniques, symptoms, and complications. The fourth guide addressed the mental health consequences of the social isolation resulting from the pandemic. It presented a brief contextualization of the reasons behind psychological distress and techniques for improving mental well-being during home care for oncology patients. The fifth and sixth guides were related to oncology treatments (namely, immunotherapy and chemotherapy) that may still be occurring during the social isolation period and therefore require specific attention.

The length of each guide varied from 6 minutes (video: "COVID-19 for Oncology") to 13.5 minutes (video: "Chemotherapy"). In order to create a welcoming viewing environment for patients, scenarios for the animations were created to represent either health care institutions or a house, depending on the context of the content being presented. The videos were watched 1244 times in a period of 6 months. The most watched animation was the COVID-19 & Oncology guide (viewed 565 times), followed by the video concerning general treatment orientations (viewed 249 times) and the video titled "Chemotherapy" (viewed 205 times). Although viewers were equally distributed among the age groups, most viewers were aged 25 to 34 years (342/1244, 27.5%). Most participants were female (745/1244, 59.9%). Demographic data are shown in Table 1.

Table 1. Demographic data (N=1244).

Characteristics	Viewers, n (%)
Sex	
Male	499 (40.1)
Female	745 (59.9)
Age (years)	
18-24	153 (12.3)
25-34	342 (27.5)
35-44	214 (17.2)
45-54	193 (15.5)
55-64	174 (14)
>65	168 (13.5)

Discussion

Principal Findings

In the field of oncology, digital patient education is relatively new and lacks an organized strategy. Nonetheless, research studies have provided promising insights. A study conducted by Sun et al [12] assessed the effectiveness of a multimedia self-management intervention for patients with lung cancer, which consisted of a video, a handbook, and phone calls for discussing disease pathophysiology and recovery care. Significantly improved postoperative emotional quality of life scores were reported from the intervention group; upward trends in the assessments of self-efficacy and surgery-related knowledge were also reported [12].

Digital media for patient education offers various advantages over traditional media (eg, pamphlets or handouts), as depicted in Table 2. Among the various digital tools, the use of multimedia or videos has been shown to be more effective than the use of pure texts [8,13]. Walker and Podbilewicz-Schuller [13] reported that patients with breast cancer who received videotaped education prior to their consultations reported higher satisfaction and reduced stress levels as well as better preparedness when asking questions during the consultations compared to those who received information booklets. Among the different formats of videos available, animations possess the advantage of illustrating complex materials in a vivid way to facilitate understanding. When combined with the guidance of spoken texts, animations may boost people's ability to process information by simultaneously exciting their audio and visual receptive channels [14,15]. A recent study demonstrated that

presenting health information through an animation combined with audible text, when compared with using illustrations or written texts, results in a significantly higher recall rate, especially among those with lower health literacy levels [8].

Table 2. Comparison among different media of patient education.

Characteristics	Digital education	Traditional education	Ideal education for patients with cancer
Accessibility	Free home access	Hospital-dependent access	Easy home access
Content	Flexible and adaptable	Fixed	Reliable
Circulation	On the internet globally	Local distribution	Personal devices
Cost	High implementation cost and low maintenance cost	High implementation cost and high maintenance cost	Free of charge

We intended for our tool and the proposed approach to the development process to maintain a high fidelity to evidence-based information while attempting to adapt them to a more engaging medium and effective platform that accommodated content that was in line with the cognitive theory of multimedia learning (CTML). An important aspect of adapting the CTML to patient education is reviewing language content to limit medical jargon and ensure that it is written at a comprehension level that accommodates different health literacy levels [16]. Studies have shown that patients understand medical information better when it is provided (ie, spoken) at a conversational pace and individual speed control is available, when simple words are used, and when a restricted amount of information is presented [14-16]. Additionally, while it is acceptable for medical videos to be as long as needed to provide enough time for vital information to be thoroughly discussed, people should also be considerate of the attention spans of a diverse audience. Detailed or complicated medical guides could be divided into several chapters to promote better engagement and retention.

Another important aspect to consider when developing a web-based medical education platform is its accessibility. Our proposed web-based platform could be accessed for free and without temporal or spatial limits, which provided patients with a channel for central, authoritative sources of medical information at home. Although this may present a financial challenge for the development of any innovation, we believe that this is crucial for achieving the conduction of adequate educational processes. To optimize support for patients with cancer during the COVID-19 pandemic, developing an accessible platform was an imperative action for health care institutions. Collaborations with the health care professionals provided patients with an introduction to the platform and allowed us to validate the platform. As such, these collaborations represented an important link to the implementation process. Partnerships between industry representatives, universities, and health care institutions were established to produce this multifaceted and integrative platform.

The acquisition of feedback from patients and health care professionals for regular evaluation and improvement was also an important aspect of our proposed tool. Through a web-based platform, we were able to obtain regular data and feedback, which allowed for modifications to be made constantly according to patients' demands. An example of feedback that generated modifications was the fact that we were able to analyze the average age of the viewers that was reported by the platform, which was different from what we expected. This information, in turn, allowed us to adapt the characters shown in the videos. Such data can also serve as indicators for making possible changes in language, style, or scenarios. This adaptability is an important advantage of using animated guides that is not present in live-action videos or printed materials.

Finally, attention to viewers' diversity in terms of cultural and linguistic backgrounds is valuable in effective communication, which in turn increases viewers' engagement and comprehension [17]. This effect may additionally be magnified for target populations such as individuals with hearing impairments, individuals with low literacy levels, or minority language speakers [18,19]. Multimedia education may aid in this context by increasing oncology patients' participation in the healing process, which is vital for better outcomes, as it improves self-care, decision making, and the overall understanding of diseases and treatments [7]. Our proposed platform addresses this diversity and maintains medical accuracy by offering animated video guides in multiple languages and the possibility of individualizing the content to target certain demographics.

This study presents limitations that are intrinsic to the methodological approach and to the implementation process. Patients were not randomized, and intervention outcomes were not quantitatively measured. The results were provided based on the descriptive analysis of the intervention, and no statistical inference testing was applicable. Future studies should pursue analyzing factors that influence oncology patients' engagement with digital education resources as well as outcome measures, such as medication adherence, the number of hospital visits, and pain control.

Conclusion

The implementation of an animated patient education platform can be designed to prepare patients and their caregivers for their treatment in an attempt to improve outcomes and satisfaction, by using a methodical and collaborative approach. Multimedia tools allow a portion of a patient's care to occur in a home setting, thereby freeing them from the need for hospital resources. During the pandemic, the rapid adoption of web-based care might not be sufficient to cover a patient's oncology and emotional needs. We describe the framework for producing and implementing web-based animations that serve as educational tools for oncology patients and their personal support networks.

Acknowledgments

Authors' Contributions

ST contributed to the implementation of the research, the data analysis, and the writing of the manuscript. GS contributed to the literature review, the design and implementation of the research, the data analysis, and the writing of the manuscript. TW contributed to the literature review, the implementation of the research, and the writing of the manuscript. RG contributed to the design and implementation of the research, the data analysis, and the writing of the manuscript. JH and WHG contributed to the writing and editing of the manuscript. The authors had full access to the data in this study and were responsible for the final decision to submit this paper for publication.

Conflicts of Interest

Coauthor RG is the founder of the company Precare Inc, which was our partner in developing the medical guide presented in this paper. Coauthor ST is the Chief Medical Officer at Prepare Inc. Coauthor GS was enrolled in and received salary support from the government-funded Mitacs Research Internship program and was affiliated with Precare through the program. No financial support was provided directly or indirectly by Precare. Coauthor TW was enrolled in and received salary support from the Natural Sciences and Engineering Research Council of Canada–funded MedTech Talent Accelerator program and was affiliated with Precare through the program. No financial support was provided directly or indirectly by Precare. There are no other conflicts of interest to declare.

Multimedia Appendix 1
Still images of animated videos.
[PNG File , 2518 KB - cancer_v7i2e23637_app1.png]

Multimedia Appendix 2
Sample video: oncology care during the COVID-19 pandemic.
[MP4 File (MP4 Video), 18929 KB - cancer_v7i2e23637_app2.mp4]

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Abbreviations

CTML: cognitive theory of multimedia learning

Original Paper

Virtual Mind-Body Programming for Patients With Cancer During the COVID-19 Pandemic: Qualitative Study

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Abstract

Background: Patients with cancer are particularly vulnerable to stress and anxiety during the COVID-19 pandemic. Social distancing is critical for patients with cancer; however, it can also reduce their access to psychosocial coping resources.

Objective: The aim of this study was to explore patient experiences to generate a model of how virtual mind-body programs can support the psychosocial well-being of patients with cancer.

Methods: We conducted a qualitative study among patients (aged ≥18 years) who participated in a virtual mind-body program offered by a National Cancer Institute–designated Comprehensive Cancer Center during the COVID-19 pandemic. The program consisted of mind-body group therapy sessions of fitness, yoga, tai chi, dance therapy, music therapy, and meditation. Live integrative medicine clinicians held each session via Zoom videoconferencing for 30-45 minutes. In semistructured phone interviews (n=30), patients were asked about their overall impressions and perceptions of the benefits of the sessions, including impacts on stress and anxiety. Interviews were analyzed using grounded theory.

Results: Among the 30 participants (average age 64.5 years, SD 9.36, range 40-80, 29 female), three major themes were identified relating to experiences in the virtual mind-body program: (1) the sessions helped the patients maintain structured routines and motivated them to adhere to healthy behaviors; (2) the sessions enhanced coping with COVID-19-related-stressors, allowing patients to "refocus" and "re-energize"; and (3) the sessions allowed patients to connect, fostering social relationships during a time of isolation. These themes informed the constructs of a novel behavioral-psychological-social coping model for patients with cancer.

Conclusions: Virtual mind-body programming supported patients with cancer during the COVID-19 pandemic through a behavioral-psychological-social coping model by enhancing psychological coping for external stressors, supporting adherence to motivation and health behaviors, and increasing social connection and camaraderie. These programs have potential to address the behavioral, psychological, and social challenges faced by patients with cancer during and beyond the COVID-19 pandemic. The constructs of the conceptual model proposed in this study can inform future interventions to support isolated patients with cancer. Further clinical trials are needed to confirm the specific benefits of virtual mind-body programming for the psychosocial well-being and healthy behaviors of patients with cancer.

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KEYWORDS

cancer; fitness; meditation; stress; COVID-19; qualitative; coping; wellbeing; psychosocial; virtual health

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Introduction

The outbreak of SARS-CoV-2, the virus that causes COVID-19, increased the stress levels of many individuals due to the threat of infection, news of overwhelmed healthcare institutions, and disruptions to daily life [1]. Stress levels may be exceptionally high for patients with cancer; social distancing is critical for this population because they are more susceptible to severe illness and mortality due to COVID-19 [2,3]. However, necessary stay-at-home orders and social distancing measures—which restrict access to parks and exercise facilities—have contributed to a worldwide decrease in physical activity [4] and a loss of usual support networks and other potential coping strategies for stress [5,6]. Thus, there is a critical need to address the enormous psychosocial burden of the COVID-19 pandemic for patients with cancer.

Patients with cancer often experience behavioral [7], psychological [8,9], and social [10] challenges, which are associated with worse cancer-related outcomes [11]. During the COVID-19 pandemic, patients have experienced higher levels of mental distress due to concerns regarding access to safe physical activity [12], significant life and health stressors [13], and loneliness [14]. For example, decreased physical activity due to social distancing or lack of adequate equipment can adversely affect the quality of life of patients with cancer and their mental health [12]. A survey (n=555) of women with current or previously diagnosed ovarian cancer showed that 89% reported "significant cancer worry" due to COVID-19 [15]. In Italy, in a prospective evaluation of patients with lymphoma, 75% of patients stated that "their worries had increased during the pandemic," and over one-third met diagnostic criteria for anxiety and depression [16]. Patients with cancer may also experience "alarmingly high rates of stress" and "extraordinarily high symptom burden," which necessitate increased vigilance among oncology providers [13]. In the Netherlands, patients with cancer expressed concerns of loneliness and fears of being in the hospital or not seeing their family due to COVID-19 [17]. Programs that address behavioral, psychological, and social stressors while complying with social distancing measures are critically important for supporting the quality of life of patients with cancer during the COVID-19 pandemic.

Mind-body therapies, such as meditation, yoga, and tai chi, have been shown to reduce stress and anxiety in patients with cancer and enhance their quality of life [18,19]. The American Society of Clinical Oncology and the Society for Integrative Oncology recommend mind-body therapies for treating cancer-related anxiety [20,21]. Exercise has also been effective for patients with cancer in combatting anxiety [22], reducing fatigue and pain [23,24], and improving quality of life [25]. Despite these benefits, patients with cancer and survivors may be limited in their ability to participate in these activities, particularly during the COVID-19 pandemic. Further, the pandemic has challenged society to operate virtually to comply with social distancing mandates [26,27], indicating a need for innovative approaches to support individuals affected by cancer.

In response to these concerns, we rapidly implemented a virtual mind-body program through the Integrative Medicine Service (IMS) at a tertiary National Cancer Institute–designated Comprehensive Cancer Center [28]. The program consisted of a series of virtual, synchronous classes offering a variety of rigorously tested mind-body therapies led by an IMS clinical therapist. The objective of this study was to explore patient experiences of the virtual program to generate a model of how virtual mind-body programs can support the psychosocial well-being of patients with cancer.

Methods

Therapy Sessions

We conducted virtual mind-body group therapy sessions using the Zoom video conferencing platform [29] beginning on April 1, 2020. Patients were contacted through the cancer center's patient messaging portal about virtual programs offered during the COVID-19 pandemic. Once registered, patients chose from a variety of weekly classes, which were held 1-4 times per week for 30-45 minutes. A licensed IMS clinician (eg, licensed dance therapist, certified yoga instructor, nurse specialist/physical trainer) with specific expertise in the oncology setting led each session. Patients could choose to participate in as many sessions as they preferred. Activities ranged from more movement-based (fitness, yoga, dance therapy, or tai chi) to meditative (guided meditation, Zen breathing, or listening to music therapy played by a licensed music therapist). All clinicians provided an overview of the session, 25-40 minutes of content, and 5 minutes for feedback and discussion. Because the program was developed in response to the COVID-19 pandemic, we conducted qualitative interviews for quality improvement between April and August 2020. The hospital's Institutional Review Board approved a retrospective protocol for the analysis of the quality improvement data.

Qualitative Interview Procedure

At the conclusion of the sessions, clinicians asked for volunteers to provide feedback on the virtual session. An IMS staff member with qualitative research training (NE) contacted the participants and arranged a telephone interview. The interviews lasted 10-35 minutes and followed a semistructured interview guide generated by study team members with content (JJM, KTL) and methodological (KAL, NE) expertise. The interview guide was organized into the following domains: (1) overall impressions, (2) perception of the benefits of the session, including impacts on stress and anxiety, and (3) unmet needs and recommendations for improvement. Consistent with the practice of semistructured interviewing, the interviewer asked flexible probing questions to further explore relevant themes and topics as they emerged. Probes were iteratively developed throughout the study period based on emerging participant feedback and iterative analysis. Interviews were conducted until thematic saturation was obtained [30], transcribed verbatim, and deidentified to ensure patient privacy.

Interview Sampling Approach

We purposively sampled participants across session types to ensure representative feedback about each modality. However,

participants were allowed—and encouraged—to participate in any virtual mind-body sessions; multiple sessions were often discussed during interviews. As this was a grounded theory study, iterative analysis of transcripts informed our subsequent sampling approach. As we aimed to create a generalized model of how virtual mind-body programs can support the psychosocial well-being of patients with cancer, we sought theoretical saturation across subgroups (ie, saturation across movement-based and meditation-based sessions). Ultimately, the three constructs reported in this manuscript were explored and refined based on participant experiences across integrative medicine (IM) modalities.

Qualitative Analysis

Two trained qualitative researchers (KAL, NE) independently coded transcripts using a grounded theory approach to facilitate the development of a coping model [31]. The transcripts were first coded in their entirety using an open coding process, wherein the coding team highlighted significant statements and assigned a descriptive or interpretive label. Through consensus meetings, the team refined common labels (eg, impacts on stress and anxiety, social isolation) into codes. This process was facilitated by analytic memo-writing: during this open-coding phase, researchers wrote margin notes on inductively emerging patterns, which were turned into codes. Then, the codebook was solidified and applied across all transcripts, data were compared against the codes (focused coding), and discrepancies in coding were resolved via consensus. Once all transcripts were coded, the lead coder (KAL) reviewed the data to ensure that all significant statements had been assigned a label. Then, the team completed a process of axial coding in which coded statements were condensed into categories, compared, and grouped under thematic labels supported by the text, thereby grounding each category in the data. The code categories were reviewed and refined via group consensus meetings (eg, "impact on life in quarantine" "impact on routines"). To identify the final constructs of the model, the researchers completed a selective coding phase, wherein statements housed within each category where recoded to identify primary themes. Each category was

iteratively revisited to identify instances of theoretical saturation, defined as the point at which no new relevant data, coding, or themes emerge. During this phase, analytic memos were used to refine our theoretical categories. After reviewing a code category, researchers independently wrote memos on the key theoretical implications (eg, "socialization as a means of coping"), which were discussed in consensus meetings. To achieve consensus on the final model, coders met with team members who have expertise in IM delivery (JJM, KTL) and refined the constructs as needed. The qualitative software NVivo Pro 12.0 (QSR International) [32] was used to facilitate the analysis and store the final codebook.

Results

A total of 30 patients participated in qualitative interviews to achieve thematic saturation (Table 1). The majority of the sample was female (29/30, 97%) and White (25/30, 83%), with an average age of 64.5 years (SD 9.36). Participants had various tumor types; breast cancer was the most common (11/30, 37%). Some participants were in active treatment, while others were in survivorship. Although the interviews focused on participant experiences with a single mind-body modality, the majority of participants participated in multiple sessions. Fitness (22/30, 73%), yoga (17/30, 57%), and tai chi (16/30, 53%) were the most popular modalities, which is supported by the authors' previous publication regarding the feasibility and acceptability of virtual mind-body programs [28].

Grounded theory analysis identified three major themes related to participant experiences in the virtual mind-body program. These themes indicated that the program (1) promoted positive health behaviors, (2) enhanced psychological coping, and (3) fostered social engagement. Taken together, these three themes informed the constructs of our behavioral-psychological-social coping model, which proposes ways in which virtual mind-body programs can support patients with cancer (Figure 1). Each of these themes and their resulting constructs are explored in detail below (summarized in Table 2).

Table 1. Participant demographics (N=30).

Characteristic	Value
Mean age (years) (SD, range)	64.5 (9.36, 40.0-80.0)
Sex, n (%)	
Male	1 (3)
Female	29 (97)
Race, n (%)[a]	
White	25 (83)
Asian	4 (13)
Black	1 (3)
Cancer type, n (%)[b]	
Breast	11 (37)
Ovarian	4 (13)
Lung	3 (10)
Uterine	2 (7)
Lymphoma	2 (7)
Tongue	2 (7)
Colon	1 (3)
Bladder	1 (3)
Liver	1 (3)
Pancreatic	1 (3)
Prostate	1 (3)
Skin	1 (3)
Primary class attendance (interview focus), n (%)	
Fitness	5 (17)
Dance	5 (17)
Guided meditation	5 (17)
Music	5 (17)
Yoga	5 (17)
Tai chi	3 (10)
Zen breathing	2 (7)
Overall class attendance, n (%)	
Fitness	22 (73)
Yoga	17 (57)
Tai chi	16 (53)
Dance	14 (47)
Guided meditation	12 (40)
Music	13 (43)
Zen breathing	9 (30)

[a] Percentage for race adds up to (99%) because percentages were rounded.

[b] Percentage for cancer type adds up to (99%) because percentages were rounded.

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Figure 1. Behavioral-Psychological-Social Coping model of how virtual mind-body programs can support the psychosocial well-being of cancer patients.
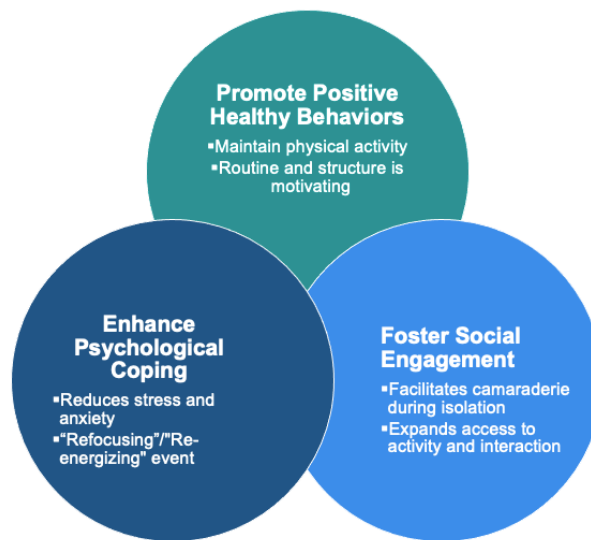

Table 2. Major theoretical constructs and associated coding.

Construct	Code category	Major codes
Health behaviors	Impacts on daily life	• Maintain movement or routine • Behavior change • Positive motivation and inspiration
Psychological coping	Impacts on stress and anxiety	• Impact on stress and anxiety • Effect on mood • "Distraction" from other stressors
Social engagement	Perception of benefit	• Social camaraderie • Reduced isolation • Web-based access

Promotion of Positive Health Behaviors

As people worldwide began to practice social distancing during the COVID-19 pandemic, appointments and social events were canceled, leaving the study participants with a large amount of unstructured time. Participating in the virtual sessions became a way to retain a sense of daily routine, as one music participant described:

> [The classes] give my day structure. I look forward to it. I can sort of plan [my day]. I'm home and I'm cleaning, [and] I can have that to look forward to.

This sense of routine became a way to cope with COVID-19-related stress. Patients described the virtual programming as "something to look forward to" amid an uncertain future. Regularly scheduled virtual live classes also motivated participants to engage with health behaviors while social distancing. Discussing their struggle with home-based exercise, a tai chi participant stated:

> Yeah, it's great because I try to do exercises on my own, but it's not regular. And, this kind of keeps me regular. Because, it's like "oh it's 1:30, I have to do Tai Chi" and it's kind of like an incentive or motivation. And, especially when there's someone on

the other side encouraging you to move or that you can do it.

An option for virtual classes was especially welcome to patients who had been physically active prior to the COVID-19 pandemic. The classes became a way to maintain physical activity and movement when other options for exercise were suddenly unavailable:

> But these classes are really, really excellent. And help you in confined spaces and need to get some exercise, you know? […] Before, I used to swim every day and walk in and ride my bike all over the city. You know, it's... now I don't have that.

As a population vulnerable to infection, patients with cancer feel extra pressure to adhere to social distancing guidelines. As the fitness participant describes above, this results in long periods of time in "confined spaces." Some participants, fearful of infection, described barely leaving their homes while COVID-19 cases peaked:

> [I]n March and April I didn't go out much and I wasn't even walking, which is my one major, you know, exercise. So... getting back to movement and moving throughout the day at whatever time, you know, it's really helpful.

For these participants, the virtual classes created a structure to engage in physical activity, promoting positive health behaviors without placing participants at risk of exposure.

Enhancement of Psychological Coping

Across interviews, participants expressed that the virtual classes enabled them to cope with the daily uncertainties of the COVID-19 pandemic. Feeling inundated with new and often-conflicting information, patients found the sessions to be a grounding experience. As one music participant described:

> I think as a patient, lots of times the problem is that you have all these kind of racing thoughts […] you feel quite like engaged in these classes. Like it can really make you focus on the current session.

Participants of the meditative sessions—music, Zen breathing, and guided meditation—found the virtual sessions to be "refocusing" events. By concentrating on their breathing and sensory experiences (ie, calming sounds, visualizations), patients felt that they were able to redirect their attention from external stressors, as one meditation participant stated:

> I think I have less stress after the session. And it... because it's calming and it's refocusing, and it helps with channeling the energies in a different place.

Similarly, participants of the movement-based sessions—fitness, dance, yoga, and tai chi—perceived a reduction in stress due to the virtual sessions. For these participants, the virtual sessions were a "re-energizing" event, presenting a distraction from COVID-19–related anxieties. In the words of a dance participant:

> It's almost like taking a shower you [are] getting rejuvenated. Now, you can recreate the whole world, right? You sit down, you're nice and calm and your body feels like you're relaxed and you don't have a care in the world about what's going on around you.

Additionally, one participant discussed that yoga classes were particularly helpful after the abrupt transition to isolation:

> It [the class] helps, it really helps. Especially in the beginning when all this started, everybody was so stressed. This has helped me a lot to keep my mind out of all this stuff […] now it's a little easier, but it still really helps me.

Both movement- and meditative-based sessions became ways for the participants to cope with the uncertainties surrounding COVID-19, particularly in the context of cancer care. As a result, participants across interviews described feeling both less anxious and less stressed after the classes:

> I'm feel[ing] less stressed, I feel relaxed, I feel energized and that continues afterward. I mean, I find it really, it helps. It really helps dealing with the stress and anxiety of this whole quarantine time.

Fostering Social Engagement

Cancer can be socially isolating, and participants perceived this isolation to be amplified during the COVID-19 pandemic. As one music participant described, the upheavals created by the pandemic caused her to feel cut off—socially and physically—from friends and loved ones:

> [Y]ou feel really alone. Fortunately, I have my husband so at least I'm not like completely alone, but still that's the only way you get to connect with other people. Some of my friends, they are really busy with kids at home, and with working from home... yeah, somehow, they actually turned out to be even busier than before. So sometimes I don't feel very...like I don't want to bother them all the time.

As she went on to describe, the virtual sessions became a way to connect with friends she had met during previous in-person classes:

> So, this [class] keeps you feeling you're connected to the community and some fellow patients you happen to see are attending the same session, and it was like, "Wow, it's you" and all this and then we start texting each other. Sometimes I receive these surprise texts is like, "Oh, is it you in the session?" And it just feels... like you need some excitement and surprises, like once in a while. So this provides like a platform for people to continue interacting that way.

Participants discussed the benefit of seeing other patients with cancer and survivors via virtual classes. Faced with unique stressors and concerns during the COVID-19 pandemic, the participants found it comforting to connect with other participants going through a similar experience. As one yoga participant stated, the classes helped her feel "less alone":

> It's helped me to calm down and feel like you're not alone. There are other people doing it and going through this also.

A few participants also stated that virtual programming enabled them to engage in mind-body group sessions for the first time. These participants were unable to attend the pre–COVID-19 in-person classes at the hospital due to geographic, time, or mobility constraints, as in the case of one dance participant:

> I'm on oxygen. And if this was anything that was done at the Integrative Medicine Center, I would never go—because of the location. So, you know, this gives me a chance to participate.

Therefore, in addition to enabling isolated patients to virtually reconnect, virtual programming enabled other patients to engage for the first time.

The Behavioral-Psychological-Social Coping Model

The three major themes identified in our analysis informed our coping model (Figure 1). Virtual mind-body programs have the potential to support patients with cancer in three interrelated ways. (1) Regularly scheduled classes motivate participants to maintain positive health behaviors and create a sense of structure and routine. (2) Through accessing therapies that allow patients to "refocus" and "re-energize," participants can enhance their ability to psychologically cope with external stressors. (3) Virtual, synchronous sessions, which enable participants to see and communicate with one another, facilitate social connection and camaraderie during a time of isolation and expand access

to vulnerable individuals. Taken together, these three constructs provide a model for how virtual mind-body programming can support psychosocial well-being among patients with cancer.

Discussion

Principal Findings

The COVID-19 pandemic disproportionately impacts the psychosocial well-being of patients with cancer and survivors due to the unique stressors they encounter as a result of public health measures. This study identifies the constructs of how virtual mind-body services can promote healthy behaviors, enhance psychological coping, and facilitate social connections for patients with cancer during the COVID-19 pandemic and potentially beyond, particularly for patients with limited physical access to the IMS. These qualitative themes form the basis of a behavioral-psychological-social coping model informing how virtual mind-body services can be an accessible and scalable way to address patients' psychosocial challenges.

Our study adds to emerging literature regarding how virtual tools, such as virtual mind-body programming, can address psychological symptoms patients with cancer face during the COVID-19 pandemic. Avancini et al [33] encouraged the use of telehealth and virtual programs for at-home exercises to increase social support and adhere to exercise guidelines. A review of web-based interventions to address the psychosocial needs of patients with cancer demonstrated "promise" in addressing pain, depression, and quality of life measures [34]. Additionally, access to clinicians through virtual web-based visits and telehealth can address existing barriers to care and has potential to fill important gaps in quality cancer care [35]. Our study builds on this literature by providing a model for how virtual mind-body programs can benefit patients with cancer. As a result of the COVID-19 pandemic, we have implemented a virtual tool that specifically identifies points of intervention for maintaining healthy behaviors, addressing psychological issues, and enhancing social connection among isolated patients with cancer.

Research on the benefits of mind-body programs for patients with cancer has focused on mindfulness through the individual use of apps or websites [36-38]. Previous mindfulness interventions are either nonsynchronous (ie, prerecorded, with no opportunities for real-time interaction) or focused on a specific cancer type. The intervention described in this study overcomes barriers to in-person delivery while offering packaged mind-body therapies to patients with all cancer types. Additionally, the program provided multiple modalities, offering patients a choice and a sense of control in selecting programs that met their needs and preferences. Real-time participant interaction with IMS clinicians and fellow patients can help treat loneliness and increase social interaction, which can, in turn, reduce the uncertainty and stressors faced by many patients with cancer [11]. The constructs of the coping model proposed in this study can inform future interventions to support isolated patients with cancer, even after the COVID-19 pandemic.

The virtual mind-body program in this study used an accessible pre-existing video conferencing platform to disseminate therapeutic modalities to patients. By using existing technologies, this program offers a more scalable model for adapting services from in-person to virtual. Although apps or software may be appealing, the costs associated with their development and maintenance may not be sustainable for all programs [39]. According to the Pew Research Center, approximately three quarters of Americans have broadband high-speed internet access at home, and a growing number use their smartphones to access the internet [40]. Thus, an internet-based program using a pre-existing user-friendly platform may provide an accessible and sustainable alternative to in-person services for patients and their providers.

Although the profound isolation associated with the COVID-19 pandemic is a unique experience, barriers to accessing IM, loneliness, and mental distress are common among patients with cancer; the virtual mind-body program has potential to provide benefits well beyond the current pandemic. The behavioral-psychological-social coping model proposed in this study complements other biopsychosocial frameworks [41,42] by focusing on the behavioral, psychological, and social aspects of virtual mind-body programs while being attentive to the unique experiences and challenges of patients with cancer. This model can be used to guide the development and evaluation of future virtual mind-body programs and can provide a structure for addressing the interconnected issues that patients with cancer face. Future application of this model may benefit clinical services and research by providing a multifaceted and patient-informed mechanism of coping with psychological distress.

Limitations

This study has a number of limitations. The sample is primarily female and White due to the nature of the voluntary interviews, and the results may not be generalizable to other populations. Although we interviewed patients with a range of cancer types, patients with breast cancer were overrepresented in this sample. Further, virtual classes may not be accessible to all patients due to limited internet or technology access, such as patients in rural areas with low bandwidth. Data on Medicare telemedicine reimbursements suggests that virtual access disparities are especially prominent in patients with lower socioeconomic status, who are older than 85 years, and who are in communities of color [43]. Additionally, mind-body classes were provided in the context of clinical care rather than in a controlled research project with participants who self-selected to participate. Therefore, the themes are based on the perspectives of patients and survivors who participated in the program and agreed to complete an interview. Differentiating programs for patients on active treatment and those in survivorship phases can further guide future interventions.

Conclusion

This study identified how virtual mind-body programs can support adherence to health behaviors, enhance psychological coping with external stressors, and increase social connection and camaraderie when in-person services are not accessible. The COVID-19 pandemic provided an opportunity to better understand the broader experiences of isolated patients with cancer, enabling us to identify critical points of intervention.

The virtual mind-body model proposed here has the potential to support patients with cancer to address the behavioral, psychological, and social challenges that they face during and beyond the COVID-19 pandemic.

Authors' Contributions

All authors contributed to the conception and design. NE and KAL acquired the data. NE, KAL, KTL, and JJM analyzed and interpreted the data. All authors contributed to the drafting and provided final approval of the manuscript.

Conflicts of Interest

JJM reports grants from Tibet Cheezheng Tibetan Medicine Co, Ltd, and from Zhongke Health International, LLC, outside the submitted work.

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Abbreviations

IM: integrative medicine
IMS: Integrative Medicine Service

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<u>Original Paper</u>

Associations Among Wearable Activity Tracker Use, Exercise Motivation, and Physical Activity in a Cohort of Cancer Survivors: Secondary Data Analysis of the Health Information National Trends Survey

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Abstract

Background: Cancer survivors who meet physical activity (PA) recommendations (≥150 minutes of moderate-to-vigorous physical activity [MVPA] per week) experience better health outcomes. With the growing availability of wearable activity trackers (WATs), it may be easier to track PA. However, it is unknown what motivates survivors to use these devices.

Objective: The aim of this study is to investigate the associations among motivations for exercise, previous WAT use for tracking a health goal or activity, and meeting the recommended amount of PA among a cohort of cancer survivors.

Methods: Data on WAT users who reported having a previous cancer diagnosis were analyzed from the National Cancer Institute's Health Information National Trends Survey 5 Cycle 3. All survivors with complete information on demographics, exercise motivations (internal guilt, external pressure, physical appearance, and exercise enjoyment), previous WAT use (yes or no), and minutes of MVPA per week (N=608) were included. Multivariate logistic regression models were used to test these associations. A separate cluster analysis was conducted to identify the profiles of exercise motivation that were associated with reporting WAT use.

Results: The mean age of the cohort was 66.9 years (SD 12.1). The majority were non-Hispanic White (473/608, 78.8%) and female (322/608, 54.9%), and skin cancer was the most commonly reported diagnosed cancer (154/608, 27.8%). Survivors who reported using WATs to track a health goal or activity were 1.6 times more likely to meet MVPA recommendations than those who did not use WATs (odds ratio [OR] 1.65, 95% CI 1.03-2.65; *P*=.04). When exercise motivations were assessed independently, survivors who reported not feeling any internal guilt as an exercise motivation were 73% less likely to report having used a WAT than those who felt any internal guilt (OR 0.27, 95% CI 0.14-0.54; *P*<.001). A total of 3 distinct motivational profiles emerged from the cluster analysis. WAT users had an increased probability of membership in profile 3, which was characterized as being strongly motivated to exercise by internal guilt, physical appearance, and exercise enjoyment (OR 4.5, 95% CI 2.1-9.7; *P*<.001).

Conclusions: Among this cohort, survivors who reported using WATs to track a health goal or activity were significantly more likely to report meeting PA recommendations. Survivors who reported feeling internal guilt as an exercise motivation were significantly more likely to report using WATs to track a health goal or activity. When examining clusters of motivation, survivors who reported previous WAT use were more likely to report being motivated to exercise by a mix of intrinsic and extrinsic motivations, including internal guilt, exercise enjoyment, and physical appearance. Given the health benefits of PA for cancer

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survivors, technology-focused interventions that use WATs and target exercise motivation may aid in cancer survivors meeting the level of recommended PA.

KEYWORDS

Introduction

Background

There are more than 16.9 million cancer survivors living in the United States, and this number is expected to reach more than 22.1 million by 2030 [1]. From 1997 to 2014, obesity increased more rapidly among adult cancer survivors than in the general population [2]. Furthermore, there is a higher prevalence of obesity among cancer survivors from underrepresented populations, such as Hispanics, compared with White cancer survivors [3-8]. In addition, Hispanic breast cancer survivors tend to have lower levels of physical activity (PA) than their non-Hispanic White counterparts [9]. Obesity has several negative health consequences that affect cancer survivors. Obesity puts survivors at a greater risk for cardiovascular disease, diabetes, and cancer recurrence [10-14]. In addition, accumulation of adipose tissue can inhibit effective cancer treatment [15].

PA plays an important role in reducing obesity and increasing quality of life among breast, colorectal, prostate, and multiple site cancer survivors [16-18]. PA can help reduce morbidity and mortality and alleviate the negative side effects of chemotherapy, including fatigue, nausea, disturbed sleep, decreased activity, and impaired quality of life [19-22]. Thus, guidelines from the American Cancer Society recommend that cancer survivors engage in at least 150 minutes per week of moderate-to-vigorous physical activity (MVPA) [23]. However, only 17% to 37% of breast cancer survivors in the United States adhere to these recommendations and most tend to exercise less after treatment [24-27].

Cancer survivors have unique health-related physical and psychological challenges resulting from the acute and long-term effects of cancer, including declines in physical functioning, decreased exercise motivation, and increased levels of anxiety and fatigue [28-31]. Innovative approaches are required to address these challenges. Wearable activity trackers (WATs) are promising tools for addressing these barriers. As of 2020, approximately 1 in 5 US adults (21%) say they regularly wear a smart watch or wearable fitness tracker [32]. WATs that monitor PA act as a motivational tool for increasing awareness of sedentary behavior and are useful for measuring and tracking activity at home or any location [33]. One of the benefits of WATs is that they have the ability to measure a variety of activity-related outcomes, including steps, distance, heart rate, active minutes, calories, and sleep, with high validity and reliability [34,35]. A large systematic review found that using WATs significantly increased the daily step count ($P<.001$), MVPA ($P<.001$), and energy expenditure ($P=.03$) in adult populations [36]. Owing to the rapid advances and relatively low cost of WATs, a growing amount of research has

successfully incorporated WATs into interventions to increase PA, reduce obesity, and manage chronic conditions such as breast cancer [22,37]. Results from a qualitative study of breast cancer survivors found that survivors reported acceptance of using WATs, confidence, and comfort in using them, and that using WATs increased their motivation for PA [38]. WATs may also be helpful for promoting PA among cancer patients who are still receiving primary therapy for the disease [39,40]. In addition, WATs have been shown to increase self-awareness of PA and reinforce progress toward meeting PA goals [41]. WATs also show promise as a tool to reduce disparities among patients with cancer and cancer survivors by overcoming barriers such as access to health care providers and health monitoring [42]. WATs are cost-effective, can be widely distributed, have the potential to minimize user burden, and provide immediate feedback in an enjoyable experience for users [43].

Overall, WATs may overcome some limitations of traditional in-person programs for PA and weight management for cancer survivors, such as overcoming travel barriers, decreasing user burden, and addressing time or schedule constraints [30,44,45].

To aid in interpreting the underlying behavior regulations associated with motivation, we examined exercise motivation through the lens of self-determination theory (SDT) [46]. SDT distinguishes between two sources of motivation that regulate a person's behavior: intrinsic (internal) and extrinsic (external). Intrinsic motivation is defined as engaging in an activity or behavior because of the inherent satisfaction a person gets. An intrinsically motivated person experiences enjoyment, accomplishment, and excitement when engaging in the behavior or action. Extrinsic motivation refers to engaging in a behavior to obtain an outcome outside of what is inherently achieved through doing a behavior. This can include social rewards, such as praise, disapproval avoidance, or monetary incentives.

Furthermore, SDT distinguishes between different types of extrinsic motivation by their style of regulation on behavior. For example, controlled regulation is the least autonomous form of extrinsic motivation. In this regulation style, behavior is primarily driven by externally administered rewards and punishments. Individuals operating from this type of motivation typically experience externally regulated behavior as controlling or alienating, leading to an externally perceived locus of causality or control [47]. In another regulation type, introjected regulation, people will perform actions to avoid feeling guilty or anxious or to satisfy their ego or pride. Although this style is still strongly externally controlled, introjection represents a type of regulation that is also contingent on ego and self-esteem. Although this regulation style is internal to the person, introjected behaviors are not experienced as fully self-determined and still operate from an external locus of control [47]. SDT conceptualizes these motivations as a constant

continuum moving between amotivation, or having no motivation, to fully self-determined motivation [46,48]. SDT postulates that meeting goals and changing behavior are more likely to occur if motivation is self-determined or autonomous [24]. Previous studies have demonstrated the efficacy of adapting and mapping SDT concepts to exercise motivations in understanding health behavior [49], particularly mapping guilt onto introjected regulation [48,50,51].

There is still a lot of uncertainty around understanding what motivates cancer survivors to engage in PA. One of the challenges to PA engagement among survivors is that they tend to have lower exercise motivation after diagnosis and treatment [24]. However, some studies have examined exercise motivation among cancer survivors, specifically through the framework of SDT. One study found that breast cancer survivors who meet PA recommendations have higher scores of intrinsic motivation and autonomous regulation, similar to exercise enjoyment as a motivation in this study, than those who did not reach PA guidelines [52]. Other research also indicates that intrinsic motivation is significantly associated with greater long-term exercise adherence [48].

Objectives

Cancer survivors who meet PA recommendations experience better health outcomes. With the growing availability and implementation of WATs, it may be easier to track PA, but it is still unknown what motivates cancer survivors to wear these devices. Therefore, the purpose of this study is to investigate the relationship among motivations for exercise (internal guilt, pressure from others, physical appearance, and exercise enjoyment), reported previous use of WATs to track health goals, and meeting the recommended amount of PA (≥150 minutes of MVPA per week) among a cohort of cancer survivors.

Methods

Data Source

First administered in 2002-2003 by the National Cancer Institute, the Health Information National Trends Survey (HINTS) is a biennial, cross-sectional survey of a nationally representative sample of noninstitutionalized American adults aged 18 years and older that is used to assess the context in which people access and use health information. There are 13 iterations of HINTS, and this study uses the 13th iteration released in January 2020, HINTS 5 Cycle 3, which represents data collected from January to April 2019. Each HINTS iteration has been approved through an expedited review by the Westat Institutional Review Board and deemed exempt by the US National Institutes of Health Office of Human Subjects Research Protections. A total of 5438 people participated in HINTS 5 Cycle 3. In this cycle, the overall response rate was 30.3%. For descriptive analysis, sample weighting was used to provide nationally representative US estimates. The HINTS survey uses weights that are designed to provide population level estimations utilizing a modified Horvitz-Thompson estimator and Jackknife replication method [53].

Participants

In this study, all cancer survivors who completed a survey for cycle 3 in 2019 with complete information on demographic variables, WAT use, exercise motivation, and minutes of MVPA per week were included (N=608).

Measures

Demographics

Demographic variables included participants' age (years), BMI, gender (male or female), marital status (married or divorced), household income range, education (less than high school, high school graduate, some college education, college graduate, or more), health insurance status (yes or no), English-speaking proficiency (very well or not very well), self-rated health (excellent, very good, good, fair, or poor), ability to take care of one's health (completely confident, very confident, somewhat confident, a little confident, or not confident at all), rural or urban designation, cancer type (breast, cervical, prostate, colorectal, skin, other, or more than one type), and time since cancer diagnosis (in years). Race or ethnicity was examined using a dichotomized variable representing survivors from a White racial or ethnic background and those from a non-White racial or ethnic background, including Hispanics, Asians, and African Americans. BMI was used to classify participants as obese (≥30), overweight (29.9-26), or normal weight or underweight (<26).

Use of WATs

Participants' responses to the question, "In the past 12 months, have you used an electronic wearable device to monitor or track your health or activity? For example, a Fitbit, AppleWatch or Garmin Vivofit..." were used to characterize the distribution of subjects who used WATs (yes or no).

Exercise Motivation

To assess motivation, we used participants' responses to questions that asked "Why the participant starts or continues exercise regularly" with separate questions asking if the reason was "pressure from others (external pressure), concern over the way you look (physical appearance), feeling guilty when you stop exercising (internal guilt), or getting enjoyment from exercise (exercise enjoyment)." Answer choices included "A lot," "Some," "A little," or "Not at all." For regression modeling, we dichotomized the response variable into *not at all* versus *any*.

Physical Activity

To investigate the association between WAT use and PA, we created a binary outcome variable derived from a composite of combining responses to questions which asks, "In a typical week, how many days do you do any physical activity or exercise of at least moderate intensity, such as brisk walking, bicycling at a regular pace, and swimming at a regular pace (do not include weightlifting)?" with option choices from *1 day per week* to *7 days per week,* and another question, which asks, "On the days you do physical activity for exercise of at least moderate intensity, how long do you typically do these activities?" and allowed participants to answer with any positive number up to 3 digits in length. To develop the outcome

variable, the number of days per week reported was multiplied by the number of minutes to obtain the average time per week of MVPA. We then created a binary variable with either *yes* or *no* options based on whether the participant met recommended weekly minutes of MVPA (yes ≥150 or no <150).

Statistical Analyses

Before the analysis, data were screened for normality, outliers, and patterns of missing data. Missing data were screened and tested in Statistical Access Software (SAS) version 9.4 using PROC MI to examine the distribution of missing values. No distinct patterns of missing data were found; therefore, the data were approached as missing at random. As no patterns in missing data were found, participants who completed the survey for cycle 3 in 2019 with complete information on demographics, exercise motivations, WAT use, and minutes of moderate-to-vigorous PA (MVPA) per week were included in the study (N=608). Descriptive data for continuous variables were reported as weighted means and SDs, and categorical variables were reported as weighted frequencies and percentages.

To assess the relationship between exercise motivation variables and WAT use, multivariable logistic regression models were used. In addition, we examined the interaction between individual exercise motivations and race or ethnicity to explore differences in motivations by race or ethnicity. A separate multivariable logistic model was used to assess the relationship between WAT use and meeting the recommended amount of PA. A cutoff of *P*<.05 was used to determine statistical significance for all analyses.

A cluster analysis was conducted to generate motivational profiles based on responses to exercise motivation questions using the PROC LCA procedure in SAS 9.4. In PROC LCA, parameters are estimated using an expectation-maximization algorithm to obtain the maximum likelihood. In addition, this procedure incorporates the Newton-Raphson method for the estimation of regression coefficients. The convergence index used in this procedure is the maximum absolute deviation (MAD). The estimation procedure continues to iterate until either a specified criterion value of MAD (the convergence criterion) is met or the maximum number of iterations is reached. Finally, LCA parameter estimates and standard errors are found by inverting the Hessian matrix to obtain the log likelihood [54]. Using this method, we tested the best-fit model as either a 2-, 3-, 4-, or 5-cluster solution. These options were then assessed further using goodness-of-fit statistics, Akaike information criterion, Bayesian information criterion, G-squared, entropy, and interpretability. Once profiles were formed, differences in WAT use were assessed using logistic modeling and chi-square tests. SAS version 9.4 was used for all data modeling and analyses carried out in this study.

Results

Demographic Characteristics of the Cohort

Multimedia Appendix 1 describes the cancer cohort. The mean age of the cohort was 66.9 years (SD 12.1), and the mean BMI was 28.3 (SD 6.1). The majority of cancer survivors were non-Hispanic White (473/608, 78.7%), female (322/608, 54.9%), married (328/608, 62.9%), and spoke English very well (546/608, 89.8%). The most frequently reported cancer was skin cancer (154/608, 27.8%), followed by more than one type of cancer (110/608, 18.1%) and breast cancer (79/608, 12.4%), which are among the most prevalent types of cancer in the general population [55]. A large proportion of the cohort completed some college or more (489/608, 71.5%) and frequently reported being in good (228/608, 38.3%) or very good health (194/608, 29.4%) and being very confident that they could take care of their health (279/608, 43.3%). In addition, the cohort overwhelmingly reported having health insurance (596/608, 96.8%). Regarding PA, the majority of this cancer cohort did not meet the recommended amount of PA (396/608, 67.9%) and most only reported between 0 and 74 minutes of MVPA per week (282/608, 49.9%). One-fifth of cancer survivors reported using a WAT device in the past month (119/608, 20.9%). The complete breakdown of exercise motivations reported by WAT users and non-WAT users in provided in Table 1.

Table 1. Exercise motivations (wearable activity tracker users vs nonwearable activity tracker users; N=608).

Characteristic and category	WAT[a] users (n=119), n (%)		Non-WAT users (n=489), n (%)	
	Participants	Participants (weighted)	Participants	Participants (weighted)
Internal guilt				
No	17 (9.6)	330,710 (9.6)	198 (42.9)	5,572,690 (42.9)
Yes	102 (90.4)	3,106,554 (90.4)	291 (57.1)	7,422,694 (57.1)
Exercise enjoyment				
No	20 (12.5)	428,160 (12.5)	123 (23.7)	3,086,204 (23.7)
Yes	99 (87.5)	3,009,105 (87.5)	366 (76.3)	9,909,181 (76.3)
Physical appearance				
No	12 (6.3)	215,926 (6.3)	110 (19.3)	2,503,455 (19.3)
Yes	107 (93.7)	3,221,338 (93.7)	379 (80.7)	10,491,930 (80.7)
Pressure from others				
No	77 (63.6)	2,184,454 (63.6)	323 (67.6)	8,784,210 (67.6)
Yes	42 (36.4)	1,252,810 (36.4)	166 (32.4)	4,211,175 (32.4)

[a]WAT: wearable activity tracker.

Exercise Motivation and WAT Use—Regression Modeling

When exercise motivations were assessed independently, adjusting for all covariates in a multivariate logistic regression model, cancer survivors who did not report internal guilt as a motivation for exercise were 73% less likely to use WATs (odds ratio [OR] 0.27, 95% CI 0.14-0.54; $P<.001$). This model was adjusted by participant's age, BMI, time since cancer diagnosis, gender, marital status, household income range, level of educational attainment, race or ethnicity, self-rated health, self-efficacy for health, region, urban or rural status, health insurance status, English-speaking ability, and type of cancer diagnosis. In addition, several demographic variables were found

to be significantly associated with WAT use in this model. An increase in age was associated with a decreased likelihood of using WATs (OR 0.95, 95% CI 0.93-0.97; $P<.001$). In addition, survivors with higher income (US $75,000-$199,000 vs US $0-$34,000; OR 2.84, 95% CI 1.22-6.59; $P=.02$) and those with better health (fair or poor vs excellent; OR 0.2, 95% CI 0.07-0.61; $P=.004$) were more likely to use WATs. The time since cancer diagnosis was included as a control variable in this model and was found to be not statistically significantly associated with WAT use ($P=.93$). Finally, when testing for interactions between individual exercise motivations and race or ethnicity, we found no significant interactions. The results are presented in Table 2.

Table 2. Results from multivariable regression modeling of exercise motivations and previous wearable activity tracker use (N=608).

Variable[a]	Odds ratio (95% CI)	P value
Pressure from others[b]	1.17 (0.70-1.97)	.54
Physical appearance[c]	0.67 (0.30-1.53)	.35
Internal guilt[b]	0.27 (0.14-0.54)	<.001
Exercise enjoyment[c]	0.82 (0.40-1.60)	.55
Age	0.95 (0.93-0.97)	<.001
Income[d]	2.84 (1.22-6.49)	.02
Self-rated health[e]	0.20 (0.07-0.61)	.004

[a]Adjusted for age, BMI, time since cancer diagnosis, gender, marital status, household income range, level of educational attainment, race or ethnicity, self-rated health, self-efficacy for health, region, urban or rural status, health insurance status, English-speaking ability, and type of cancer diagnosis.

[b]None versus any motivated.

[c]Any versus not motivated.

[d]US $75,000-$199,000 versus US $0-$34,000.

[e]Fair or poor versus excellent.

Exercise Motivation and WAT Use—Cluster Analysis

Figure 1 displays the 3 motivational profiles that emerged from the cluster analysis. The profiles differed significantly across motivation and class membership.

Profile 1 (100/608, 16.4%) is characterized by cancer survivors who did not report being influenced to exercise by any of these motivations (internal guilt, pressure from others, physical appearance, and exercise enjoyment).

Profile 2 (117/608, 19.2%) profile is characterized by cancer survivors who reported exercising because of exercise enjoyment (intrinsic motivation with autonomous regulation) and physical appearance (extrinsic motivation with introjected regulation).

Profile 3 (394/608, 64.4%) is characterized by cancer survivors who reported being motivated by exercise enjoyment (intrinsic with autonomous regulation) and strongly by both physical appearance and internal guilt (extrinsic motivation with introjected regulation).

WAT users had an 86% probability of membership in profile 3 (gamma=0.86; SE 0.04; *P*<.001) versus profile 1, whereas non-WAT users only had a 58% (gamma=0.58; SE 0.04; *P*<.001) chance of being in this profile. When assessed in a logistic regression model, profile 3 was also the only cluster that was significantly associated with WAT use (OR 4.5, 95% CI 2.1-9.7; *P*<.001) after adjusting for participants' age, BMI, time since cancer diagnosis, gender, marital status, household income range, level of educational attainment, race or ethnicity, self-rated health, self-efficacy for health, region, urban or rural status, health insurance status, English-speaking ability, and type of cancer diagnosis.

Figure 1. Latent class analysis of motivation profiles (N=608), adjusting for age.
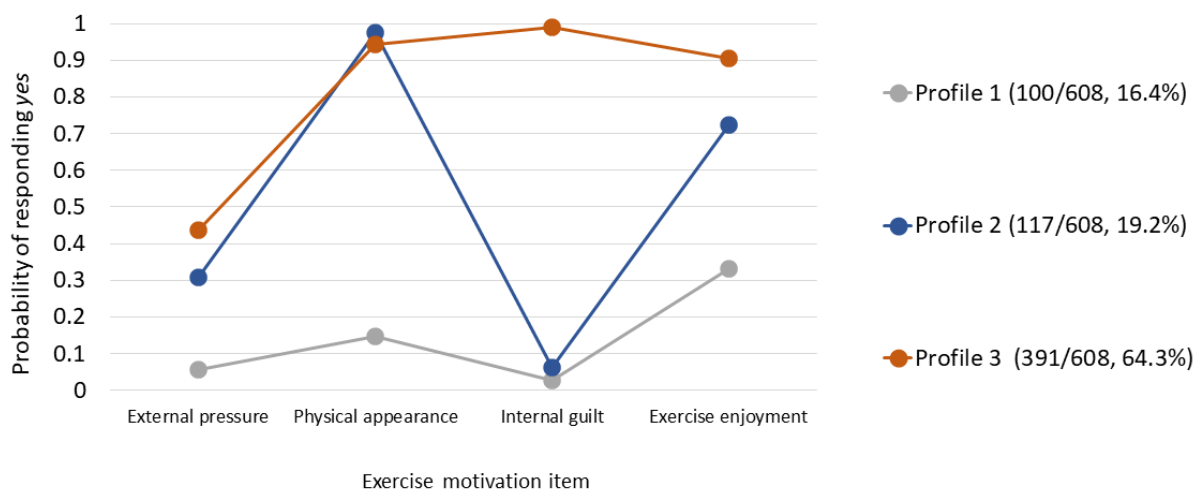
Association Between WAT Use and PA

Cancer survivors who used WATs were 1.6 times more likely to meet PA recommendations than those who did not use WATs (OR 1.65, 95% CI 1.03-2.65; *P*=.04). In addition, in this model, we found that survivors who had lower BMI (OR 0.92, 95% CI 0.89-0.96; *P*<.001), had higher household income (US $200,000+ vs US $0-$35,000; OR 2.62, 95% CI 1.11-6.19; *P*=.03), and were in better health (fair or poor vs excellent; OR 0.18, 95% CI 0.07-0.44; *P*<.001) were more likely to meet weekly PA recommendations. The results can be found in Table 3.

Table 3. Association between wearable activity tracker use and meeting the recommended amount of physical activity (N=608).

Variable[a]	Odds ratio (95% CI)	*P* value
Previous wearable activity tracker use[b]	1.65 (1.03-2.65)	.04
BMI	0.92 (0.89-0.96)	<.001
Household income[c]	2.62 (1.11-6.19)	.03
Self-rated health[d]	0.18 (0.07-0.44)	<.001

[a]Adjusted for age, BMI, time since cancer diagnosis, gender, marital status, household income range, level of educational attainment, race or ethnicity, self-rated health, self-efficacy for health, region, urban or rural status, health insurance status, English-speaking ability, and type of cancer diagnosis.

[b]Yes versus no wearable activity tracker use.

[c]US $200,000+ versus US $0-$35,000.

[d]Fair or poor versus excellent.

Discussion

Principal Findings

One of our primary objectives was to examine the associations of internal guilt, exercise enjoyment, pressure from others, and physical appearance as motivations for exercise with reporting having used WATs to track a health goal among a cohort of cancer survivors. The second objective was to examine clusters of exercise motivations associated with reporting previous WAT use. When exercise motivations were assessed independently, only internal guilt was significantly associated with WAT use among this cohort of cancer survivors. However, in the cluster analysis, 3 distinct motivational profiles emerged with distinctly different class memberships. WAT users were significantly more likely to be in profile 3, a group characterized by being motivated by internal guilt, physical appearance, and exercise enjoyment (autonomous with high introjected regulation). The cluster analysis provided a unique examination on not only how a single exercise motivation is associated with reporting WAT use but also how a combination of motives can be identified.

In both analyses, external guilt as a motivation for exercise emerged as being significantly associated with reporting previous WAT use. There is concern that guilt as a motivation can be harmful to healthy behavior adherence and that using WATs can cause additional stress or induce negative affect [56]. However, in this study, we observed a significant relationship between health-related internal guilt and reporting using WATs to track a health goal or activity. Health-related guilt in this context is a negative feeling about a person's own behavioral shortcomings related to health, often through self-blame. For example, a person may feel guilty when they have not exercised, although having been given recommendations from a health provider to do so. This experience typically involves a sense of anxiety or regret [50]. However, the experience of guilt is typically in response to a specific behavior, unlike shame, which is a negative feeling about oneself or global self-blame. Therefore, the experience of guilt is typically less painful than shame [50]. This may explain why previous studies have found an association between guilt and higher levels of MVPA among breast cancer survivors [51].

Understanding exercise motivation through a framework of SDT helps us to identify and differentiate sources of exercise motivation (internal vs external) and allows us to conceptualize different forms of control or behavior regulation within extrinsic motivation (eg, introjected regulation and controlled regulation). In this context, we can think of health-related guilt as an emotion. However, considering the underlying behavior regulation associated with guilt, we apply an SDT framework, specifically mapping guilt onto extrinsic motivation with introjected regulation [48,50,51].

Understanding the type of behavioral regulation linked with guilt can inform the planning and design of technology-based mobile health (mHealth) interventions that focus on addressing the behavioral regulation aspect of health-related guilt while not directly leveraging or increasing the emotional aspect that may negatively impact healthy behavior adherence.

Given that motivation in the context of SDT exists on a continuum, viewing the results of this study through an SDT framework can potentially inform the development of interventions that focus on moving survivors from extrinsically motivated regulations such as introjected regulation (eg, guilt) to more autonomous forms of motivational control (eg, enjoyment). One approach is to design intervention components such as motivational messages that avoid guilt- or shame-inducing language and instead aid the user in becoming more accountable for meeting MVPA recommendations while creating enjoyable experiences. This can potentially be achieved by using mHealth intervention components such as gamification and motivational affordances (eg, leaderboards, badges, and challenges), which help to foster more autonomous forms of regulation and motivation (eg, enjoyment and mastery). Clinicians may also play a role in guiding their patients toward making more positive cognitive appraisals directed at managing feelings of guilt. This process distinguishes between health-related guilt and engaging in self-blaming behavior (eg, failure and shame), which has been found to be associated with negative health consequences and decreased PA motivation [51].

On the basis of these findings, motivational regulation is likely to be an important factor linking body-related emotions and MVPA. WAT interventions typically contain behavior change techniques that include monitoring and tracking but rarely address extrinsic motivation with introjected regulation (eg, guilt). There is a need to recognize that health- and body-related guilt exists among cancer survivors and consider the implications of the relationship between guilt and health behaviors among this population.

Another objective of this study is to examine the association between WAT use and meeting the recommended amount of weekly MVPA among this cohort of cancer survivors. Reporting previous WAT use for tracking health goals was statistically significantly associated with meeting MVPA recommendations. Given the health benefits of PA for cancer survivors and the potential barriers to in-person PA programs, interventions aimed at aiding cancer survivors in meeting MVPA recommendations could leverage WATs to help survivors reach these goals.

Comparison With Previous Work

Similar to previous findings, we found that enjoyment (intrinsic motivation), a more autonomous form of behavioral regulation, was found to play a role in reporting WAT use when looking at clusters of motivation [57]. However, contrary to previous work, we did not find that external pressure from others to exercise was associated with WAT use [58].

Although previous studies have investigated the relationships among demographic, health, and lifestyle variables associated with meeting PA guidelines in cancer survivors, few have investigated the role of reporting previous WAT use in meeting PA guidelines among cancer survivors [49]. A large systematic review found that cancer survivors showed an increase in PA when using WATs and that increased PA played an important role in alleviating the adverse health effects of breast cancer therapy [22]. Another study found that WATs motivated breast cancer survivors to be physically active and created more

awareness of their sedentary lifestyle [37]. Results from a qualitative study found similar findings in that WATs increased self-awareness and motivation among breast cancer survivors [38].

Future Considerations

Findings from this study can provide insights into the relationship between reporting internal guilt as an exercise motivation and reporting meeting MVPA recommendations for cancer survivors. The results can also provide some insights into possible ways to interpret guilt as an exercise motivation and potentially understand the underlying behavior regulation of this emotion through a framework of SDT. There remains an opportunity for future researchers to address questions regarding the intensity of WAT use among cancer survivors and the amount of PA. There also remains uncertainty as to whether WATs act as a facilitator of PA or a primary driver of health behavior [59]. In addition, there are technological difficulties to consider (initial setup, troubleshooting, etc) that can create barriers to PA adherence in home-based PA interventions among cancer survivors [59]. In addition, there is concern that WATs can cause stress or induce negative effects on healthy behavior, which can also be problematic [56]. However, studies have shown successful integration of WATs into interventions with no reported increase in negative affect or causing unwanted stress [60]. This study will also serve to inform a follow-up paper focused on the intensity of WAT use, exercise motivation, and PA.

Limitations

Although HINTS is designed to be nationally representative, the data were collected through a self-report, cross-sectional survey. Thus, we are unable to analyze trends in WAT use, motivations, and PA over time and must rely on a person's recollection of events and behaviors. In addition, because this is a cross-sectional survey, we were limited to the questions and variables that were included in the survey, such as being limited to examining only the range of the exercise motivations included in the survey and being unable to know what specific health measures or activities the participants were tracking on their wearable devices. There is also the possibility of unmeasured confounding, which might be associated with mHealth engagement that would influence the interpretation of these results. Although our analyses showed a statistically significant association, it does not indicate a causal relationship, and we cannot address the issue of temporality, given the cross-sectional nature of the study. For example, we cannot determine whether a motivation leads to WAT use or if WAT use leads to motivation. Our goal was to determine associations among motivations for exercise, WAT use, and meeting PA recommendations among this cohort of cancer survivors; thus, our results should not be generalized to populations outside of survivors. Finally, because of smaller data cell counts, we had to examine interactions for race using a dichotomized variable derived from cancer survivors reporting if they were from a White racial or ethnic background or if they were from a non-White racial or ethnic background. Due to this dichotomization, we may have been unable to detect more subtle but significant differences in motivations by race. Finally, we need to consider that those who used WATs had more access to devices based on higher socioeconomic status (SES) and must consider the implications for cancer survivors with lower SES. Although this study was a secondary analysis of cross-sectional data, the results add to the literature supporting the notion that previous WAT use among cancer survivors is associated with reported meeting MVPA guidelines.

Conclusions

When assessed individually, internal guilt as an exercise motivation (extrinsic motivation with introjected regulation) was found to be significantly associated with reporting previous WAT use among a cohort of cancer survivors. In a cluster analysis, WAT users were more likely to be in a profile that reported being motivated to exercise by internal guilt, exercise enjoyment, and physical appearance, demonstrating a combination of intrinsic and extrinsic motivations (autonomous with high introjected regulation). This provides us with insights on not only how one motivation but how a confluence of motivations was found to be associated with reporting previous WAT use for tracking health goals among a cohort of cancer survivors. However, in both analyses, we found that internal guilt was consistently reported as an exercise motivation associated with reported WAT use. We can also apply an SDT framework to better understand the underlying behavioral regulation that underlies health-related guilt. In addition, among this cohort of cancer survivors, WAT use was significantly associated with meeting the PA recommendation guidelines. The results of this study can aid in identifying which cancer survivors are more or less likely to use WATs and the potential underlying motivations and behavior regulations that are associated with their use. Given the health benefits of PA for cancer survivors, technology-focused interventions targeting exercise motivation may aid cancer survivors in meeting MVPA recommendation guidelines.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Descriptive characteristics of the cancer cohort (wearable activity tracker users vs nonwearable activity tracker users; N=608). [PDF File (Adobe PDF File), 175 KB - cancer_v7i2e24828_app1.pdf]

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Abbreviations

HINTS: Health Information National Trends Survey
MAD: maximum absolute deviation
mHealth: mobile health
MVPA: moderate-to-vigorous physical activity
OR: odds ratio
PA: physical activity
SDT: self-determination theory
SES: socioeconomic status
WAT: wearable activity tracker

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Original Paper

A Novel Behavioral Intervention for Rural Appalachian Cancer Survivors (weSurvive): Participatory Development and Proof-of-Concept Testing

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Abstract

Background: Addressing the modifiable health behaviors of cancer survivors is important in rural communities that are disproportionately impacted by cancer (eg, those in Central Appalachia). However, such efforts are limited, and existing interventions may not meet the needs of rural communities.

Objective: This study describes the development and proof-of-concept testing of *we*Survive, a behavioral intervention for rural Appalachian cancer survivors.

Methods: The Obesity-Related Behavioral Intervention Trials (ORBIT) model, a systematic model for designing behavioral interventions, informed the study design. An advisory team (n=10) of community stakeholders and researchers engaged in a participatory process to identify desirable features for interventions targeting rural cancer survivors. The resulting multimodal, 13-week *we*Survive intervention was delivered to 12 participants across the two cohorts. Intervention components included in-person group classes and group and individualized telehealth calls. Indicators reflecting five feasibility domains (acceptability, demand, practicality, implementation, and limited efficacy) were measured using concurrent mixed methods. Pre-post changes and effect sizes were assessed for limited efficacy data. Descriptive statistics and content analysis were used to summarize data for other domains.

Results: Participants reported high program satisfaction (acceptability). Indicators of demand included enrollment of cancer survivors with various cancer types and attrition (1/12, 8%), recruitment (12/41, 30%), and attendance (median 62%) rates. Dietary (7/12, 59%) and physical activity (PA; 10/12, 83%) behaviors were the most frequently chosen behavioral targets. However, the findings indicate that participants did not fully engage in action planning activities, including setting specific goals. Implementation indicators showed 100% researcher fidelity to delivery and retention protocols, whereas practicality indicators highlighted participation barriers. Pre-post changes in limited efficacy outcomes regarding cancer-specific beliefs and knowledge and behavior-specific self-efficacy, intentions, and behaviors were in desired directions and demonstrated small and moderate effect sizes. Regarding dietary and PA behaviors, effect sizes for fruit and vegetable intake, snacks, dietary fat, and minutes of moderate-to-vigorous activity were small (Cohen d=0.00 to 0.32), whereas the effect sizes for change in PA were small to medium (Cohen d=0.22 to 0.45).

Conclusions: *we*Survive has the potential to be a feasible intervention for rural Appalachian cancer survivors. It will be refined and further tested based on the study findings, which also provide recommendations for other behavioral interventions targeting rural cancer survivors. Recommendations included adding additional recruitment and engagement strategies to increase demand and practicality as well as increasing accountability and motivation for participant involvement in self-monitoring activities through the use of technology (eg, text messaging). Furthermore, this study highlights the importance of using a systematic model (eg, the ORBIT framework) and small-scale proof-of-concept studies when adapting or developing behavioral interventions, as

doing so identifies the intervention's potential for feasibility and areas that need improvement before time- and resource-intensive efficacy trials. This could support a more efficient translation into practice.

Introduction

Cancer survivors comprise approximately 5% of the US population, and the number of cancer survivors is expected to increase by almost 30% over the next 10 years [1]. Although cancer survivors live longer, evidence suggests that they continue to engage in behaviors that increase their risk for recurrence, new cancers after treatment, and other chronic diseases that could impair survivorship outcomes [2,3]. Health behaviors that are recommended for cancer survivors to engage in include healthy diet and weight, being physically active, avoiding or stopping tobacco use, limiting alcohol consumption, and practicing sun safety [4,5]. Cancer survivors may be primed to change their health behaviors, as the cancer diagnosis and treatment may serve as *teachable moments* that motivate them to improve health behaviors. Therefore, addressing the health behaviors of cancer survivors has been identified as a priority in both clinical and community settings [6].

Addressing the health behaviors of cancer survivors is particularly important in health disparate communities, such as those in rural Central Appalachia. These communities are disproportionately impacted by cancer, as indicated by higher cancer mortality rates than those of nonrural communities [7]. There are also high rates of low educational attainment and low socioeconomic status in this region [8], and these social determinants of health are associated with a greater likelihood of engaging in unhealthy behaviors after treatment [2]. In addition, these communities often have a high prevalence of other chronic health conditions, such as type 2 diabetes, obesity, and heart disease [9-12], which can adversely impact cancer outcomes and mortality. Importantly, the development and management of these health conditions can be impacted by changing health behaviors. However, efforts to address the health behaviors of cancer survivors in Appalachia, similar to other rural areas, have been limited [13].

Increasing efforts to integrate interventions for cancer survivors that target modifiable health behaviors may be a strategic way to reduce cancer disparities in this region and others. Although there are existing behavioral interventions for cancer survivors, most of them are designed for survivors of a specific type of cancer and use one mode of delivery [14-17]. In addition, few of these existing interventions have been specifically developed for the needs of rural cancer survivors. Therefore, existing interventions would need to be adapted or a new intervention would need to be developed to meet the needs of cancer survivors in Appalachia.

Using a systematic process to develop or adapt an intervention allows for the assessment of the intervention's potential relevance, clinical efficacy, and sustainability. This information is particularly vital for interventions that have the ultimate goal of being translated into real-world settings. The Obesity-Related Behavioral Intervention Trials (ORBIT) model presents a systematic process of translating basic and clinical behavioral science findings into behavioral interventions [18]. Although initially designed for the development of obesity-focused trials, the systematic steps of the ORBIT model are applicable for the design of behavioral interventions targeting other health conditions. This paper describes how researchers affiliated with the University of Virginia (UVA) Cancer Center and community stakeholders from its rural Appalachia catchment area in southwest Virginia employed phase 1 and phase 2 of the ORBIT model to adapt or develop and pilot test a behavioral intervention for cancer survivors.

Methods

Design

This two-phase mixed methods study describes the development and initial pilot testing of a behavioral intervention for rural cancer survivors. The process, guided by the ORBIT model [18] and feasibility framework by Bowen et al [19], provides a conceptual framework for the evaluation of a proof-of-concept study. The ORBIT model includes 4 phases—phase 1: define and refine basic elements, phase 2: preliminary testing, phase 3: efficacy testing, and phase 4: effectiveness testing. This study focused on the first 2 phases. The feasibility framework by Bowen et al [19] identifies 8 key domains to measure during feasibility trials at both the participant and organizational levels. This study measures indicators for the 5 domains that are appropriate for the early proof-of-concept trial phase: acceptability, demand, implementation, practicality, and limited efficacy testing. The domains are listed in Table 1.

Table 1. Summary of measures used in the feasibility trial of *we*Survive.

Feasibility domain, definition, indicator, and measure	Baseline	Postassessment	Process evaluation
Acceptability: extent to which the intervention is judged as suitable, satisfying, or attractive to recipients			
Organizational perceptions			
Recruitment memos	—[a]	—	✓[b]
Participant satisfaction			
Summative evaluation	—	✓	—
Demand: extent to which the intervention is likely to be used			
Organizational adoption			
Recruitment memos	—	—	✓
Recruitment rates			
Recruitment logs	—	—	✓
Participant engagement			
Attendance logs	—	—	✓
Class and call memos	—	—	—
Class or call artifacts	—	—	—
Behavioral target chosen by participants			
Summative evaluation	—	✓	✓
Class or call artifacts	—	—	—
Practicality: extent to which the intervention can be carried out with intended participants using existing means, resources, and circumstances and without outside intervention			
Barriers and facilitators of participant engagement			
Summative evaluation	—	✓	—
Implementation: extent the intervention can be successfully delivered to intended participants			
Recruitment execution			
Recruitment memos	—	—	✓
Recruitment logs	—	—	—
weSurvive delivery			
Class or call memos	—	—	✓
Limited efficacy: the promise of the intervention to be successful with the intended population			
Changes in cancer-related beliefs			
Cancer belief questions from HiNTS[c]	✓	✓	—
Changes in diet and physical activity self-efficacy			
Scaled survey questions	✓	✓	—
Changes in diet and physical activity intentions			
Scaled survey questions	✓	✓	—
Changes in dietary behaviors			
NCI[d] multifactor screener	✓	✓	—
Changes in physical activity behaviors			
Modified Godin	✓	✓	—
L-CAT[e]	—	—	—
Changes in social network size			
Cancer survivor social networks measure	✓	✓	—

Feasibility domain, definition, indicator, and measure	Baseline	Postassessment	Process evaluation
Changes in quality of life			
Quality of life patient or cancer survivor version	✓	✓	—

[a]Related data were not collected.

[b]Related data were collected.

[c]HiNTS: Health Information National Trends Survey.

[d]NCI: National Cancer Institute.

[e]L-CAT: Stanford Leisure-Time Activity Categorical Item.

ORBIT Model Phase 1: Define and Refine Basic Elements

Intention of Phase

The purpose of phase 1 of the ORBIT model is to develop a hypothesized pathway through which behavioral intervention could impact health and determine components, duration, mode of delivery, and tailoring needs [18]. For our study, the intention for this phase was to identify and adapt an existing intervention or, if needed, develop a novel intervention using best practices. We approached this phase by (1) conducting literature searches and (2) engaging an advisory team of local stakeholders in a participatory development process.

Literature Search

We conducted a search of those listed in the National Cancer Institute's (NCI) Research Testing Intervention/Program website [20] and through PubMed to identify existing behavioral interventions for cancer survivors. The identified interventions were reviewed during participatory processes.

Participatory Process

This process was guided by a comprehensive participatory planning and evaluation process [21] (described below). It incorporated the Putting Public Health Evidence in Action training [22] and focused on the sessions related to identifying, selecting, and adapting evidence-based interventions.

To recruit advisory team members, the study was presented to all members of the Cancer Center Without Walls Southwest Virginia Community Advisory Board (CAB) during a quarterly CAB meeting. The CAB consists of representatives from local health care systems and other organizations that work on cancer-related issues, community members, and the UVA Cancer Center faculty and staff. The CAB members who were interested in joining the advisory team contacted the research team. The resulting advisory team consisted of 10 members: 6 community stakeholders, 1 UVA Cancer Center Outreach and Engagement staff member, and 3 interdisciplinary UVA faculty members with expertise in behavioral interventions, oncology, and community engagement. Community stakeholders represented local health systems (n=2), the social services sector (n=2), and higher education (n=2). The 3 members were cancer survivors.

The advisory team engaged in 6 meetings over 6 months, three 1-hour in-person meetings, and three 1-hour conference calls. The intention of these meetings was to identify key recommendations for what the intervention should address and

to use these recommendations to identify and either adapt or develop a behavioral intervention. Planned activities included sharing previous experiences with behavioral interventions for cancer survivors and perceptions of needed and acceptable components, reviewing and commenting on existing behavioral interventions for cancer survivors, and deciding upon the intervention and identifying adaptations. Notes and reflection worksheets completed during meetings were reviewed, summarized, and used to identify key action steps between meetings. During this process and based on the literature review, it became evident that existing interventions did not meet local needs and that a novel intervention would need to be developed.

Through the participatory process, the advisory team identified 4 key recommendations that an ideal behavioral intervention for rural Appalachian cancer survivors would need to take into account: (1) incorporation of both in-person and telehealth components so that participants could engage even if they had barriers to one delivery mode; (2) utilization of strategies that promoted action planning and storytelling; (3) addressing multiple behaviors; and (4) opening the program to all adult cancer survivors regardless of gender or cancer type. A conceptual model and program design were developed using these recommendations and a review of the best practices (Figure 1).

The resulting intervention, *we*Survive, was rooted in Social Cognitive Theory (SCT) [23] and targeted improving participant quality of life (QoL) through the improvement of 11 health behaviors associated with better cancer survivorship outcomes, including dietary and physical activity (PA) behaviors (Figure 1) [4,5]. Participants self-selected 1 or 2 behaviors they wanted to focus on in the first in-person group class. To make this selection, participants engaged in a guided reflection through which they assessed their level of engagement with each healthy behavior, whether they wanted to improve upon it, and their confidence in making the improvements or changes.

Participants received 10 hours of contact over 13 weeks. There were 3 in-person group classes, 4 group telehealth calls, and 2 individualized telehealth calls. Telehealth activities were assessed using Zoom (Zoom Video Communications Inc) [24]. Each component was led by KP. The activities in each component addressed 6 SCT constructs: outcome expectations, behavioral capability, self-efficacy, goal intention, self-regulation, and supportive environment [23]. Behavior change techniques, including self-monitoring [25], that tapped into the theory constructs and addressed aspects of QoL were included in each component. To support the execution of the components and behavior change, participants received a

physical workbook that included class and call content, action planning materials, and evidenced-based resources (eg, exercise DVDs). Group components also provided avenues for discussion about participants' experiences as a cancer survivor to extend social networks to include other cancer survivors.

Figure 1. *we*Survive program conceptual model and component design. SCT: Social Cognitive Theory.

ORBIT Framework Phase 2: Preliminary Testing

Intention of Phase

The goal of phase 2 of the ORBIT model is to determine the potential of the intervention to produce clinically significant findings and evaluate intervention feasibility. A hallmark of this phase is the establishment of a clearly articulated intervention protocol (eg, curriculum, protocols for recruitment, retention, and data collection). This phase consists of proof-of-concept studies, followed by pilot studies. Proof-of-concept studies aim to determine whether the intervention warrants more rigorous testing or whether modifications are needed before additional testing. Proof-of-concept studies are usually conducted using quasi-experimental designs and usually have small sample sizes. Small sample sizes are acceptable, as the intention is to identify clinically significant impacts, not statistically significant ones.

The *we*Survive proof-of-concept study used a single-group pre-post design and a concurrent mixed methods approach [26]. All study procedures were approved by the UVA Institutional Review Board (IRB). As study measures were completed over the telephone to reduce participant burden, participants provided verbal informed consent. They received US $25 in gift cards to complete each of the baseline assessments and postassessments. Participants also received a US $5 gas card for each in-person class attended to assist with cover transportation costs.

Recruitment

Recruitment strategies were executed at the organizational and participant levels. At the organizational level, 2 local health care organizations that provide clinical care to cancer survivors were approached to be a part of this study. Importantly, a member of the advisory team worked for one of these organizations. To recruit the organizations, we presented the intention and design of the *we*Survive intervention and the proof-of-concept trial to key clinical staff. After the organizational staff expressed interest, we reviewed the participant recruitment protocol with them and tailored the recruitment strategy, including a communication plan, to their needs. As needed, we obtained approval from the IRB of the organizations.

Following organization recruitment, *2* cohorts of participants were recruited from 2 recruited organizations. To be eligible, participants had to be cancer free, had to have completed primary treatment within the past 5 years, and be English speaking. Inclusion was not limited by cancer type or gender. The initial recruitment protocol involved selecting clinical staff who interacted with cancer survivors during their follow-up appointments to directly present the *we*Survive intervention to eligible survivors and solicit their interest. Then, for interested survivors, the clinician would securely share their contact information with the research team or show the prospective participant how to contact us. This strategy was expanded to include other active (eg, direct communication with research staff during follow-up appointments, booths at survivorship dinners, Relay-4-Life events) and passive (eg, flyers in waiting rooms) recruitment strategies.

Data Collection and Measures

Participant-level data were collected at baseline and postassessment. Process data were collected during the execution of the proof-of-concept trial. Table 1 describes the measures used to assess the indicators for the assessed feasibility domains.

During recruitment, research and organizational staff maintained recruitment logs and kept recruitment memos of interactions with prospective participants. These logs included the gender, age, and decision of all prospective participants with whom staff members spoke about joining *we*Survive as well as where and by whom they were approached. The research staff also kept notes during meetings with the organizational staff.

Research staff maintained attendance logs, recording attendance for each component.

Class artifacts, including action plans during the first group class, were photographed. The research staff also kept delivery memos of how each component went and the completeness of each activity. Tracking sheets were also used to monitor adherence to the intervention protocols (eg, sending reminder messages, contacts for individual calls).

To measure limited efficacy measures, participants completed a survey packet at baseline and postintervention. The packet was completed over the phone with a trained research staff member. The included measures were validated, cancer survivor specific, and/or successfully used in the region before. A total of 2 questions from the Health Information National Trends Survey were used to identify beliefs about cancer [27]. Single-item questions were used to assess self-efficacy and behavioral intentions to change dietary and PA behaviors [28]. The targeted dietary and PA health behaviors were assessed using scales from the NCI Multifactor Screener [29], Stanford Leisure-Time Activity Categorical Item (L-CAT) [30], and modified Godin [28]. Although behaviors, intentions, and self-efficacy were also assessed for other health behaviors, they were not reported in this paper because of the infrequency with which they were selected by participants. The Cancer Survivor Social Networks Measure [31] was used to assess participants' social networks. QoL was measured using the Quality of Life Patient/Cancer Survivor version [32]. Additional details regarding the measures can be found in Table 2.

Following completion of the postassessment survey, participants completed a *summative evaluation*. This semistructured interview assessed indicators of acceptability (ie, satisfaction), demand (ie, chosen behavioral target, reasons for choosing the behavioral target), and practicality (ie, barriers and facilitators of attendance) [33].

Participant *demographics* (ie, gender, age, race or ethnicity, income, educational attainment) and cancer experience (ie, type, staging, type of treatment, date of primary treatment completion) were collected at baseline. Health literacy was also measured using a validated 3-item brief questionnaire [34].

Table 2. Limited efficacy-related outcomes.

Variable type and specific variable	Scale	Preassessment (n=11), mean (SD)	Postassessment (n=11), mean (SD)	Direction of change	t statistic (P value)	Cohen d
Cancer beliefs and knowledge						
There are so many recommendations about preventing cancer, it's hard to know which ones to follow	5-point Likert scale (1=strongly disagree; 5=strongly agree)	4.0 (1.34)	3.6 (1.51)	↓[a]	1.102 (.30)	−0.28
Cancer is most often caused by a person's behavior or lifestyle	5-point Likert scale (1=strongly disagree; 5=strongly agree)	2.6 (1.63)	3.3 (1.62)	↑[b]	1.295 (.22)	0.43
Self-efficacy						
Self-efficacy to eat 5-9 servings of fruits and vegetables a day	10-point Likert scale (1=not at all confident; 10=totally confident)	6.7 (2.65)	6.6 (1.63)	↓	0.118 (.91)	−0.05
Self-efficacy to eat a diet with less saturated fat	10-point Likert scale (1=not at all confident; 10=totally confident)	7.6 (1.92)	7.4 (1.96)	↓	0.319 (.76)	−0.10
Self-efficacy to be physically active for 150 min a week	10-point Likert scale (1=not at all confident; 10=totally confident)	6.5 (3.39)	6.8 (2.79)	↑	0.498 (.63)	0.10
Behavior-specific intentions						
Eat 5-9 servings of fruits and vegetables a day	5-point scale (1=no intention to engage in at all; 5=already doing)	3.2 (1.40)	3.6 (1.29)	↑	1.174 (.27)	0.30
Eat a diet with less saturated fat	5-point scale (1=no intention to engage in at all; 5=already doing)	3.9 (1.38)	4.0 (1.18)	↑	0.289 (.78)	0.08
Be physically active for 150 min a week	5-point scale (1=no intention to engage in at all; 5=already doing)	3.2 (1.32)	3.9 (1.14)	↔[c]	2.667 (.02)	0.57
Health behaviors						
Fruit and vegetables	Daily portions	1.8 (1.38)	1.8 (.92)	↔	0.096 (.93)	0.00
Snack foods	Daily portions	1.1 (.84)	1.0 (1.58)	↓	0.178 (.86)	−0.08
Dietary fat	Daily portions	5.3 (6.53)	3.5 (4.45)	↓	1.402 (.19)	−0.32
Moderate-vigorous physical activity	Minutes per week	115.0 (137.20)	158.6 (237.78)	↑	0.889 (.40)	0.22
Self-reported frequency of physical activity	6-point scale (1=very little physical activity; 6=30 min of vigorous activity 5 or more times a week)	2.4 (.84)	2.8 (.92)	↑	1.809 (.10)	0.45
Social network						
Cancer-specific social support network size	Score of 0-15	9.6 (2.01)	10.5 (2.50)	↑	1.423 (.19)	0.40
Quality of life						
Overall	11-point Likert scale (0=extremely negative; 10=extremely positive)	8.1 (1.39)	7.8 (1.78)	↓	1.055 (.32)	−0.19
Physical	11-point Likert scale (0=extremely negative; 10=extremely positive)	8.6 (1.47)	7.8 (2.43)	↓	1.173 (.27)	−0.40
Emotional	11-point Likert scale (0=extremely negative; 10=extremely positive)	7.7 (1.77)	7.3 (2.26)	↓	1.303 (.22)	−0.20

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Variable type and specific variable	Scale	Preassessment (n=11), mean (SD)	Postassessment (n=11), mean (SD)	Direction of change	t statistic (P value)	Cohen d
Social	11-point Likert scale (0=extremely negative; 10=extremely positive)	7.8 (2.40)	7.6 (2.33)	↓	0.578 (.58)	−0.08
Spiritual	11-point Likert scale (0=extremely negative; 10=extremely positive)	8.4 (1.74)	8.4 (2.17)	↔	0.120 (.91)	0.00

[a]Decrease in score from pre to postassessment.

[b]Increase in score from pre to postassessment.

[c]No change in score from pre to postassessment.

Data Analysis

Descriptive statistics (frequencies, means, medians, and ranges) were used to summarize participant demographics, participant satisfaction, recruitment and engagement rates, and selected behavioral targets. Limited efficacy measures were scored using standard procedures, and paired, two-tailed t tests were used to compare baseline and posttest responses for limited efficacy measures for program completers (n=11). Cohen d was calculated for each limited efficacy outcome. Open-ended data related to participant satisfaction, facilitators and barriers to engagement, component execution, and perceptions of organizations were content coded by one researcher and reviewed by another. Quantitative and qualitative data for each indicator were triangulated [26].

Results

Participants

A total of 12 participants were enrolled in 2 sequential pilot cohorts (n=5 and n=7). The participants were 75% (8/12) female and 100% (12/12) White. The average age of participants was 64 (SD 6.37) years, and 75% (9/12) were married. Half (6/12, 50%) of the participants were employed full-time, 33% (4/12) had a high school degree or less, and 25% (3/12) made under US $25,000 a year. All participants had medical insurance, either private (5/12, 42%) or Medicare (7/12, 58%). The majority of the participants (n=11) had adequate health literacy.

The participants were survivors of 6 types of cancer: breast (6/12, 50%), prostate (3/12, 25%), skin (2/12, 17%), colon (1/12, 8%), cervical cancer (1/12, 8%), and large B-cell lymphoma (1/12, 8%). Two participants (2/12, 17%) had multiple cancers. The participants had completed chemotherapy (8/12, 67%), radiation (5/12, 42%), surgery (8/12, 67%), and stem cell treatment (1/12, 8%). Over half of the participants (7/12, 58%) received multiple treatment types. On average, participants had completed primary treatment for 13.8 months (SD 13.5; range 1-40 months) before joining the trial.

Feasibility Indicators

The outcomes for acceptability, demand, practicality, and implementation are presented in Table 3, whereas limited efficacy outcomes are presented in Table 2.

Table 3. Findings related to the feasibility domains of acceptability, demand, practicality, and implementation.

Feasibility domain and indicator	Quantitative findings	Qualitative findings
Acceptability		
Organizational perceptions	__a	Staff from the 2 organizations that were approached to host *we*Survive felt it would be beneficial to their patients
Participant satisfaction	Overall rating, mean 10.0/10.0 (SD 0.00) • Group classes, mean 9.7/10.0 (SD 0.65) • Group calls, mean 9.5/10.0 (SD 0.87) • Individualized calls, mean 9.7/10.0 (SD 0.53)	Perceived program benefits: • Knowledge gained • Opportunity to share their experiences and learn about others' experiences • Felt the program was an important wakeup call • Saw the program as an opportunity to improve their lives or give back to others • No facets of the program identified as "unacceptable"
Demand		
Organizational adoption	• The 2 (100%) health care organizations approached agreed to take part in the *we*Survive proof-of-concept trial	—
Recruitment rates	• Recruitment rate=30% (12/41) • 59% (17/29) of nonenrolment was due to lack of ability to follow up with prospective participant to schedule or complete the survey • 38% (11/29) of nonenrolment was due to lack of interest	—
Participant participation	• Attrition=8% (1/12) Overall attendance: median 62% (average 56%): • Group class attendance: median 84% (average 72%) • Group call attendance: median 50% (average 42%) • Individual call attendance: median 50% (average 50%) • Of the 8 participants who attended group calls, only 3 (38%) used the video portion of the telehealth platform	• When completing action plans, participants often only partially completed them or just discussed their plans without writing them down. Participants appeared hesitant to set SMART[b] goals • During individual calls, 3 participants asked for and received support for specific dietary matters beyond what was in the standard curriculum
Behavioral target chosen by participants	100% (12/12) selected diet or PA[c]: • 83% (10/12) selected PA • 59% (7/12) selected a dietary behavior • 42% (5/12) chose both PA and diet • 50% (6/12) chose a behavior other than diet or PA: sleep (3/12, 25%), stress reduction (4/12, 33%)	Reasons for choosing behaviors: • Priority for personal or disease-specific reasons • Perceived as easier to address
Practicality		
Barriers and facilitators of participant engagement	—	Barriers to attendance: • Personal and work obligations Facilitators of attendance: • Participants found reminder texts helpful • Expanded texting reminder system in cohort 2 to include reminder day before and 2 hours before
Implementation		

Feasibility domain and indicator	Quantitative findings	Qualitative findings
Recruitment execution	Eligible participants (n=41) were approached through office visits (25/41, 61%), community events (13/41, 32%), and word of mouth (3/41, 7%): • 100% of office visit referrals were executed jointly by site and research staff • 100% of community event referrals were completed by research staff • 100% of word-of-mouth referrals were completed outside of the clinic by site staff	• At one of the 2 sites, a provider (MD or NP) introduced *we*Survive to an eligible participant. If the participant was interested, they invited the research team member to come in to speak with the participant. This process did not occur at the other site due to the distance to the site and inconsistent communication between research and site staff • Organization staff were very interested in the idea of the program but were unable to follow the recruitment protocol on their own (ie, refer eligible patients without the presence of a research team member) but were able to execute when working in conjunction with research staff
*we*Survive delivery	• 100% fidelity (of researchers) to the execution of intervention components and the participant retention protocol	—

[a]Quantitative or qualitative data was not collected for the feasibility domain indicator.

[b]SMART: specific, measurable, attainable, relevant, time-based.

[c]PA: physical activity.

Acceptability

Participants who completed the intervention (n=11) reported high satisfaction with the program (mean 10, SD 0.0) and with the individual components: group classes (mean 9.7, SD 0.65), group calls (mean 9.5, SD 0.87), and individual calls (mean 9.7, SD 0.53). Participants described benefits related to knowledge attainment, feeling that *we*Survive was a *wakeup call* to improve their health, sharing their cancer experiences and hearing others' cancer experiences, and knowing that by being in the trial they were helping future cancer survivors. In addition, staff from the participating organizations expressed positive reactions to the program and viewed it as having the potential to be beneficial to their patients.

Demand

The 2 local health care organizations approached to participate in the proof-of-concept trial agreed to participate. The participant recruitment rate for the trial was 30%, with 12 of 41 eligible individuals approaching enrolment in the program. Among individuals who did not enroll, 38% (11/29) expressed a lack of interest in the program or prohibitive barriers (eg, language difficulties, transportation) and 59% (17/29) had barriers that limited scheduling surveys or completed the web-based presurvey.

Intervention attrition for the program was low, with only 1 participant (1/12, 8%) not completing the program. The median participation rate for all activities was 62%, with the medians for class, group call, and individual being 84%, 50%, and 50%, respectively. Of the 8 participants who completed group calls, only 3 (38%) used the video portion of the telehealth platform. The other 5 called into the platform using the telephone number and did not use the phone, tablet, or computer application that would have allowed for video.

Research staff noted that participants did not fully engage in self-monitoring activities, such as setting a specific behavioral goal and writing SMART (specific, measurable, attainable, relevant, time-based) goals, even with prompting. For example, a participant would broadly describe their target behavior (ie, "eat healthy" instead of "eat 5 fruits and vegetables 3 days a week day") and would not include a plan for how they would make the change.

Although participants could choose among 11 behaviors, 100% chose either a diet (7/12, 59%) or PA behavior (10/12, 83%) and 42% (5/12) chose both. Of the 6 nondiet or PA behaviors, only 2 were selected: stress (n=3) and sleep (n=4).

Practicality

Participants identified personal and work obligations as their primary barriers to participate in intervention activities. They identified the reminder texts as facilitators of attendance.

Implementation

Staff from both organizations were unable to follow the original recruitment protocol and did not refer participants to the program without on-site support from the research staff. Therefore, it was necessary to adapt the recruitment protocol to provide on-site research staff support at the clinic and recruit through community events. Eligible participants were identified in 3 ways: during office visits (25/41, 61%), at community events (13/41, 32%), and word of mouth (3/41, 7%). Organizational staff made all word-of-mouth referrals, whereas research staff made referrals through community events. All office visit referrals occurred with the organizational and research staff working together. Organizational staff would introduce *we*Survive to an eligible participant and, if interested, a research team member provided further detail and collected their contact information to complete the surveys.

There was 100% fidelity to the delivery and retention protocols by the research staff. All planned activities for the components were executed as designed, and participant retention strategies (eg, reminder texts) were adhered to as intended.

Limited Efficacy

Regarding behavior-related psychosocial variables, participants changed their beliefs about cancer with respect to knowing

which recommendations to follow (Cohen d=0.28) and the impact of lifestyle behaviors on cancer risk (Cohen d=0.43) in the desired direction. Self-efficacy to meet the PA guidelines changed in the desired direction, whereas changes in self-efficacy to reduce dietary fat and increase fruits and vegetables were in the undesired direction (ie, lower self-efficacy). The effect sizes for the behavioral self-efficacy variables were very small (≤0.10). Although not statistically significant, behavioral intentions to eat more fruits and vegetables, eat less fat, and meet PA guidelines changed in the desired direction. The change in intentions specific to PA was statistically significant (P=.02) and demonstrated a medium effect size (Cohen d=0.57).

Baseline to postassessment changes in dietary and PA behaviors were in the desired directions but were not statistically significant. Effect sizes for fruit and vegetable intake, snack foods, dietary fat, and minutes of moderate-vigorous activity were small (Cohen d=0.00 to 0.32), whereas the effect size for L-CAT score was medium (Cohen d=0.45).

Participants' social networks specific to their cancer support networks increased. Although not significant, this change had a small-to-medium effect size of 0.40.

Regarding QoL indicators, there were nonsignificant decreases (ie, worsening of QoL) in all indicators. The magnitude of these changes was small for overall QoL, emotional QoL, social QoL, and spiritual QoL (Cohen d=0.00 to 0.20); However, the change in physical QoL from baseline to postassessment was small or medium (Cohen d=0.40).

Discussion

Principal Findings

Taken together, our results suggest that the *we*Survive intervention has the potential to be feasible. Our findings also highlight how the design and execution of the intervention and its components could be improved to further enhance its feasibility, including increasing efficacy among cancer survivors. Furthermore, outcomes also provide support for using a participatory process and a systematic planning model, such as the ORBIT model, to inform the design of behavioral interventions for cancer survivors.

Implications for *we*Survive's Feasibility

Our findings suggest high feasibility related to indicators of acceptability (ie, high satisfaction), demand (ie, high adoption rate by organizations, diversity of cancer survivors by cancer type and gender, low attrition rate, recruitment, and component engagement rates similar to other behavioral interventions for rural participants and/or cancer survivors [28,35-38]), and implementation (ie, high researcher fidelity to protocols). However, findings related to indicators of practicality (eg, consistent barriers to participation), implementation (eg, ability of organizational staff to follow intended delivery, retention, and recruitment protocols), and limited efficacy highlight opportunities to adjust aspects of the intervention design and delivery protocols that could improve feasibility.

Although our results do not fully confirm the feasibility of *we*Survive, they identify areas where modifications to *we*Survive's design and protocols could strengthen feasibility. As proof-of-concept studies focus on the feasibility of the intervention, the evidence collected provides integral preliminary data not only about its clinical efficacy but also its relevance and potential sustainability. This preliminary evidence can help build an intervention that is both effective and more readily translated into practice. This is particularly important for behavioral interventions for rural cancer survivors, as efforts to address the health behaviors of cancer survivors in rural regions are limited [13].

Recommendations to Improve Feasibility of *we*Survive and Other Behavioral Interventions for Rural Cancer Survivors

A total of 6 recommendations that impact all measured feasibility domains from this proof-of-concept study were identified. In addition to being directly relevant to the *we*Survive intervention, many of these recommendations are broadly applicable and can be used to inform future behavioral interventions for cancer survivors.

Tighten the Behavioral Focus of weSurvive (Demand and Efficacy)

Including a wide array of behaviors important for positive survivorship outcomes was suggested by the advisory team to ensure the applicability of the program to regional cancer survivors. However, demand findings clearly demonstrated that diet and PA were the most popular choices, with all participants choosing one or the other. In addition, limited efficacy outcomes suggest that *we*Survive impacted these behaviors and related psychosocial variables in the desired direction, with some of the PA outcomes having small-to-moderate effects. Making this adjustment would streamline *we*Survive's behavioral focus, potentially impacting the magnitude of effects for the targeted behaviors. Although the recommendation to include a variety of behaviors may have hindered feasibility, incorporating this suggestion from the advisory team during this initial phase allowed us to better ascertain the wants of regional cancer survivors. Importantly, although the behavioral focus of *we*Survive will shift to energy-balance–related behaviors, the program will still include content related to stress reduction and sleep.

Add Additional Recruitment Strategies (Demand)

Although we recruited a diverse group of participants with regard to gender and cancer experience, the overall group sizes were small, and the recruitment rate of 30% was modest. During the trial, we added and adapted strategies to maximize the recruitment efforts. Successful strategies included having an on-site research staff recruit in tandem with organizational staff and promoting *we*Survive at community events targeting cancer survivors. For future trials of *we*Survive, these strategies should be incorporated into recruitment from the start.

An additional recruitment strategy was to promote *we*Survive during survivorship care plan meetings. Survivorship care plans are a highly recommended part of survivorship care [39], and more clinics are systematically using them. Suggestions for

behavioral changes may be included [40], but not all clinics have the resources to facilitate behavioral changes, including those related to diet, PA, and weight change behaviors. Therefore, aligning *we*Survive with cancer care survivorship plans could make the intervention more relevant for organizations and provide a natural place for it within the workflow, which could motivate organizational staff to promote *we*Survive. Although this seems to be a logical connection, few known behavioral interventions for cancer survivors reported tying their intervention in survivorship care plans [41]. If future behavioral interventions were designed to address needs highlighted by their participants' survivorship care plans, this could increase the demand for the program from both the participant and organizational sides and could help cancer survivors better execute their plans.

Recruitment into behavioral interventions can be one of the most difficult aspects of executing an intervention, and underaccrual of participants hinders many interventions. Past lifestyle interventions for cancer survivors have reported a range of recruitment rates ranging from 4% to 70%. Although this difficulty is prevalent in densely populated regions, it may be even greater in rural regions, such as Appalachia, which have smaller populations and lack large academic medical centers and large cancer centers. Therefore, using preliminary data to create a tailored, adaptable, and multi-faceted approach to recruitment may aid in the successful recruitment of other behavioral interventions as well [42].

Incorporate Strategies to Support Program Engagement (Demand and Practicality)

The participation rates from our trial were similar to those of other behavioral interventions for cancer survivors [28,35-38]. However, these rates can be improved by addressing the barriers to attendance identified by the participants (eg, conflicts with personal and work scheduling, forgetting). Future strategies include (1) having at least 2 formal day or time opportunities to participate in all group activities, (2) sending reminder texts the day before and 2 hours before the scheduled call time for virtual components, and (3) offering virtual makeup sessions. These changes could improve feasibility related to participant perceptions of acceptance and practicality for *we*Survive and could be applicable strategies for similar interventions.

In addition to overall participation rates, findings show that engagement with the video portion of the teleconferencing platform was underused. Most of the 8 participants who attended at least one group call only used the audio capabilities of the platform (82.5%), and none of the participants used the video feature for all group calls they completed. We suspect that reasons include unfamiliarity with the technology and poor internet or cellular access and/or quality. During the proof-of-concept trial, participants received a written instruction sheet, and the researcher delivered the first group class talked through the instructions. Additional activities to encourage use could include a platform demonstration, a formal system for troubleshooting barriers to using the teleconferencing platform, and structured conversations about the benefits of participation in virtual components. Providing this additional support may be valuable for rural participants in lifestyle programs, as

previous studies have shown that they may hesitate to use teleconferencing platforms due to low digital literacy, privacy concerns, and fear that it might limit group connection [43]. Importantly, as found in other studies with rural populations, the video portion of teleconferencing calls enabled participants to experience greater engagement and feelings of support than they would have if these components were absent [43]. Importantly, as this study was conducted before the COVID-19 pandemic, during which the general public started regularly using Zoom and other teleconferencing platforms, this experience may make future participants more comfortable with the video feature.

Improve Engagement in Behavioral Self-Monitoring Strategies by Creating More Accountability and Motivation (Implementation)

Behavioral self-monitoring encompasses vital behavior change techniques, such as goal setting and self-monitoring activities, which are linked to better behavioral changes [44]. Action planning, sharing goals, and discussing progress and struggles were included in each component of *we*Survive. However, participants in this trial did not fully engage in self-monitoring activities, particularly action plans. The behavior change literature suggests that this is common and that strategies can be employed to increase engagement with action planning, such as sending motivational messages, sending text messages or email reminders, and providing feedback [45,46]. In this proof-of-concept trial for *we*Survive, personalized approaches to keep participants motivated toward and accountable for their goals were not included, as our focus was on solidifying the curriculum content and recruitment, retention, and data collection protocols. Adding accountability structures appropriate to rural populations could increase engagement with behavioral self-monitoring activities. It might also be necessary to create norms within the group activities to make participants feel comfortable to share their goals, progress, and struggles and to help one another troubleshoot their issues. Employing this recommendation will not only increase the implementation of behavioral self-monitoring activities but also limit the behavioral targets of the program and impact the intervention's efficacy on behavioral outcomes and QoL.

Capture the Overall Health Experiences of the Participants During the Trial Timeline

For this proof-of-concept study of *we*Survive, there were no statistically significant yet undesired changes in QoL indicators. This undesired change is not unusual, as postassessment scores on QoL measures sometimes go in the *wrong* direction due to participants rating themselves higher at baseline, potentially because they are primed to have higher expectations for QoL. In addition, through informal conversations with participants, we learned that 3 of them had substantial negative health experiences unrelated to the trial (ie, hospitalization, injury that required surgery, negative reaction to adjuvant therapy). When they were removed from the analyses, the changes either moved in the desired direction or the magnitude of the undesired changes was reduced. If captured systematically during interventions, these participant experiences could be factored into the actual outcome analyses or provide context to their

interpretation. This will allow for more context from which to interpret QoL outcomes and identify whether they are unintended consequences of the intervention.

Use a Participatory Process to Engage Stakeholders During Intervention Development or Adaptation Interventions (Demand)

Engaging stakeholders identified the key features that aided feasibility. Features identified by the *we*Survive advisory team impacted indicators of demand and included suggestions to blend group and individual activities and were not limited by cancer type or gender. In addition, these considerations informed the decision to measure social networks, which were found to moderately, though not significantly, increase. Interestingly, 4 of the 5 participants who did not include survivors or support groups as part of their network at baseline did at postassessment. This measurement of social networks along with broad inclusion criteria added innovative features to *we*Survive, which may aid in its future translation to practice. Although there is evidence that stronger social networks are linked to improved cancer survivorship outcomes [47] and that rural cancer survivors may be less connected than survivors in other regions [48], measuring and seeking to enhance social networks is not a common feature of behavioral interventions for cancer survivors. In addition, the advisory team recommended that the intervention allow participants to have authentic opportunities to share their stories and hear from others. Although storytelling is a noted cultural tradition in Appalachia [49] and has been used in cancer-focused interventions to transfer knowledge and address emotional and existential or spiritual concerns [50], it most likely would not have been included at this early stage of development of *we*Survive if not for the advisory team. Finally, our first site was identified by one of our community stakeholders. Stakeholder participation can strengthen the design and execution of behavioral interventions by identifying unique needs or resources within the community. Although not all the comments from the advisory team aided feasibility (ie, focusing on multiple behaviors), without our stakeholder's input and support, many of these other features would not have been included.

Limitations

When interpreting this study's conclusions, it is important to consider these limitations. The participant sample for the proof-of-concept trial was small. Although this impacts statistical power and interprets limited efficacy outcomes, it was still adequate to identify effect sizes and inform other feasibility indicators. The sample was not racially diverse; however, the racial makeup of the study reflects the geographical region, which is approximately 95% non-Hispanic White [8]. In addition, the sample was diverse in terms of gender and cancer experience and represented an underserved rural population. Finally, data were primarily collected at the participant level and, as such, findings are limited to feasibility at the organizational level. Future trials of *we*Survive will need to include a more robust evaluation of organizational-level indicators, including acceptability, practicality, and feasibility at this level and the potential for integration and penetration [19], to more fully understand

feasibility and identify modifications to protocols, particularly those related to recruitment.

Conclusions

Findings from our study will inform changes to the *we*Survive intervention's conceptual model, program design, and recruitment and delivery protocols. The recommendations identified through our study will be incorporated into the next version of *we*Survive. Engagement in the participatory development process and initial proof-of-concept testing strengthens *we*Survive and will lead to the development of a behavioral intervention that could positively impact the health of cancer survivors in rural Appalachia and be more readily translated into practice. Importantly, the findings also stress the importance of using a model, such as the ORBIT framework, when developing or adapting behavioral interventions for cancer survivors. By conducting small-scale proof-of-concept studies, the feasibility of the novel or adapted intervention can be assessed relatively quickly and inexpensively, and the necessary revisions can be made before larger-scale testing.

Conflicts of Interest

None declared.

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Abbreviations

CAB: Community Advisory Board
IRB: Institutional Review Board
L-CAT: Stanford Leisure-Time Activity Categorical Item
NCI: National Cancer Institute
ORBIT: Obesity-Related Behavioral Intervention Trials
PA: physical activity
QoL: Quality of Life
SCT: Social Cognitive Theory
SMART: specific, measurable, attainable, relevant, time-based
UVA: University of Virginia

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Original Paper

A Home-Based Mobile Health Intervention to Replace Sedentary Time With Light Physical Activity in Older Cancer Survivors: Randomized Controlled Pilot Trial

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Abstract

Background: Older cancer survivors are at risk of the development or worsening of both age- and treatment-related morbidity. Sedentary behavior increases the risk of or exacerbates these chronic conditions. Light-intensity physical activity (LPA) is more common in older adults and is associated with better health and well-being. Thus, replacing sedentary time with LPA may provide a more successful strategy to reduce sedentary time and increase physical activity.

Objective: This study primarily aims to evaluate the feasibility, acceptability, and preliminary efficacy of a home-based mobile health (mHealth) intervention to interrupt and replace sedentary time with LPA (standing and stepping). The secondary objective of this study is to examine changes in objective measures of physical activity, physical performance, and self-reported quality of life.

Methods: Overall, 54 cancer survivors (aged 60-84 years) were randomized in a 1:1:1 allocation to the tech support intervention group, tech support plus health coaching intervention group, or waitlist control group. Intervention participants received a Jawbone UP2 activity monitor for use with their smartphone app for 13 weeks. Tech support and health coaching were provided via 5 telephone calls during the 13-week intervention. Sedentary behavior and physical activity were objectively measured using an activPAL monitor for 7 days before and after the intervention.

Results: Participants included survivors of breast cancer (21/54, 39%), prostate cancer (16/54, 30%), and a variety of other cancer types; a mean of 4.4 years (SD 1.6) had passed since their cancer diagnosis. Participants, on average, were 70 years old (SD 4.8), 55% (30/54) female, 24% (13/54) Hispanic, and 81% (44/54) overweight or obese. Malfunction of the Jawbone trackers occurred in one-third of the intervention group, resulting in enrollment stopping at 54 rather than the initial goal of 60 participants. Despite these technical issues, the retention in the intervention was high (47/54, 87%). Adherence was high for wearing the tracker (29/29, 100%) and checking the app daily (28/29, 96%) but low for specific aspects related to the sedentary features of the tracker and app (21%-25%). The acceptability of the intervention was moderately high (81%). There were no significant between-group differences in total sedentary time, number of breaks, or number of prolonged sedentary bouts. There were no significant between-group differences in physical activity. The only significant within-group change occurred within the health coaching group, which increased by 1675 daily steps (95% CI 444-2906; *P*=.009). This increase was caused by moderate-intensity stepping rather than light-intensity stepping (+15.2 minutes per day; 95% CI 4.1-26.2; *P*=.008).

Conclusions: A home-based mHealth program to disrupt and replace sedentary time with stepping was feasible among and acceptable to older cancer survivors. Future studies are needed to evaluate the optimal approach for replacing sedentary behavior with standing and/or physical activity in this population.

KEYWORDS

light-intensity physical activity; physical activity; sedentary behavior; mobile health; cancer survivors; consumer wearable; activity monitor; mobile phone

Introduction

Background

By 2030, there will be 22.1 million cancer survivors living in the United States, and two-thirds of them will be more than 65 years old [1]. Older cancer survivors are faced with both age- and treatment-related morbidity that increase their risk of physical function impairment and other comorbidities, including cardiovascular disease, diabetes mellitus, and osteoporosis [2-5]. These comorbidities further increase the risk of functional limitations. Compared with individuals without a history of cancer, cancer survivors have a 2- to 5-fold increased risk of having one or more functional limitations [5]. These chronic conditions are associated with diminished quality of life (QoL), premature death, and substantial financial costs [6-11]. Physical inactivity and sedentary behavior (too much sitting, which is distinct from too little exercise [12]) can increase the risk of or exacerbate these chronic conditions [13-19].

Recent research suggests that sedentary behavior has molecular and physiological effects distinct from a lack of exercise [20,21]. Sedentary behavior is defined as any waking behavior (ie, not sleep) characterized by minimal energy expenditure (≤1.5 metabolic equivalents [METs]) while in a sitting, lying, or reclining position [22]. Sedentary behavior is associated with an increased risk of cardiovascular disease [23,24], premature all-cause mortality [23,25-27], greater fatigue [28,29], and decreased physical function [11,29,30]. Furthermore, how sedentary time is accumulated throughout the day is important, as frequent short breaks in sedentary time can attenuate the negative physiological response associated with prolonged, uninterrupted periods of inactivity [31-34].

Among cancer survivors, less than 2% of waking hours are spent in moderate-to-vigorous physical activity (MVPA), up to 70% of waking hours are spent in sedentary activities, and the remaining time is spent in light-intensity physical activity (LPA) [35]. LPAs are associated with better physical health [36,37], including better physical function [37-40], reduced risk of incident disability [39,41], and better emotional well-being [36,40,42,43], independent of MVPA. The association between LPA and health outcomes is either only apparent or appears stronger in older adults and adults who are less physically active or have impaired lower extremity function [41,44-47]. Thus, disrupting and replacing sedentary time with LPA, rather than MVPA, are likely a more feasible approach to reducing sedentary behavior in older cancer survivors.

Behavior change interventions based on theory are generally more effective than atheoretical approaches [48-50]. Recent reviews suggest that goal setting, feedback, self-monitoring, problem solving, and social support are the most promising behavioral change techniques for interventions designed to reduce sedentary behavior [51-53]. Unlike simple pedometers, consumer wearable activity trackers include multiple behavior change techniques [54,55]. The ability to provide feedback in real time is particularly salient for sedentary behavior, as it is a largely subconscious behavior [51]. Furthermore, wearable activity trackers are readily available and low cost and, if effective, represent a scalable option for expanding the reach to a large number of cancer survivors, including in rural areas.

Given the deleterious effects of sedentary behavior on health, including cardiovascular disease and diabetes mellitus, conditions that are commonly observed in older cancer survivors, or for which they are at an elevated risk [56], the role of sedentary behavior in cancer survivorship has been identified as a research priority [35,57]. However, to date, few interventions have been designed to reduce sedentary time among cancer survivors [51]. Recently, several mobile health (mHealth) pilot or feasibility interventions have evaluated text messaging or wearable activity trackers as an intervention tool to decrease sedentary behavior in breast, prostate, and colorectal cancer survivors [58-60]. These interventions encouraged standing and stepping to replace sedentary behavior, with a primary focus on moderate-intensity activity. Preliminary results suggest that mHealth interventions are feasible and acceptable in this population and have the potential to replace sedentary behavior with physical activity, at least in the short term. However, additional research is needed to further evaluate effective strategies to reduce sedentary time by either replacing it with standing, stepping, or both.

Objectives

The purpose of this study is to examine the feasibility, acceptability, and preliminary efficacy of an mHealth intervention for disrupting (frequent breaks) and replacing sedentary time with intermittent bouts of LPA (standing and stepping). The 13-week intervention used the Jawbone UP2 activity monitor and associated smartphone app to promote awareness and enable self-monitoring of both physical activity and inactivity. We evaluated 2 versions of the mHealth intervention: a low-touch approach providing only tech support and a higher resource approach that included health coaching in addition to the tech support. This would allow us to determine whether a low-cost, consumer-based technology (wearable activity tracker plus smartphone app) is effective in meeting the goals or whether health coaching is needed to cover additional behavior change techniques not provided in the wearable activity tracker. Our primary objective is to determine the feasibility and acceptability of the 2 versions of the mHealth intervention by assessing recruitment, retention, and adherence rates; monitoring adverse events; and evaluating satisfaction with the program. In addition, we examined the preliminary

efficacy of the intervention on changes in objective measures of daily total sedentary time and the number of breaks in sedentary time. Our secondary objective is to explore changes in objective measures of physical activity, physical performance, and self-reported QoL.

Methods

Study Design

This study was a 3-arm pilot randomized controlled trial (RCT). Older cancer survivors were randomized in a 1:1:1 allocation to the tech support intervention group, the tech support plus health coaching intervention group, or a modified waitlist control group. The intervention used a consumer wearable activity tracker (Jawbone UP2 wristband) that was paired with a smartphone app to promote awareness and enable self-monitoring of both inactivity (band gently vibrates after a specified time of inactivity) and physical activity (eg, steps per day). We evaluated 2 versions of the intervention: a low-touch approach providing only tech support and a higher resource approach that included health coaching in addition to the tech support. Each intervention group was compared with the waitlist control group. Recruitment for the trial began in June 2016, and data collection was completed in July 2017.

Eligibility

Eligibility criteria for the feasibility study included (1) men and women aged 60 years and older (reduced from 65 years to increase the number of participants who own a smartphone); (2) those who were diagnosed as having an invasive, local or regionally staged cancer within the past 7 years (time frame increased the likelihood that address and phone number in cancer registry were still current) and completed primary treatment (surgery, radiation, and chemotherapy); (3) those who owned a smartphone capable of running the Jawbone UP2 smartphone app; (4) those who were willing to be randomized to any of the 3 study arms, attend 2 clinic visits, and wear activity monitors; (5) those who were able to read, speak, and understand English; (6) those who were living independently and were capable of walking 3 blocks (approximately 1/4 mile or 1300 steps) without an assistive device (eg, cane and walker); (7) self-reported sedentary time (during waking hours) of ≥6 hours/day (Longitudinal Aging Study Amsterdam Sedentary Behavior Questionnaire: hours and minutes in a day spent in 10 activities, on average, during a weekday [61]); (8) those who were not currently participating in a program to decrease sedentary time or increase physical activity and not currently using a fitness tracker; (9) those who had no paid employment or volunteer position for more than 20 hours per week (to avoid potential confounding by occupational activity/inactivity); (10) those who had no severe impairments (in seeing or hearing) or preexisting medical limitations for engaging in daily LPA (eg, severe orthopedic conditions, pending hip/knee replacement, dementia, and oxygen dependent); (11) those who had residence within 60 miles of the research clinic (to reduce travel burden

and improve retention and compliance); and (12) those who had a wrist size of 14 cm to 20 cm to wear the Jawbone UP2 activity wristband during the intervention. Individuals who met the physical activity guidelines (150 minutes per week of MVPA) [17,62] were eligible because sedentary behavior is a risk factor for morbidity and mortality independent of MVPA.

Recruitment

The population-based New Mexico Tumor Registry, a founding member of the Surveillance, Epidemiology, and End Results Program [63], was used as the primary source for identifying potential study participants. Additional sources included posting flyers at selected locations, including senior centers and libraries. After identifying potentially eligible study participants, the New Mexico Tumor Registry mailed a letter that introduced the study and gave potentially eligible participants the opportunity to decline further contact. Contact information for individuals not refusing further contact was provided to the study team after a 3-week waiting period. Potential participants were then mailed a letter explaining the study and a consent form. One week later, the staff telephoned to discuss the study, answer questions, begin the consent process, and verify eligibility. Up to 3 attempts (later expanded to 4) were made to reach individuals who had a valid telephone number. A written informed consent for the interested and eligible participants was obtained during the baseline clinic visit.

Randomization

After a 1-week run-in period, a member of the research team opened the next sequentially numbered sealed envelope (created by a biostatistician) to reveal the randomization status. Participants were block randomized with equal allocation to 3 arms (tech support, tech support plus health coaching, or modified waitlist control) according to obesity status (BMI <30 vs ≥30 kg/m^2).

mHealth Intervention

Theoretical Framework

The theoretical framework used to guide this intervention was the social cognitive theory [64,65]. The intervention primarily targeted the theoretical constructs of knowledge, behavioral skills, behavioral capability, and self-efficacy. Wearable activity trackers, such as Jawbone, include a number of behavioral change techniques associated with decreasing sedentary behavior and increasing physical activity (eg, goal setting, graded tasks, and self-monitoring) [54,55]. However, some of the key techniques are missing and were supplemented with educational materials and technology support. Additional behavior change techniques were provided by the health coaches for the health coaching intervention, such as the identification of barriers and problem solving. Health coaches also provided encouragement and support and encouraged positive support from family and friends. A list of the behavior change techniques, theoretical constructs, and examples of strategies to promote behavior change in this mHealth intervention is presented in Table 1.

Table 1. Behavior change techniques and strategies to promote behavior change via educational materials, the Jawbone tracker and app, or tech support coaching or health coaching.

Behavior change technique	Theoretical construct	Examples of strategies	TS[a] group			HC[b] group		
			EM[c]	JB[d]	TS	EM	JB	HC
Information on consequences of behavior	Knowledge	Educational materials on harms of physical inactivity and sedentary behavior; also discussed with health coach	✓[e]			✓		✓
Goal setting (behavior)	Behavioral skills; self-efficacy	Set weekly short-term and long-term step goals; tech support for changing goal settings on app; idle alert goal (every 30 min) and step goal (graded increase in steps)		✓	✓		✓	✓
Barrier identification and problem solving	Barrier self-regulatory efficacy	Work with health coach to assess barriers and identify solutions to breaking up sedentary time and getting more steps throughout the day						✓
Set graded tasks	Self-efficacy	Encourage incremental and achievable sedentary (breaks) and step goals		✓			✓	
Review of behavioral goals	Behavioral skills	Using Jawbone app to review daily progress and weekly patterns for longest idle time and steps		✓			✓	
Generalization of a target behavior	Behavioral capability	Educational materials with suggestions for breaking up sedentary time in different ways and locations; additional support from health coach	✓			✓		✓
Self-monitoring of behavior	Behavioral skills	Using Jawbone app to review daily progress and weekly patterns and provide immediate feedback (idle alert and longest idle time)		✓			✓	
Feedback on behavior	Behavioral skills	Jawbone tracker and app provide immediate feedback; health coach to discuss whether goals were met		✓			✓	✓
Information on where and when to perform behavior	Behavioral capability	Education materials to suggest tips for disrupting SB[f]; Jawbone idle alert to prompt when to stand up and move	✓	✓		✓	✓	
Instructions on how to perform the behavior	Self-efficacy; behavioral skills	Print materials and coaching provide instructions on setting up and using the Jawbone tracker and app	✓		✓	✓		✓
Social support	Social support	Health coach provides support and encouragement; provide information and suggestions when asked; encourage enlisting positive support from family members and friends to take more steps throughout the day						✓
Use prompts/cues; prompt practice	Cues to action	Jawbone idle alert will prompt user to disrupt sitting with standing or stepping; Jawbone alerts will prompt more steps to reach daily goal		✓			✓	

[a]TS: tech support.

[b]HC: health coaching.

[c]EM: educational material.

[d]JB: Jawbone tracker and app.

[e]Primary source for the behavior change technique.

[f]SB: sedentary behavior.

Components of the Intervention

The mHealth intervention consisted of educational materials; a Jawbone (in)activity tracker; a free, commercially available smartphone app; and support via 5 telephone calls. The only difference between the 2 intervention groups was the level of telephone support. One group received only support related to the use of technology (tracker and app, tech support group), whereas the other group received additional health coaching to meet the study goals (tech support plus health coaching group).

Educational Materials

Upon randomization, both intervention groups received brief educational materials by mail. These materials explained the negative consequences of sedentary behavior, especially prolonged periods of sitting, and included suggestions for how to disrupt and replace sedentary time with LPA. Examples of suggestions provided included walking around the house during television commercial breaks, standing while talking on the telephone, and parking the car further away from the entrance [66]. The summary graph representing the most active and least active days from the week-long collection of objectively measured sedentary time, standing, and stepping (output from the activPAL3 monitor) was mailed to study participants (for later discussion with their coach; Multimedia Appendix 1). The waitlist control group received educational materials at the

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postintervention follow-up when they received their activity tracker and smartphone app.

Jawbone UP2 Activity Tracker

Upon randomization to either of the 2 intervention groups, participants were mailed the Jawbone UP2 activity wristband and provided detailed instructions for installing the free, commercially available app on their smartphone and for using the wristband with the app. At the time the study was designed (2015), this was one of the few consumer wearable activity trackers that had the ability to alert the wearer after a specified time of inactivity. For the Jawbone monitor, this feature was known as an *idle alert*, which notified the user of inactivity via a gentle vibration of the wristband (eg, users select time in increments of 15 minutes). The assigned coach telephoned participants to assist with the installation and setup of the activity tracker and smartphone app.

The goal was to decrease daily total sedentary time and increase the number of breaks in sedentary time by replacing/disrupting sedentary time with intermittent bouts of LPA (standing and stepping). The key message for the activity prescription was to "sit less, stand more, and move more, throughout the day, every day." This message was included in the educational materials and was repeated during each of the 5 support telephone calls. Participants were encouraged to stand up and move at least once

every 30 minutes. To encourage more movement than standing, participants were provided with a graduated steps per day goal of adding 3000 steps per day above their baseline level by week 9 (schedule in Figure 1). This target represents approximately 40 extra minutes of leisurely paced walking [67] and is associated with health benefits [36,68]. When combined with 20 minutes of standing, this would result in replacing 1 hour of sedentary time with 1 hour of LPA per day. A minimum intensity and a minimum bout duration for stepping were not provided, thus allowing the participant to self-select how to accumulate their extra daily steps.

The participants were instructed to wear the Jawbone during waking hours and were encouraged to track their activity at least once a day by viewing their results on the app. A commercially available app was used without any modifications by the research team. The app included a daily summary of total steps, total and longest active time, and longest idle time (longest time spent sedentary). To promote gradual and sustained change in LPA, participants were asked to increase the number of steps per day (above their individual baseline level), during weeks 1 to 9, and then work to maintain their goal during weeks 10 to 13 (Figure 1). Similarly, the *idle alert* setting began at 1 hour, decreased to 45 minutes, and then every 30 minutes. Participants in both intervention groups received guidance from their coaches on how to change the settings in their app.

Figure 1. Weekly schedule for the tech support and health coaching intervention groups.

Week	Telephone support calls	Idle alert setting (min)	Steps per day above baseline	Minimum days per week
		Intervention schedule		
-2		baseline clinic visit activPAL 1-week data collection		
-1		Randomization Mail Jawbone UP2		
0	Call #1	Setup Jawbone UP2 Establish baseline steps/day		
1	Call #2	60	1000	4
2		60	1000	7
3	Call #3	45	1500	4
4		45	1500	7
5		45	2000	4
6		45	2000	7
7	Call #4	30	2500	4
8		30	2500	7
9	Call #5	30	3000	4
10		30	3000	7
11		30	3000	7
12		30	3000	7
13		30	3000	7
		activPAL 1-week data collection follow-up clinic visit		

Tech Support and Health Coaching Calls

The coaches were graduate students who received study-specific training, including 4 practice calls with staff members before calls to study participants. One coach was assigned to each intervention group participant based on their type of phone, for example, iPhone vs android or other mobile operating system. Phone scripts were used to guide the coaches to deliver only

tech support versus tech support plus health coaching. During the first telephone call (week 0; Figure 1), coaches helped the participants to set up their Jawbone monitor. During the second telephone call (week 1), each coach reviewed the activPAL3 baseline summary data (total and percentage of time spent sedentary, standing, and stepping for best and worst days) with the participant and discussed the importance of reducing sedentary time, especially prolonged periods of inactivity.

Additional telephone calls (15-20 minutes) were made during weeks 3, 7, and 9 to verify completion or to assist participants with changing the steps per day goal and *idle alert* setting on their app (if needed). Tech support coaches provided support related only to the technology (Jawbone UP2 activity tracker and/or smartphone app), including troubleshooting technical issues. In contrast, health coaches provided additional support to help their participants identify a list of LPAs to replace/disrupt sedentary time and to achieve the ≥3000 steps per day goal, review the importance of goal setting and self-monitoring, and help troubleshoot problems and find solutions to meet their goals.

Problems With Jawbone UP2 Monitors

During the intervention, the Jawbone UP2 wristbands started to fail (ie, losing settings, losing connection with app, and not syncing data), affecting 13 of 36 intervention group participants. New Jawbone UP2 wristbands were purchased by the study team through other sources (Amazon website), but many of these wristbands also failed. We were able to buy and test UP2 wristbands to replace the failed units for the intervention group participants. Given these major issues and lack of support from Jawbone, waitlist control participants enrolled later in the study were provided with a Fitbit Alta (Fitbit Inc) at the end of the 13-week study. This product was similar to the Jawbone UP2 in that it provided an inactivity alert (reminder to move every hour) and allowed the user to set a step goal and track their steps.

Waitlist Control Group

Upon completion of the study, the control group received a shortened version of the intervention, that is, education materials, tracker, and smartphone app, and instructions for use to track their activity/inactivity. During the postintervention clinic visit, a study team member helped the participant to install the app on their smartphone; pair the tracker to their phone; and select settings for the idle alert and step goal. Each participant in this group was also offered up to 2 telephone calls with one of the coaches to receive tech support or other support to meet their personal goals for reducing sedentary behavior and increasing their activity via steps.

Procedures

Baseline Assessment

Pre- and postintervention clinic visits were conducted at the University of New Mexico Clinical and Translational Science Center. Assessments were conducted primarily by study team members not involved in intervention delivery; however, occasionally, there was overlap owing to limited resources. The baseline assessment included obtaining written informed consent, simple anthropometric measurements (height and weight), and objective physical function measures (physical tests of lower extremity function and mobility). At the end of the visit, study participants were instructed on how to attach the activPAL3 research-grade activity monitor and then observed to verify correct placement. Participants were instructed to wear the activPAL3 monitor for 24 hours/day for 1 week and on how to remove and return (via self-addressed stamped mailer) the monitor to study staff at the end of that week.

Follow-Up Assessment

At the end of the intervention, the activPAL3 research-grade monitor, attachment supplies, and instructions were mailed to all participants to collect 1 week of sedentary behavior and physical activity data. The project manager called to review the instructions for use and answer any questions. Additional postintervention outcome measures were collected at the clinic visit at the end of week 13. Participants received US $50 gift cards to complete the baseline and follow-up assessments and to help cover the costs of accessing the app on their smartphone. In addition, participants were allowed to keep the Jawbone UP2 activity tracker at the end of the study.

Device-Based Measures

Sedentary behavior and physical activity were measured using an activPAL3 research-grade monitor (PAL Technologies Ltd). activPAL3 is a lightweight device worn on the thigh and includes both an inclinometer (to detect changes in position) and a triaxial accelerometer. activPAL is the gold standard in sedentary behavior research and provides accurate measures of sitting (or lying), standing, and stepping [69-72]. Participants wore the device for 24 hours per day for 7 days, before and after the intervention. The device was only removed for bathing or swimming or if an adverse reaction occurred to the Tegaderm dressing used to attach the device. Participants recorded in their diary, the day/time when the device was attached, each time it was removed and reattached, and the time they went to bed at night and woke up in the morning.

Outcomes and Measurements

Feasibility and Acceptability Outcomes

The feasibility and acceptability of the mHealth intervention were determined by achieving the following goals: (1) to recruit 60 older cancer survivors; (2) to retain 80% of the sample; (3) to achieve 80% adherence to the intervention; (4) to have no serious adverse events attributable or possibly attributable to the intervention, defined as any condition that is life threatening and results in overnight hospitalization or a physical or cardiac event serious enough to require medical attention; and (5) to achieve high satisfaction (acceptability) rates with the intervention; to have 75% or more of participants report agree or strongly agree on a 5-point Likert scale.

Retention was calculated as the percentage of participants who completed the follow-up clinic visits and accelerometer assessment. Adherence to wearing the Jawbone UP2 tracker, checking the app daily, and acting on the *idle alert* was assessed with 4 questions. Response items included never, rarely, sometimes, often, or very often. For adherence to the intervention, we calculated the percentage of intervention group participants who responded *often* or *very often* to the 4 questions regarding their use of the Jawbone tracker and app. In addition, the completion of telephone support calls was tracked. Acceptability and evaluation of the Jawbone UP2 technology (UP2 tracker and app) were assessed using 7 questions. Response items included strongly disagree, disagree, neutral, agree, or strongly agree. For acceptability, we calculated the percentage of respondents who responded *agree* or *strongly agree* to the 7 questions regarding ease of use, motivation,

intention for continued use, and recommendations of this technology. Adherence and acceptability were stratified based on whether participants received a replacement Jawbone tracker owing to severe malfunctioning.

Primary Preliminary Efficacy Outcomes

The primary behavioral outcomes of interest were changes in total sedentary time (average minutes per day) and number of breaks from sitting (average breaks per day). As the opportunity to interrupt sitting while standing or stepping is dependent on the amount of sedentary time, the break ratio was also calculated. The break ratio was defined as the number of absolute breaks divided by total sedentary time.

Secondary Preliminary Efficacy Outcomes

Device-Based Measures of Sedentary Behavior and Physical Activity

activPAL was also used to assess changes in total minutes spent in prolonged sedentary bouts, minutes per day spent standing, number of steps per day, and minutes of light- and moderate-intensity physical activity (reported separately). A prolonged sedentary bout was defined as 30 or more continuous minutes in a seated or lying position [73]. LPA was defined as stepping at a cadence equivalent to 1.5 to 3.0 METs [73]. A MET is a multiple of resting energy expenditures. With resting (sitting quietly) energy expenditure defined as 1 MET, a 3-MET activity expends the energy of rest by 3 times, whereas a 5-MET activity expends the energy of rest by 5 times. Standing is also considered an LPA and has been reported separately from light stepping. Moderate-intensity physical activity was similarly defined, but with MET values from 3.0 to 5.9. Vigorous-intensity physical activity was defined as MET values of ≥6.0 or higher. As the guidelines at the time this intervention were designed specified that MVPA be accumulated in minimum bouts of 10 minutes, we also evaluated guideline bouts of MVPA [17,62]. The activPAL monitor provides accurate and precise categorization of sedentary time, LPA, and MVPA in a free-living setting (96.2% accuracy compared with direct observation) [73].

Objectively Measured Physical Performance

The emphasis on frequent interruptions of sedentary behavior with standing and stepping has the potential to improve lower extremity physical function. This was measured using the Short Physical Performance Battery (SPPB). The SPPB includes tests of standing balance, walking speed (timed 8-ft walk at usual speed), and lower body strength (time to rise from a chair 5 times) [6,74]. Scores range from 0 (not attempted) to 4 (highest score) for each test, with a total score ranging from 0 to 12. This battery has strong predictive validity and is responsive to changes [6,74].

Subjective Measures

Given the inverse association reported between sedentary behavior and QoL [29,75,76], we evaluated changes in QoL as a secondary outcome. The Medical Health Outcomes Study Short Form 36-item survey (SF-36, version 2) was used to assess health-related QoL. The SF-36 includes 8 individual scale scores and 2 component summary scores for physical and mental health and well-being. This instrument is valid and reliable for use in healthy and chronically ill adults [77,78]. Surveys were scored using QualityMetric [79]. Raw scores range from 0 to 100, with higher scores indicating better functioning and well-being. T-scores represent a linear transformation, normed to the US population, with a mean of 50 (SD 10). Pain and fatigue were assessed using the patient-reported outcomes measurement information system (PROMIS) Pain Interference Short Form 8A and the functional assessment of chronic illness therapy (FACIT)-Fatigue scale (version 4) [80,81]. The pain interference survey included 8 questions on whether and the degree to which pain interfered with various activities during the past 7 days. The fatigue scale included 13 questions on whether fatigue affected a person's life during the past 7 days and the degree to which fatigue affected a person's life during the past 7 days.

Other Measures

In addition, sociodemographics, cancer-related data, comorbidities, and simple anthropometrics were ascertained via paper surveys to characterize the study population. Sociodemographic data were assessed via questionnaires at baseline, including age, sex, race/ethnicity, education, income range, and marital status. Smoking status (current, former, or never smoker) was also assessed at baseline. Cancer data were obtained from the New Mexico Tumor Registry (cancer type, stage, and date of diagnosis) and from self-reported surveys (treatment [yes/no]: surgery, chemotherapy, radiation, hormone therapy, and date primary therapy completed). The Self-Administered Comorbidity Questionnaire [82] was used to assess the number of conditions and their impact on usual activities. The number of comorbidities and whether they limited activities were summed and categorized as 0 or 1 comorbidity (activities not limited), 1 comorbidity (activities limited), and 2 or more comorbidities (activities limited). Height (nearest 0.5 cm) was measured at the baseline clinic visit. Weight (nearest 0.1 kg) was measured at both the baseline and follow-up clinic visits. BMI (kg/m^2) was calculated and categorized as normal weight (18.5 kg/m^2-24.9 kg/m^2), overweight (25.0 kg/m^2-29.9 kg/m^2), and obese (≥30 kg/m^2).

Data Processing and Statistical Analysis

Processing of activPAL Data

activPAL3 data were downloaded using activPAL software (version 7; PAL Technologies Limited). The event files (start/stop time for sitting/lying, standing, and stepping) were processed using the activPALProcessing R package (version 1.0.2) [73,83]. After converting the event file into a second-by-second data file (second-by-second R function), other R functions were used to calculate the sedentary behavior and physical activity metrics. Only days with 10 or more hours of wear per awake time were included, and only the first 7 valid days were included (extra days were excluded). To be included in the analyses, a participant needed at least one valid day of activPAL3 data from baseline, which is consistent with the intention-to-treat principle and similar to other recent trials [58,84]. Owing to the large variability in the within- and between-person average number of awake per wear hours, all activPAL metrics were standardized to a 15-hour awake per

wear day (average in this study sample). Additional details of the activPAL data collection and processing are included in Multimedia Appendix 2 [69-73,83,85], similar to other studies [59,85].

Efficacy Outcomes

Baseline descriptive characteristics (mean, SD or frequency, %) were used to characterize the study population. Intent-to-treat analyses were conducted to evaluate changes in sedentary behavior metrics and secondary outcomes. Linear mixed methods were used to estimate the within- and between-group differences for each outcome. Each model included a fixed effect for group (tech support, health coaching, and waitlist control), time (before and after the intervention), and group by time interaction. A subject-level random effect was included to account for the correlation between repeated measurements of the same individuals over time. Statistical analyses were performed using SAS (version 9.4) and R (v.3.4.3).

Complete case analyses were conducted that only included individuals with complete data (12 tech support, 17 health coaching, and 18 controls). A sensitivity analysis was conducted that excluded individuals with fewer than 4 valid days of activPAL data (3 participants from the tech support only group). In addition, a sensitivity analysis was conducted by excluding the 12 intervention participants who experienced major problems with their Jawbone tracker (ie, required 1 or more tracker replacements, excluding 6 participants in each intervention group). For this sensitivity analysis, the control group was restricted to control participants who completed their baseline visit during the same period as the intervention participants, to account for potential seasonality effects (ie, before mid-February 2017, excluding 6 controls).

The proposed pilot intervention was a feasibility and acceptability intervention and thus was not powered to detect small effect sizes for change in any outcome. However, for sedentary time, with 20 people per group, assuming a 2-sided alpha level of 0.05 and an SD of 1.4 hours, there was 80% power to detect a difference of 1.3 hours in sedentary time between 2 groups [86,87].

Results

Feasibility

The New Mexico Tumor Registry identified 421 potentially eligible participants and, after accounting for a 3-week opt-out period, forwarded contact information on 354 individuals to study staff. Of the 364 individuals (including 10 self-referrals) we attempted to contact by telephone, 76 refused to participate, 101 were ineligible, and 118 were considered passive refusals after 3 to 4 attempts to contact via telephone (Figure 2; see Multimedia Appendix 3 for CONSORT [Consolidated Standards of Reporting Trials] checklist). The overall response rate was 20.5%. The top 3 reasons for ineligibility included not owning a smartphone, volunteering or working for more than 20 hours per week, and mobility limitations. The top 2 reasons for refusal included a lack of interest and feeling that they were already active enough. An additional 15 individuals were eligible and interested but were unable to begin the intervention before the end of the enrollment period. Owing to the major malfunctions with the Jawbone UP2 monitors during the second half of the study, enrollment was stopped early with a final enrollment of 54 participants.

Retention in this 13-week intervention for older cancer survivors was moderately high (47/54, 87%). All of the dropouts occurred in the intervention groups, with the majority in the tech support group (6 of 7). The reasons included personal or severe family illness (n=2), move out of state (n=1), inconvenience (n=1), frustration with technology (n=1), and loss to follow-up (n=2). Notably, 3 of the 7 dropouts occurred among individuals who experienced malfunctioning with their Jawbone monitor (tech support group). Individuals who dropped out or were lost to follow-up were more likely to be female (5/7, 71% vs 25/47, 53%), have a higher BMI (34.4 kg/m^2 vs 29.5 kg/m^2), and report poor or fair health at baseline (3/7, 43% vs 5/47, 11%) compared with individuals who completed the study.

The characteristics of the 54 cancer survivors enrolled in this study are presented in Table 2. The mean age at study enrollment was 69.6 years (SD 4.8, range 60-84 years), 44% (24/54) were male, 24% (13/54) were Hispanic, and 57% (31/54) had graduated from college. Most study participants (44/54, 81%) were overweight or obese, 44% (24/54) reported very good or excellent general health, and 50% (27/54) reported 1 or more comorbidities that limited their general activity. There were no significant differences between groups. Among the participants, 39% (21/54) had been diagnosed as having breast cancer, 30% (16/54) had prostate cancer, and 31% (17/54) had a variety of other cancer types. Most patients (40/53, 75%) had been diagnosed as having local-stage disease. The mean age at diagnosis was 65.2 (SD 4.8) years, and the mean number of years between diagnosis and study enrollment was 4.4 (SD 1.6) years.

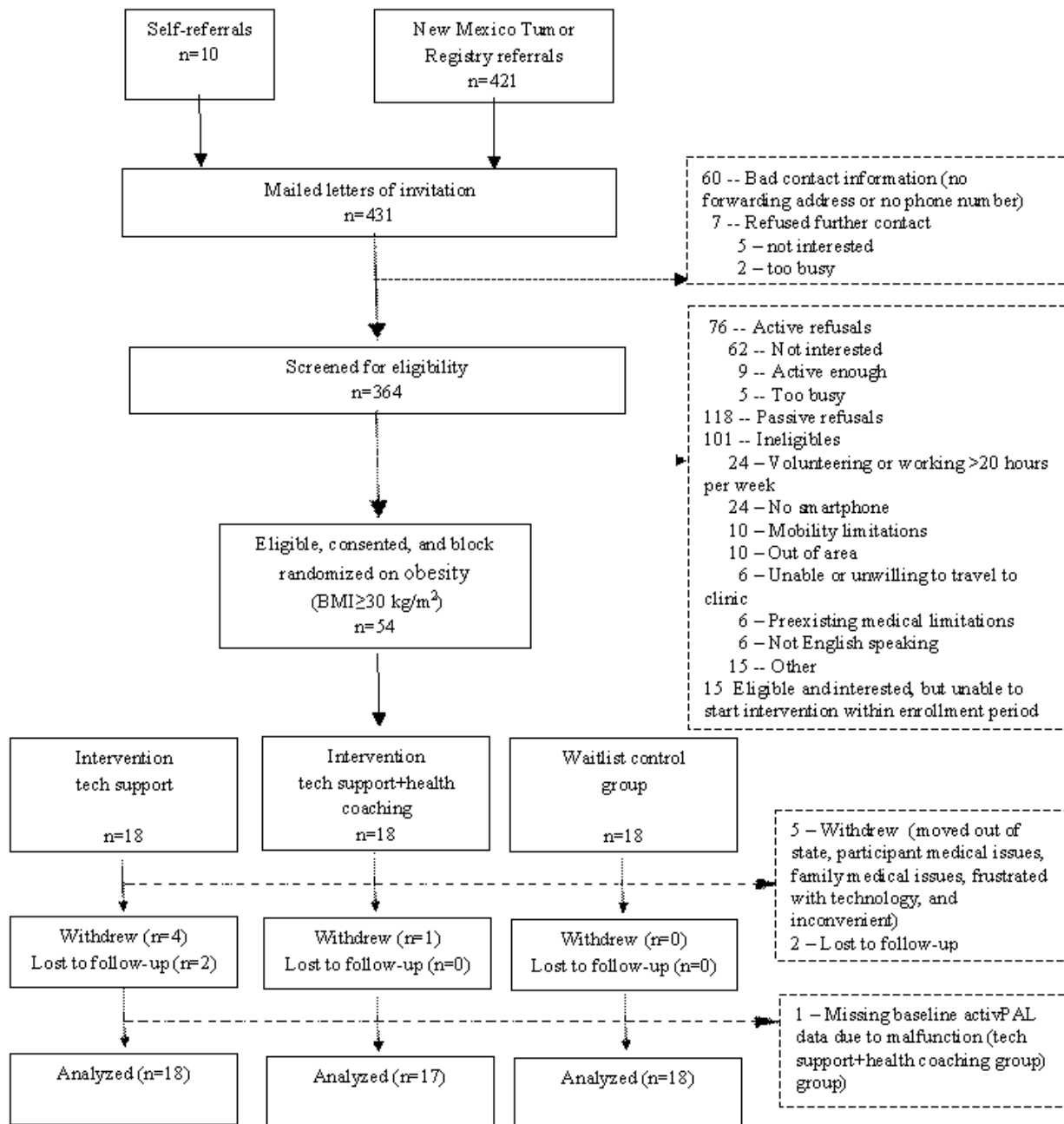**Figure 2.** CONSORT (Consolidated Standards of Reporting Trials) diagram.

Table 2. Baseline characteristics of the mobile health intervention study participants.

Characteristic	Combined groups (N=54)	Intervention group: tech support (n=18)	Intervention group: tech support+health coaching (n=18)	Waitlist control group (n=18)
Sociodemographic characteristics				
Age (years), mean (SD)	69.6 (4.8)	69.6 (4.5)	69.1 (4.0)	70.2 (5.9)
BMI, mean (SD)	30.1 (5.7)	30.2 (6.0)	29.8 (4.8)	30.4 (6.5)
BMI, n (%)				
Normal weight	10 (18)	4 (22)	2 (11)	4 (22)
Overweight	21 (39)	6 (33)	9 (50)	6 (33)
Obese	23 (43)	8 (44)	7 (39)	8 (44)
Male, n (%)	24 (44)	10 (56)	6 (33)	8 (44)
Ethnicity, n (%)				
Hispanic	13 (24)	5 (28)	4 (22)	4 (22)
Non-Hispanic	41 (76)	13 (72)	14 (78)	14 (78)
Race, n (%)				
Non-White	4 (7)	1 (6)	2 (11)	1 (6)
White	50 (93)	17 (94)	16 (89)	17 (94)
College degree, n (%)	31 (57)	11 (61)	11 (61)	9 (50)
Household income, n (%)				
<US $50,000	19 (35)	7 (39)	8 (44)	4 (22)
≥US $50,000	32 (59)	10 (56)	9 (50)	13 (72)
Missing or refused	3 (6)	1 (6)	1 (6)	1 (6)
Health and physical functioning				
Ever smoker, n (%)[a]	24 (44)	8 (44)	7 (39)	9 (50)
General health status, n (%)				
Fair or poor	8 (15)	4 (22)	2 (11)	2 (11)
Good	22 (41)	9 (50)	6 (33)	7 (39)
Very good or excellent	24 (44)	5 (28)	10 (56)	9 (50)
Number of comorbidities, n (%)				
0-1; does not limit activities	27 (50)	10 (56)	8 (44)	9 (50)
1-2; limits activities	16 (30)	6 (33)	5 (28)	5 (28)
≥3; limits activities	11 (20)	2 (11)	5 (28)	4 (22)
Self-reported physical function, mean (SD)				
Raw score (0-100)	73.7 (20.7)	68.1 (22.4)	77.5 (15.4)	75.6 (23.2)
T-score[b]	47.5 (7.9)	45.3 (8.6)	48.9 (5.9)	48.2 (8.9)
Short Physical Performance Battery (0-12), mean (SD)	10.7 (1.6)	10.4 (2.2)	11.1 (0.9)	10.7 (1.5)
Clinical characteristics				
Cancer type, n (%)				
Breast	21 (39)	7 (39)	9 (50)	5 (28)
Prostate	16 (30)	7 (39)	3 (17)	6 (33)

Characteristic	Combined groups (N=54)	Intervention group: tech support (n=18)	Intervention group: tech support+health coaching (n=18)	Waitlist control group (n=18)
Other[c]	17 (31)	4 (22)	6 (33)	7 (39)
Stage at diagnosis[d], n (%)				
Local	40 (75)	14 (78)	14 (78)	12 (71)
Regional	13 (25)	4 (22)	4 (22)	5 (29)
Treatment received[e], n (%)				
Surgery	42 (78)	13 (72)	13 (72)	14 (78)
Chemotherapy	10 (18)	3 (17)	3 (17)	4 (22)
Radiation	30 (56)	12 (67)	10 (56)	8 (44)
Hormone therapy	12 (22)	2 (11)	6 (33)	4 (22)
Time since diagnosis (years), mean (SD)	4.4 (1.6)	4.3 (1.4)	4.2 (1.9)	4.6 (1.4)
Other characteristics				
Comfort level with using smartphone, n (%)				
Very or extremely comfortable	38 (70)	11 (61)	13 (72)	14 (78)
Slightly or not comfortable	16 (30)	7 (39)	5 (28)	4 (22)
activPAL data, mean (SD)				
Number of valid wear days[f]	6.7 (0.7)	6.6 (1.0)	6.8 (0.4)	6.7 (0.5)
Average awake hours	14.5 (1.0)	14.1 (1.1)	14.6 (0.6)	14.6 (0.9)

[a]Only 1 participant was currently smoking at baseline.

[b]T-scores represent a linear transformation, normed to the US population, with a mean of 50 (SD 10).

[c]Other cancers include bladder, cervical, colon, endometrium, kidney, lymphoma, or melanoma cancers.

[d]Stage at diagnosis is missing for 1 participant.

[e]Percentages do not add up to 100% because participants may have had more than 1 type of treatment.

[f]Up to the first 7 days of 10 hours or more of awake/wear time were included in the analyses; additional days of wear beyond the first 7 days were excluded.

Adherence

Adherence during the intervention was moderately high for wearing the Jawbone activity monitor most days of the week (100% very often) and checking the app daily for the number of steps taken (23/29, 79% very often and 5/29, 17% often; Figure 3). However, few participants checked the app for the longest *idle time* (aka longest sedentary bout; 7/29, 24% often or very often), and on a typical day, most participants ignored the vibration on their tracker and remained seated when reminded to stand up and move (18/29, 62% sometimes and 6/29, 21% often or very often). As indicated in Figure 3, adherence related to the sedentary features of the tracker and app was lower in participants who experienced malfunctions with their initial Jawbone UP2 monitor. Among the participants who completed the trial, 93% (27/29) completed all 5 coaching calls.

Figure 3. Adherence to wearing the Jawbone UP2 activity tracker and using the smartphone app, stratified by whether the intervention participant experienced malfunctions with the Jawbone UP2 tracker.
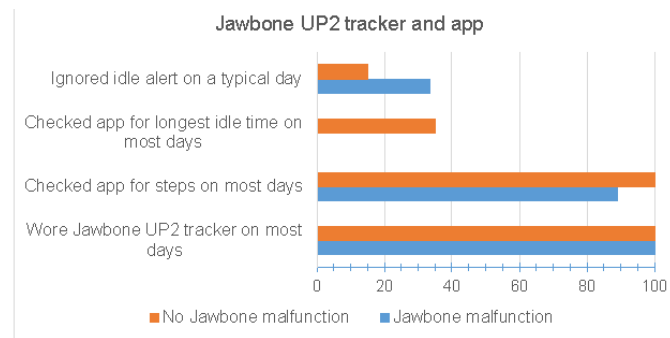

Adverse Events

There were no serious adverse events attributable or possibly attributable to the intervention.

Acceptability

Despite initial Jawbone UP2 malfunctions among one-third of the intervention group, the acceptability of the intervention was moderately high (Figure 4). Overall, 79% (23/29) of the participants agreed or strongly agreed that the Jawbone UP2 technology (monitor plus app) was easy to use and the same percentage indicated that they would use the Jawbone UP2 in the future. Despite the lack of tracking of sedentary data, most participants agreed or strongly agreed that this technology made them more aware of how much time they spent sitting and motivated them to decrease their sedentary time (27/29, 93% and 24/29, 83%, respectively). Participants who started with a malfunctioning Jawbone tracker reported lower acceptability scores than those with properly functioning trackers, with the greatest difference related to ease of use and recommending the tracker and app to others.

Figure 4. Acceptability and participant evaluation of the mobile health intervention using the Jawbone UP2 activity tracker and smartphone app to sit less, stand more, and move more, throughout the day, and every day. Results are stratified by whether the intervention participant experienced malfunctions with the Jawbone UP2 tracker.
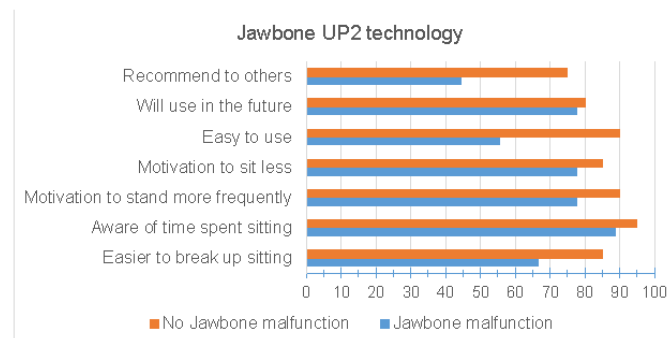
Efficacy Primary Outcomes

Of the 54 cancer survivors enrolled in the study, data for the primary and secondary outcomes for sedentary behavior and physical activity were available for 53 participants (1 monitor malfunction at baseline). On average, participants wore the activPAL monitor for 6.7 days (SD 0.7, range 3-7 days), for an average of 14.5 (SD 1.0) awake/wear hours per day. During a standardized 15 hour awake/wear day, study participants spent 9.6 hours (SD 1.7 h) in sedentary (sitting/lying) activities. Approximately half (5.1, SD 1.7 h) of the number of sedentary minutes were spent in prolonged bouts (30 minutes or longer). The average number of breaks from sitting was 46.6 (SD 14.0) per 15 hour day. Standing accounted for one-quarter of the awake hours (3.8, SD 1.5 h). The remaining time was spent in light- and moderate-intensity stepping (36.8, SD 14.8 minutes and 56.5, SD 25.5 min, respectively; zero minutes in vigorous-intensity stepping). At baseline, only 5 participants met the physical activity guidelines that were recommended at the time the study began (150 minutes per week of moderate-intensity or 75 minutes of vigorous-intensity physical activity, minimum bout duration of 10 min) [17]. On the basis of current guidelines, which no longer require that activity occurs in bouts of at least 10 minutes, 46 participants met the minimum recommendation of at least 150 minutes per week of moderate-intensity activity [88,89].

Between- and within-group comparisons of changes in sedentary behavior are presented in Table 3. The tech support and the tech support plus health coaching groups did not reduce their daily sedentary time compared with the control group (least square means 8.5 min, 95% CI −50.5 to 67.5; P=.77 and least square means 10.4 min, 95% CI −43.5 to 64.3; P=.70, respectively). There were no significant differences between the intervention and control groups in the daily number of breaks from sitting (least square means −0.1, 95% CI −7.6 to 7.4; P=.97 and least square means −2.2, 95% CI −9.0 to 4.7; P=.52, respectively). There were no significant or meaningful changes in these sedentary behavior outcomes within any of the 3 groups.

Table 3. Between- and within-group comparisons of change in sedentary behavior and physical activity after a 13-week mobile health intervention.[a,b]

Sedentary behavior and physical activity metrics	Baseline, least square mean (95% CI)	Follow-up, least square mean (95% CI)	Within-group change, least square mean difference (95% CI)	P value	Between-group change[c], least square mean difference (95% CI)	P value
Sedentary, minutes per 15 hours awake						
Tech support	598.5 (550.1 to 646.9)	604.6 (549.1 to 660.0)	6.0 (−39.5 to 51.6)	.79	8.5 (−50.5 to 67.5)	.77
Health coaching	567.7 (517.9 to 617.5)	575.6 (525.0 to 626.1)	7.9 (−30.8 to 46.6)	.68	10.4 (−43.5 to 64.3)	.70
Control	555.4 (507.0 to 603.8)	552.9 (503.8 to 602.0)	−2.5 (−40.0 to 35.0)	.89	N/A[d]	N/A
Prolonged sedentary bouts (≥30 min), minutes per 15 hours awake						
Tech support	319.8 (258.8 to 380.8)	331.9 (263.8 to 400.0)	12.1 (−38.2 to 62.4)	.63	4.7 (−60.3 to 69.7)	.88
Health coaching	287.0 (224.2 to 349.7)	305.5 (242.0 to 369.0)	18.5 (−23.9 to 61.0)	.38	11.2 (−48.0 to 70.3)	.71
Control	289.7 (228.7 to 350.7)	297.1 (235.4 to 358.8)	7.4 (−33.8 to 48.6)	.72	N/A	N/A
Breaks from sitting, number per 15 hour awake						
Tech support	50.6 (44.2 to 57.1)	50.5 (43.2 to 57.9)	−0.1 (−5.9 to 5.8)	.97	−0.1 (−7.6 to 7.4)	.97
Health coaching	48.8 (42.2 to 55.4)	46.6 (39.9 to 53.4)	−2.2 (−7.1 to 2.7)	.38	−2.2 (−9.0 to 4.7)	.52
Control	46.2 (39.7 to 52.6)	46.2 (39.6 to 52.7)	0.0 (−4.7 to 4.8)	1.00	N/A	N/A
Break ratio, number of breaks per sedentary hour						
Tech support	5.4 (4.5 to 6.2)	5.4 (4.5 to 6.4)	0.06 (−0.66 to 0.77)	.87	−0.08 (−1.00 to 0.85)	.87
Health coaching	5.3 (4.4 to 6.2)	4.9 (4.0 to 5.8)	−0.39 (−0.99 to 0.21)	.20	−0.52 (−1.36 to 0.32)	.22
Control	5.1 (4.2 to 5.9)	5.2 (4.3 to 6.0)	0.13 (−0.45 to 0.72)	.65	N/A	N/A
Standing, minutes per 15 hours awake						
Tech support	213.9 (174.2 to 253.7)	202.8 (157.6 to 248.0)	−11.2 (−47.4 to 25.0)	.54	−8.7 (−55.6 to 38.2)	.71
Health coaching	243.0 (202.1 to 283.9)	220.4 (178.9 to 261.8)	−22.6 (−53.3 to 8.1)	.14	−20.1 (−62.9 to 22.6)	.35
Control	241.9 (202.2 to 281.6)	239.4 (199.2 to 279.7)	−2.5 (−32.3 to 27.3)	.87	N/A	N/A
Steps per 15 hour awake						
Tech support	6686 (5166 to 8206)	7339 (5594 to 9085)	654 (−794 to 2101)	.37	420 (−1456 to 2297)	.65
Health coaching	6663 (5099 to 8227)	8338 (6749 to 9926)	1675 (444 to 2906)	.009[e]	1441 (−273 to 3156)	.10
Control	7898 (6378 to 9418)	8132 (6590 to 9674)	233 (−961 to 1428)	.70	N/A	N/A
Light-intensity physical activity, minutes per 15 hours awake						
Tech support	34.4 (27.2 to 41.5)	33.1 (25.4 to 40.9)	−1.2 (−6.0 to 3.6)	.61	−4.2 (−10.4 to 2.0)	.18
Health coaching	37.3 (29.9 to 44.7)	36.9 (29.5 to 44.4)	−0.3 (−4.4 to 3.7)	.86	−3.3 (−8.9 to 2.3)	.24
Control	38.8 (31.6 to 45.9)	41.7 (34.5 to 49.0)	3.0 (−0.9 to 6.9)	.13	N/A	N/A
Moderate-intensity physical activity (MPA), minutes per 15 hours awake						
Tech support	53.2 (40.2 to 66.1)	59.5 (44.5 to 74.6)	6.4 (−6.6 to 19.3)	.33	4.6 (−12.2 to 21.4)	.58
Health coaching	52.1 (38.8 to 65.4)	67.2 (53.7 to 80.8)	15.2 (4.1 to 26.2)	.008[e]	13.4 (−2.0 to 28.8)	.09
Control	64.0 (51.0 to 76.9)	65.7 (52.6 to 78.9)	1.8 (−9.0 to 12.5)	.74	N/A	N/A

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Sedentary behavior and physical activity metrics	Baseline, least square mean (95% CI)	Follow-up, least square mean (95% CI)	Within-group change, least square mean difference (95% CI)	P value	Between-group change[c], least square mean difference (95% CI)	P value
MPA (guideline bouts), minutes per 15 hours awake						
Tech support	5.8 (−3.2 to 14.8)	13.0 (2.2 to 23.8)	7.3 (−3.1 to 17.6)	.17	7.1 (−6.4 to 20.6)	.30
Health coaching	3.0 (−6.3 to 12.2)	19.7 (10.2 to 29.1)	16.7 (7.8 to 25.7)	<.001[e]	16.6 (4.1 to 29.0)	.01[e]
Control	12.1 (3.1 to 21.1)	12.3 (3.1 to 21.4)	0.2 (−8.5 to 8.8)	.97	N/A	N/A

[a]Intent-to-treat analyses.

[b]All variables were standardized to a 15-hour awake per wear day before calculating the pre- to postintervention changes.

[c]Comparisons are between each intervention group and the control group.

[d]N/A: not applicable.

[e]Statistically significant (P<.05) results.

Secondary Outcomes

Between- and within-group comparisons of changes in daily steps and time spent stepping are presented in Table 3. Although time spent standing is considered an LPA, it was evaluated separately from the time spent stepping at a light intensity. There were no significant between-group changes in the time spent standing for either intervention group compared with controls (tech support vs control: least square means −8.7 min, 95% CI −55.6 to 38.2; P=.71 and health coaching vs control: least square means −20.1 min, 95% CI −62.9 to 22.6; P=.35). There were no significant changes in daily steps between the intervention groups and the control group (tech support vs control: least square means 420 steps, 95% CI −1456 to 2297; P=.65 and health coaching vs control: least square means 1441 steps, 95% CI −273 to 3156; P=.10). There was a borderline significant difference between moderate-intensity stepping in the health coaching group compared with the control group (least square means 13.4 min, 95% CI −2.0 to 28.8; P=.09), but there was no difference between the tech support and control groups (least square means 4.6 min, 95% CI −12.2 to 21.4; P=.58). The between-group differences for moderate-intensity stepping accumulated in guideline bouts of 10 minutes or longer were least square means of 16.6 minutes (95% CI 4.1-29.0; P=.01) and 7.1 minutes (95% CI −6.4 to +20.6; P=.30), respectively, for health coaching group vs controls and tech support group vs controls.

The only significant within-group change occurred in the health coaching group. There was a significant increase of 1675 daily steps (95% CI 444-2906; P=.009). Although there was no appreciable change in light-intensity stepping, there was a significant increase in moderate-intensity stepping overall and guideline bouts among the health coaching group (least square means 15.2 extra minutes per day, 95% CI 4.1-26.2; P=.008 and least square means 16.7 extra minutes per day, 95% CI 7.8-25.7; P<.001). There was neither a significant decrease in sedentary time (least square means 7.9 min, 95% CI −30.8 to 46.6; P=.68) nor increase in standing (least square means −22.6 min/day, 95% CI −53.3 to 8.1; P=.14). There were no significant within-group changes for either the tech support group or the control group.

QoL Analysis

There were no significant between-group changes in subjectively measured health-related QoL (Multimedia Appendix 4). However, between-group differences of 4 or more points, representing the minimally clinically significant difference for the SF-36 QoL survey [90], occurred in several subscales. For health coaching compared with controls, these scales included general health, role physical, social functioning, and vitality. For tech support compared with controls, these scales included physical function and social functioning (favoring tech support) and mental health and role emotional (favoring controls). No significant or meaningful between- or within-group differences were observed for the FACIT-Fatigue or the PROMIS pain scales.

Physical Performance

The average baseline scores on the SPPB were relatively high at baseline for each of the 3 groups (tech support: 10.4, health coaching: 11.2, and control: 10.7). There were no significant between-group changes (P>.4); the difference between the health coaching and control groups was at the lower limit of the minimally meaningful change for this scale (0.3-0.8 points) [91].

Additional Analyses

The results of the complete case analyses, including participants with both baseline and follow-up data, did not differ substantially from the intent-to-treat analyses regarding sedentary behavior and physical activity (data not shown). The results of a sensitivity analysis excluding people with fewer than 4 days of valid activPAL data were not appreciably different from the intention-to-treat analyses (data not shown). No significant between-group differences were found in a sensitivity analysis, excluding participants who experienced issues/failures with the Jawbone tracker. The results for tech support versus controls were as follows (least square mean, 95% CI): sedentary time (−28 min, −99 to 43), standing (17 min, −42 to 76), total daily steps (1290 steps, −403 to 2982), and moderate-intensity stepping (13 min, −2 to 28). The results for health coaching versus controls were as follows: sedentary time (10 min, −56 to 76), standing (−18 min, −72 to 36), total daily steps (1102 steps, −460 to 2663), and moderate-intensity stepping (11 min, −3 to 25).

Discussion

Principal Findings

This study explored the feasibility, acceptability, and preliminary efficacy of a home-based mHealth intervention to disrupt and replace sedentary time with LPA (standing and stepping) among older cancer survivors. Despite technical issues with one-third of the Jawbone UP2 activity trackers, an mHealth intervention in older cancer survivors was feasible (high retention and adherence) and acceptable. However, although participants reported that the mHealth intervention increased their awareness of sedentary behavior, this did not translate into a reduction in total sedentary time, prolonged sedentary time, or an increase in breaks from sitting in either intervention group.

The lack of a reduction in total sedentary time was an unexpected finding, given ample room for improvement (nearly 10 hours of sedentary time per day at baseline). In contrast, this group of older, primarily retired, cancer survivors was already taking frequent breaks from sitting, averaging 3 breaks per hour. However, despite the average number of hourly breaks, the amount of time spent in prolonged sedentary bouts (≥30 min) was not reduced, suggesting that there is room for improvement in this metric. Only a few studies have reported a significant increase in the number of breaks from sitting [66]. A large proportion of our study participants reported ignoring the *idle alert* on a typical day. Whether this represented a valid opportunity to stand up and move (eg, alerted while watching television) or an inopportune time (eg, eating, driving, or in a social setting) is unknown. Other studies using the Jawbone tracker reported overall acceptability, including the usefulness or interest in continued use of the *idle alert* [92,93]; however, other studies noted that some participants found the *idle alert* very irritating and inaccurate [94].

In our study, both the postintervention evaluation and comments received from many participants during coaching calls support their focus on the step goal. Similar to other activity tracker apps, the predominant tracking features of the Jawbone apps are related to daily steps rather than sedentary behavior, which may have reinforced the step goal. More support for replacing rather than merely disrupting sedentary time with a suggested minimal bout duration may have been more helpful for individuals already taking frequent breaks from sitting. In addition, research suggests that given the automaticity of sedentary behavior, different and more effortful strategies are required to break existing habits compared with forming new habits [95-97].

Additional unexpected findings were the 6-fold higher time spent standing compared with light-intensity stepping (both before and after intervention) and the suggested decrease in standing, especially in the health coaching group (22 fewer minutes per day). Interventions that report LPA separately indicate that cancer survivors spend 2 to 5 hours per day in these activities [59,60,98,99]. In comparison, our study measured, on average, only 30 to 40 minutes per day. This likely involves measurement differences. Importantly, many interventions have not been able to determine the amount of time spent standing, and standing still is often combined with sedentary time. The activPAL monitor, which is worn on the upper thigh and includes both an inclinometer and accelerometer, provides a more accurate measure of sedentary time (sitting or lying) and standing compared with the ActiGraph accelerometer [70,72], which is the gold standard in MVPA research.

Another research challenge is measuring daily steps in a free-living population (vs in a controlled lab setting), especially if all steps are of interest rather than just higher intensity steps (ie, MVPA). In a free-living population measured during awake hours, stepping ranges from slow, intermittent stepping to fast, continuous stepping. The accuracy of step accumulation by research-grade monitors varies according to walking speed (less accurate at slower speeds) and intermittent (less accurate) versus continuous (more accurate) stepping [100,101]. Therefore, slow or intermittent stepping may be classified as standing rather than light-intensity stepping [100,101]. In our study, overall, there was no reduction in sedentary time, which was measured with high accuracy. Instead, the increased step accumulation among each group, especially the health coaching group, likely represents a shift from standing and slow or intermittent stepping to moderate-intensity and continuous stepping.

There was much flexibility allowed to achieve the goals of the study, that is, no minimum bout duration (standing or stepping) or intensity level (stepping) was provided to participants. The results suggest that most of the intervention group participants focused on the step goal rather than standing more frequently. Furthermore, participants self-selected to accumulate steps in longer bouts and at a moderate versus light intensity. However, only the intervention group with additional health coaching (vs only tech support) achieved significant and meaningful increases in the total daily steps and number of moderate-intensity steps. Although the average number of additional daily steps was below the 3000 goal, it is similar to that reported from meta-analyses using consumer wearable activity trackers, which report 400 to 475 additional daily steps [52,102].

Comparison With Previous Work

On the basis of recent reviews, interventions with a sedentary behavior focus were more effective (greater reduction in sedentary time) than interventions with a focus on increasing MVPA or both increasing MVPA and reducing sedentary time [103,104]. Reviews of interventions with device-based measurement of sedentary behavior (eg, activPAL and ActiGraph) report, on average, a decrease of 35 minutes per day of sedentary time; however, there was significant heterogeneity detected [51,52,102]. Although device-based measures of sedentary behavior are more accurate than self-report measures, there are also differences in accuracy between device-based measures. For example, hip-worn accelerometers estimate sedentary behavior based on lack of movement (eg, <100 counts per minutes on an ActiGraph), whereas thigh-worn monitors base their estimation on posture (eg, activPAL) [105]. As a result, a hip-worn accelerometer cannot distinguish between standing and sedentary time and can overestimate the change in sedentary time if both sitting and standing are reduced.

To date, few interventions have been designed specifically to decrease sedentary behavior in cancer survivors [106]. In

contrast to our findings, several studies have reported a reduction in sedentary time among breast, prostate, and colorectal cancer survivors [58-60]. However, our study compares favorably with the increase in daily steps, especially moderate-intensity stepping. Lynch et al [58] designed an RCT to both reduce sedentary behavior and increase MVPA using the Garmin Vivofit activity tracker among 80 breast cancer survivors (mean age 62 years, SD 6.4). They reported a 37 minutes per day decrease in sitting (95% CI −72.0 to −2.0), which was primarily replaced with standing (27 minutes; 95% CI −2 to 56), and an increase of 933 steps per day (95% CI −215 to 2082). Gomersall et al [59] designed a text-message enhanced clinical exercise intervention (RCT) to reduce sitting time and increase activity among 36 participants, representing several cancer types, primarily colorectal and prostate cancer. The significant decrease in total daily sitting (mean difference −48 minutes/16 h awake day; 95% CI −90 to −6) was primarily replaced with standing (mean difference 42 minutes; 95% CI −4 to 88) and light-intensity stepping (mean difference 7.0 minutes; 95% CI 0.4-14). The RiseTx web-based program designed by Trinh et al [60] included 46 prostate cancer survivors (mean age 73.2 years, SD 7.3) who were given a Jawbone UP 24 activity monitor (model preceding the UP2). The goal was to increase daily steps by 3000 and to reduce sedentary time over a 12-week period in a single-arm trial. There was a significant decrease in sitting time (−455.4 minutes per week; 95% CI −766.6 to −144.2), a nonsignificant decrease in LPA (−91.0 minutes per week; 95% CI −236.4 to 54.4), and a significant increase in MVPA (44.1 minutes per week; 95% CI 11.1-77.0; all measured with the hip-worn ActiGraph). There was also an increase in daily steps (1535; P<.001), which was measured using the Jawbone wearable activity tracker rather than a research-grade accelerometer.

Limitations and Strengths

The limitations of our feasibility study include the potential for selection bias because smartphone ownership was an eligibility criterion. Individuals not familiar with a smartphone (if provided with a loaner phone) may have had more difficulty with adherence or uptake of an mHealth intervention. In addition, individuals who were enrolled were likely more motivated to change their inactivity. The results of this study may not be generalizable to cancer survivors who are less healthy, less physically active, or less comfortable with smartphones than those enrolled in the study. Recruitment was more challenging than anticipated, resulting in a low response rate. Another limitation is the lack of fidelity measures to ensure that the intervention components were delivered as intended. The use of a consumer activity monitor, in this case the Jawbone UP2, is both a limitation and a strength. We experienced substantial technical issues/failures with the device, affecting one-third of the intervention group, as the manufacturing company quit the production, stopped providing support, and eventually closed. While adversely affecting intervention delivery (starting over

with tech support/health coaching calls) and possibly retention (3 of 7 dropouts had issues with their Jawbone UP2 monitor; all tech support group), the intervention acceptability scores were moderately high. Most importantly, as reported during follow-up interviews, many intervention participants switched to a different consumer activity monitor to track their steps (Fitbit or Garmin), suggesting a transfer of knowledge and skills gained during the intervention. The strengths of this study include the RCT design and a diverse study sample in terms of sociodemographics, cancer type, and health characteristics. Another strength is the measurement of sedentary behavior with the activPAL research-grade monitor, which is the gold standard for distinguishing between sitting, standing, and stepping [69-72].

Several lessons were learned from this pilot study. First, despite the tremendous growth in the consumer wearable activity tracker market, the disadvantages of using these devices for research studies include technical issues/failures, changes in availability, changes in the user interface or algorithms behind the app, and the potential lack of support from the manufacturer. However, this mHealth approach has been popular among researchers because of its low cost, the ability to reach a large number of participants, and the potential for maintenance of behavior change. The advantages for participants include receiving feedback in real time to prompt change and reducing the burden of tracking weekly/monthly steps (eg, participant recording steps in diary vs automated recording and tracking with app).

Second, sedentary behavior is a strongly ingrained habit that is mostly initiated subconsciously [94]. Research suggests that, given the automaticity of sedentary behavior, different and more effortful strategies are required to break existing habits compared with forming new habits [95-97]. This may require different or multiple behavioral theories to inform the intervention. Although many consumer activity trackers have several behavioral change techniques built into the tracker and/or the app, including Jawbone [54,55,107], accumulating evidence suggests that additional behavior change techniques are needed to achieve meaning change [92,102]. Until activity tracker apps advance to provide features for tracking daily sedentary behavior, researchers will need to provide participants with other strategies. Finally, the daily step goal (+3000 steps above baseline) may have been too high, although participants were able to self-select the minimum bout duration and intensity level for stepping. Nevertheless, the step goal may have competed with messaging to reduce sedentary time.

Conclusions

This low-touch, home- and technology-based intervention designed to disrupt and replace sedentary time with LPA (standing and stepping) was feasible and acceptable for a diverse group of older cancer survivors. Future studies are warranted to evaluate strategies for replacing sedentary time with standing and/or physical activity.

Acknowledgments

Conflicts of Interest

None declared.

Multimedia Appendix 1
An example of the activPAL monitor summary data from baseline discussed with intervention group participants in an mHealth study.
[PNG File , 22 KB - cancer_v7i2e18819_app1.png]

Multimedia Appendix 2
activPAL3 data collection and processing details.
[DOCX File , 31 KB - cancer_v7i2e18819_app2.docx]

Multimedia Appendix 3
CONSORT (Consolidated Standards of Reporting Trials)-EHEALTH checklist (v 1.6).
[PDF File (Adobe PDF File), 1566 KB - cancer_v7i2e18819_app3.pdf]

Multimedia Appendix 4
Effects of mHealth intervention on health-related Quality of Life.
[DOCX File , 22 KB - cancer_v7i2e18819_app4.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
LPA: light-intensity physical activity
MET: metabolic equivalent
mHealth: mobile health
MVPA: moderate-to-vigorous physical activity
NIH: National Institutes of Health
QoL: quality of life
RCT: randomized controlled trial
SF-36: Short Form 36-item survey
SPPB: Short Physical Performance Battery

Original Paper

Home-Based Telehealth Exercise Intervention in Early-On Survivors of Childhood Acute Lymphoblastic Leukemia: Feasibility Study

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Abstract

Background: Acute lymphoblastic leukemia is the most common type of pediatric cancer. Acute lymphoblastic leukemia causes an altered bone mineral homeostasis state, which can contribute to osteopenia, and bone fractures, most commonly vertebral fractures. With the increasing number of childhood cancer survivors, late adverse effects such as musculoskeletal comorbidities are often reported and are further influenced by inactive lifestyle habits. Physical activity has been shown to increase the mechanical workload of the bone, mitigating bone impairment in other cancer-specific populations.

Objective: This interventional pilot study aims to investigate the use of telehealth to deliver a home-based exercise intervention for early-on survivors of bone marrow–related hematological malignancies and to assess its impact on survivors' musculoskeletal and functional health.

Methods: We aimed to recruit a group of 12 early-on survivors of acute lymphoblastic leukemia, within 6 months to 5 years of treatment, to participate in and complete the proposed telehealth intervention with a parent. The 16-week intervention included 40 potential home-based physical activity interventions supervised by a kinesiologist through a telehealth internet platform, with monthly progression. Patients were recruited to the cohort if they were able to participate in the intervention during the first month (minimum 12 weeks of intervention). Evaluation before and after the intervention protocol highlighted differences in functional capacities and musculoskeletal health of patients using mechanography, peripheral quantitative computed tomography, 6-minute walk test, and grip force test.

Results: The recruitment rate for the intervention was low (12/57, 21% of contacted patients). Of 12 patients, 3 were excluded (1=relapse, 1=failure to meet technical requirements, and 1=abandoned). The 9 patients who completed the intervention (6 girls; mean age 10.93, SD 2.83 years; mean BMI 21.58, SD 6.55 kg/m^2; mean time since treatment completion 36.67, SD 16.37 months) had a mean adherence of 89% and a completion rate of 75%. In addition, these patients showed functional improvements in lower

limb muscle force and power as well as in the 6-minute walk test distance. Participants also showed improved bone health after the intervention on the following parameters: bone mineral content, stress-strain index, total and cortical cross-sectional area at the 14% site (P=.03, P=.01, P=.01, and P=.001, respectively) and 38% site of the tibia (P=.003, P=.04, P=.001, and P=.003, respectively).

Conclusions: High adherence and participation rates suggest that telehealth is a feasible method to deliver exercise interventions to young early-on survivors of acute lymphoblastic leukemia. The proposed intervention seems promising in providing benefits to patients' functional performance and bone health, but a large-scale study is needed to confirm this assumption.

Introduction

Background

Acute lymphoblastic leukemia is the most common type of cancer among the pediatric population. Over the past 50 years, the survival rates for pediatric hematological malignances have increased significantly from nearly 0 to >80% because of the scientific advancements and improved therapeutic protocols [1]. Consequently, an increasing number of survivors are likely to experience long-term effects of the disease, treatment toxicities, and increased inactive lifestyles [2,3]. Furthermore, the specific immune cells at the origin of the acute lymphoblastic leukemia originate from stem cells in the bone marrow. Therefore, it is not surprising that the disease, treatments, and modified lifestyle habits contribute to comorbidities and late adverse effects of the musculoskeletal system in long-term survivors [4]. Among these comorbidities, a decrease in muscle strength [5], bone mass [6,7], and an increased prevalence of vertebral fractures [8,9] have been reported. These musculoskeletal adverse effects can be apparent on initial diagnosis, increase in severity during the acute phase of treatment [9], and remain present [10] or appear during remission [11] and survival [12,13].

Physical activity and exercise provide physiological and mechanical stimulation that are beneficial for muscle and bone health [14] and the cardiovascular system [15]. Specific types of exercises, such as plyometric (defined as high impact, eg, jumping) and resistance exercises, have been shown to decrease bone impairments in other cancer populations with bone-specific deficits (breast cancer and prostate cancer) [16]. Therefore, an exercise rehabilitation intervention administered to early-on survivors of hematological malignancies, with plyometric and resistance exercises aiming at improving muscle function and bone strength, could limit the musculoskeletal late adverse effects reported in long-term survivors.

Medical follow-up visits for survivors of acute lymphoblastic leukemia are generally performed 1-4 times per year in pediatric oncology centers, limiting the feasibility of an in-clinic exercise intervention. In this regard, studies have shown that patients and survivors would rather exercise at home, school, or a fitness club, than at a hospital or physiotherapy clinic [17,18]. For these reasons, home-based exercise interventions are considered the most appropriate intervention method for this population. Only a few studies have addressed the effects of home-based exercise

interventions on muscle function of children with acute lymphoblastic leukemia in maintenance or early-on survivorship, with equivocal results. In a study by Tanir and Kuguoglu [19], a home-based physical exercise intervention was provided to the patients for 3 months, with muscle strength, aerobic, and stretching exercises. The results showed significant improvements in flexibility and muscle and cardiopulmonary functions. Similarly, a study by Esbenshade et al [20] yielded similar results for a 6-month home-based exercise intervention. In contrast, studies by Marchese et al [21] and Hartman et al [22] showed only minor improvements in muscle function (increased knee extensors and ankle dorsiflexor strength) and no improvement in cardiopulmonary function [21] and bone health [22]. Both studies that showed significant improvements in physical fitness, that is, the studies by Tanir and Kuguoglu [19] and Esbenshade et al [20], reported a high adherence rate (mean 82%, SD 7%), whereas the studies by Marchese et al [21] and Hartman et al [22] reported low adherence rates. Taken together, the results of these studies suggest that patients with acute lymphoblastic leukemia in the maintenance or early-on survivorship can benefit from a home-based exercise intervention but that high adherence rates are required to achieve significant improvements in the musculoskeletal system.

Adherence rates tend to be lower in the absence of supervision in home-based exercise interventions. For example, both studies (Marchese et al [21] and Hartman et al [22]) that showed minimal or no effect of the home-based exercise intervention reported a minimal follow-up approach (between biweekly and monthly phone calls with the sole objective to assess adherence), likely resulting in the reported low adherence rates. In contrast, both studies that showed improvements following the home-based exercise intervention had set up a stringent supervision (weekly or biweekly follow-up calls to discuss factors of adherence), resulting in high adherence rates [19,20]. In this regard, a recent literature review suggests that home-based exercise interventions with telehealth supervision improve adherence rates compared with no supervision [23] because of patients receiving positive reinforcement [24], improving on the exercise technique [24] and feeling self-efficient [25]. Another potential positive impact of supervision is the greater overall volume of exercise achieved during individual sessions, which can be associated with better structured and controlled exercised sessions under supervision compared with no supervision [26]. These observations suggest that supervision by health care providers during home-based

exercise training may help patients achieve higher adherence rates and obtain additional benefits compared with no or minimal supervision.

Telehealth is defined as a method of delivering health interventions (eg, physical activity, nutritional, and psychological counseling) or follow-ups from a remote location through information technologies (eg, the internet). The research field associated with telehealth has experienced significant growth over the past 10 years, leading to an exponential increase in its application in light of the current COVID-19 global pandemic. Over the past decade, telehealth has been shown to be efficient in achieving high adherence rates compared with traditional home-based exercise intervention in patients with musculoskeletal, neurological, cardiorespiratory, and various other conditions [27,28]. However, to our knowledge, this study is the first to report the feasibility of implementing a home-based exercise intervention with telehealth supervision in early-on survivors of pediatric cancer.

Objectives

The primary aim of this study is to assess the feasibility of implementing a home-based exercise intervention with telehealth-based supervision for early-on survivors of acute lymphoblastic leukemia. Telehealth can be administered using various technologies. Desktops, laptops, tablets, and smartphones have the ability to provide and receive telehealth services. Although tablets and laptops provide mobility options compared with a desktop solution, this study was designed to favor accessibility; therefore, families could select the technology of their choice to receive the intervention, be it a fixed desktop or a mobile phone and tablet. In addition, as having companions for exercising has been identified as a facilitating element in adherence [17], we grouped patient-parent pairs with one or two other pairs. The feasibility of the pilot intervention was evaluated by assessing the completion and adherence rate of patients, in addition to the occurrence of training adaptation because of participants' pain and adverse events. It is hypothesized that direct supervision, possible through telehealth technologies, will lead to an adherence rate of 80% and a completion rate of 75% [15]. The secondary aim of this study is to explore the effects of the intervention on functional performance, muscle function, and bone health. It is hypothesized that the intervention will lead to improvements in musculoskeletal and cardiopulmonary function.

Methods

Study Design and Recruitment

This prospective pre- and postintervention cohort pilot study was initiated in 2018 at Sainte-Justine University Health Center to assess the feasibility of home-based exercise interventions in early-on survivors of hematological bone marrow–related malignancies who have been treated under Dana-Farber Cancer Institute–acute lymphoblastic leukemia 2005 or 2011 protocols. As the research design was a pilot interventional study, no sample size calculation was made, and a convenience sample of 10 participants for intervention completion was set as the aim. The initial inclusion criteria were diagnosis of acute lymphoblastic leukemia or B lymphoblastic lymphoma, age

between 6 and 18 years, and within 6 months to 5 years of treatment completion. Exclusion criteria were unresolved fractures, unresolved avascular osteonecrosis, and bone marrow transplantation as part of their treatment; physical or functional impairment at the time of recruitment was excluded. If patients had no or unstable internet connection, they would further be excluded. Owing to recruitment challenges for the first cohort, a first amendment was submitted to the ethical review board to increase the oldest age of eligibility from 10 to 14 years. Owing to recruitment challenges for the second cohort, a subsequent amendment was submitted to further increase the age range from 6 to 18 years, in addition to modifying the criterion of time since treatment completion from 6 months to 2 years to 6 months to 5 years. Patients could be included in the cohort if they participated in the exercise intervention within the first month of the intervention to receive between 12 and 16 weeks of the intervention.

Patients were screened for eligibility by the hematology oncology service medical team (nurses and physicians) at Sainte-Justine University Health Center.

Healthy age- and sex-matched participants were retrospectively included as controls for muscle function and bone analyses. Owing to the retrospective nature of this cohort, participants in the control group were not subjected to the intervention, and muscle and bone data were available at only one time point. These controls were drawn from our local historical database, including healthy siblings of patients and children of hospital staff who were part of a previous study. Control participants were selected based only on sex and age to avoid any selection bias, for example, in selecting patients that would decrease the difference between controls and patients in muscle and bone parameters.

The Sainte-Justine University Health Center institutional review board approved this study (2018-1555: e-S@@VIE). Parents of patients aged <18 years provided signed informed consent, and patients aged between 6 and 17 years provided informed consent. Families were contacted via phone to provide details of the project and check for interest. If they were interested in the study, a baseline evaluation was performed.

Study Procedures

The study procedure was divided into the following four phases: (1) baseline evaluation, (2) home-based visit, (3) intervention, and (4) postintervention evaluation.

Baseline Evaluation

After informed consent or assent was provided, patients completed baseline (and postintervention) measurements at 2 pediatric health care centers in the Montreal area: Sainte-Justine University Health Center and Shriners Hospital for Children, Canada. The baseline and postintervention visit schedule followed the same pattern: at Sainte-Justine University Health Center, weight and height of the patients were measured, and 6-minute walk test (6MWT), upper limb grip force test, and lower limb mechanography were evaluated. All participants were assessed by the same trained evaluator (GL). At Shriners Hospital for Children, patients underwent bone imaging testing (peripheral quantitative computed tomography [pQCT]).

Home-Based Visit

Following the baseline evaluation, a kinesiologist visited the families at their homes to help them prepare for the intervention. The kinesiologist delivered the following materials to the patients: an exercise step, a training elastic, a weighted 5-pound ball, and a training watch (Polar A370, Polar Electro Oy 2020, Polar FlowSync 3.0.0.1337) and its charger. At the same time, an assessment was performed for the suitability and safety of the space (1.8 m^2 of free space required). Support was provided for the installation of the software (for the watch and the videoconferencing system) on their own technologies (tablet, laptop, and computer) [29].

Intervention

All home-based exercise interventions were performed using a teleconferencing system (Zoom license Pro, Zoom Video Communications, Inc) with a kinesiologist at the hospital center and the study patients and their parents in their homes. This system was chosen because it provides encrypted communication between the kinesiologist and the families, which is compliant with the Canadian federal law about the privacy of companies, the *Personal Information Protection and Electronic Documents Act*. Families were sent an email 24 hours before every training with the link to connect to the virtual *meeting room* for their respective group. Interventions were live interactions that enabled direct supervision and immediate correction or adaptation of the exercise intervention when needed (for safety purposes). Study patients were divided into three groups of two families and two groups of three families based on language (English or French), age, and availability. Three cohorts were supervised at different time points (May-August 2018, January-April 2019, and September-December 2019). The original 16-week intervention included a progression every 4 weeks. Weeks 1-4 involved two sessions of 35 minutes per week. There was an additional 5 minutes of training per session during weeks 5-8, that is, two sessions of 40 minutes per week. During weeks 9-12, one session was added every week, that is, three sessions of 40 minutes per week. Finally, during weeks 13-16, an additional 5 minutes was added to each of the three sessions per week, bringing the duration to 45 minutes per session [30]. For the first 8 weeks, the training sessions were held on weekday evenings, and for the last 8 weeks, a third training session was added either on weekday evenings or on a weekend day. The general organization of a training session was as follows: a 5-minute warm-up, followed by whole-body resistance exercises (of progressive duration through the 16-week intervention), and finally, 5-minute stretching. The resistance exercises part of the training consisted of whole-body exercises (eg, push-ups, squats, and deadlifts) combined with plyometric exercises (eg, drop jumps, hopping, and jumping lunges). The training sessions and exercises were adapted according to the participants' pain reports. Pain was evaluated at the beginning and end of the session, as well as during sessions when pain was present at the beginning of the session. Pain was rated on a scale from 0 to 10 (Numerical Rating Scale-11 [31]), a description of the perception of pain (sensation and location) and its evolution through time and movement. The adaptations were personalized according to the location and intensity of the pain. For example,

patients with moderate knee pain would not do impact exercises such as *high-knees jogging* but would do low impact exercises such as *walking* or no impact exercises with *chair squats* or *calves raise* instead.

Postintervention Evaluation

The same evaluations assessed at baseline were performed at the end of the home-based exercise intervention, in the same context as the baseline evaluation.

Outcome Measures

Primary Endpoints: Feasibility

To determine the feasibility of administering a home-based intervention through telehealth to this population, recruitment rate, reasons for declining participation, the mean adherence rate and the completion rate to the intervention were computed. The recruitment rate was defined as the number of consented patients divided by the contacted potential patients. The adherence rate was defined as the number of sessions attended by the patients divided by the total number of possible sessions. Individual reasons for missing sessions have been reported. In addition, the specific information technologies (tablet, mobile phone, or computers) used for the interventions were reported for each household. Completion rate was defined as the number of patients who completed the intervention divided by the total number of patients who consented. The total number of training sessions with modified exercises owing to participant's pain was recorded. Finally, the nature and extent of adverse events during the training sessions were assessed by the kinesiologist according to the type and severity of events defined as potentially sequelae in a study by Ory et al [32].

Secondary Endpoints: Functional Performance and Bone Health

Muscle Parameters: Mechanography and Grip Force Test

Mechanography is a technique developed to investigate lower limb muscle function using a ground reaction force–measuring platform (Leonardo Mechanograph Ground Reaction Force Plate; Novotec Medical GmbH). Forces were recorded over time at a sampling rate of 800 Hz. All parameters reported here were derived from these force-time data using proprietary software (Leonardo Mechanography GRFP Research Edition software, version 4.2-b05.53-RES; Novotec Medical GmbH).

In total, two tests were performed using mechanography: the single two-legged jump (S2LJ) test for maximal power and the multiple two-legged hopping (M2LH) test for maximal force. The methodology is described in detail elsewhere [33,34]. Briefly, the S2LJ is a countermovement jump, and maximal power (kW) and maximal relative power (W/kg) are the main outcome parameters for this test. The M2LH test consists of hopping on the forefeet with stiff knees and without the heels touching the ground (similar to rope skipping). The M2LH provides information on the near-maximal ground reaction forces during eccentric contraction generated by patients. Relative muscle force (calculated in multiples of body weight) has been identified as the main parameter of this objective, as it is strongly associated with bone strength [35]. The participants were asked to perform three trials for each test. A trial for the

S2LJ consists of performing one jump, whereas a trial for M2LH consists of 10 consecutive hops. If the trials were not performed properly, an additional two trials were attributed to acquiring three valid test results. The trials with the highest peak power and peak force for S2LJ and M2LH, respectively, were selected for analysis.

The grip force test was performed using a handgrip dynamometer (Jamar Hand Dynamometer, Jamar Technology Inc.), which evaluates the maximal isometric force of the upper limb muscles. The patients were instructed to stand, feet shoulder-width apart, with arms in a neutral resting position on both sides of the body. They were then given a dynamometer that had previously been adjusted to an individual patient's hand. Finally, patients were instructed to press the handle as hard as possible until they were told otherwise. The test was performed on one arm at a time; both sides were repeated twice, and the best result of both sides was selected as the participant's result. The dynamometer provides force data in kilograms, and the evaluator was instructed to round the result to the nearest kilogram [36]. Scores were calculated based on grip force test reference data to compare the patients' results with a healthy sex- and age-specific population [37].

Cardiopulmonary Function: 6MWT

The 6MWT evaluates the ability of an individual to maintain a moderate level of physical activity over a 6-minute period [38]. Therefore, the result of the 6MWT is a reflection of the patient's daily activities [39]. The 6MWT correlates significantly with maximal oxygen uptake in typically developing children as well as in patients and survivors. This indicates that these two tests measure related functional capacities [39-41]. Study patients followed the instructions from the *American Journal Respiratory and Critical Care Medicine* published guidelines (2002): to walk back and forth in a hallway between two cones distanced by 30 m for 6 minutes as fast as possible at a pace that would make them tired by the end of the walk; encouragement and feedback are given every minute. During the test, patients were allowed to rest if needed. Expected results equations are available for calculating the percentage of age- and sex-specific norms [42]. The 6MWT has been shown to be reliable and valid in typically developing children (2-4 weeks apart between test and retest) and obese children (same-day test-retest), with a reliability reported from 0.73 to 0.949 [40,43]. Expected results were used to compare the results of the patients with a healthy sex- and age-specific population (*equations to predict the 6-minute walk distance in children and adolescents* [42]).

Bone Health: pQCT

pQCT was performed on the left tibia, unless there was a medical history of fracture of the bone, using the Stratec XCT2000 (Stratec Inc). This method is described in detail elsewhere [44,45]. The lower leg was scanned at 4% (metaphysis and trabecular bone), 14% (metaphyseal-diaphyseal transition site and cortical bone), 38% (diaphyseal transition site and cortical bone), and 66% (muscle parameters scan and midsection of the gastrocnemius muscles, therefore being the largest outer calf diameter [46]) of tibia length, measured as the distance from the reference line. The tomography images were then ranked using the movement artifact scale from 1 to 5, 1 being

an image without the artifact and 5 being there was too much movement to have a proper image. Scans scoring ≤3 were deemed usable. If the scan scored 4 or 5, the test was redone [47].

The main bone outcome parameters of pQCT analysis were measured at the 4%, 14%, and 38% sites of the tibia length, with 4% being the distal part of the tibia. The following parameters were measured: total bone cross-sectional area (CSA; mm^2), cortical bone CSA excluding marrow space (mm^2), bone mineral content (BMC) per millimeter of cross-sectional slice thickness (mg/mm), total volumetric bone mineral density (vBMD; mg/cm^3), trabecular CSA (mm^2; 4% site only), trabecular vBMD (mg/cm^3; 4% site only), cortical vBMD (mg/cm^3), and polar stress-strain index (SSI; assessed as a surrogate of bone strength; mm^3). The two main pQCT muscle outcome parameters were measured at the 66% site: muscle CSA (unit: mm^2; 66% site) and muscle density (unit: mg/cm^3; 66% site) [32].

Statistical Analysis

As this study was a pilot study to investigate the feasibility, no sample size calculation was performed. The normality of the data was tested using the Shapiro-Wilk test (n=9) [48]. The means and SDs were reported when the data were normally distributed, and the median and range were reported when the normality assumption was violated.

To assess feasibility, recruitment, completion, and adherence rates were analyzed. A one-sample Wilcoxon signed-rank test was performed on the adherence rate of patients with a set threshold of 80%, based on the hypothesis. The threshold was based on a study involving home-based distance-delivery exercise interventions administered to patients with acute lymphoblastic leukemia in remission, which showed an 80% adherence rate for a 75% completion rate [15].

To determine the effect of the exercise intervention on patients' functional and musculoskeletal health, pre- and postintervention test results from the pQCT, mechanography, grip force, and 6MWT were compared using the paired-samples two-tailed *t* test when the data were normally distributed and the related-sample Wilcoxon signed-rank test when they were not. In addition to these pre- to postanalyses, postintervention results of pQCT, mechanography, and grip force [37] were compared with sex- and age-matched typically developing controls using independent-samples *t* tests (for normally distributed parameters) and the independent-samples Mann-Whitney *U* test (for parameters not normally distributed). Additional analysis included a one-sample *t* test analysis to determine if the mechanography results were clinically significant by comparing patients' change in lower limb muscle function with the minimal detectable difference reported by Veilleux et al [33]. For the 6MWT, an independent-samples *t* test was performed on the distance traveled after the intervention and expected distance of the 6MWT from sex- and age-related calculations [42]. Patients' changes in 6MWT distance were compared in a one-sample *t* test analysis with the SE of 15 m reported by Li

et al [40] to establish if the results were deemed clinically significant.

To assess the muscle-bone functional unit, a Spearman correlation was performed for nonnormally distributed parameters. The correlation between maximal force (absolute; N) and BMC at 14% of the tibia was established for both pre- and postintervention patient-related data as well as for the typically developing controls [35].

All statistical tests were performed using Predictive Analytics Software Statistics software version 24.0 (SPSS Inc), with the CI and significance level preset at 95% and .05, respectively.

Results

Feasibility and Baseline Characteristics

The recruitment flowchart is shown in Figure 1. A total of 104 patients aged 6-17.1 years within 5 years of complete remission were considered as potential participants. Of the 57 potential participants who were contacted, 12 patients (21%; 9 girls) provided informed consent or assent (Table 1 provides participant clinical information). The specific motive to decline participation was recorded in 27% (12/45) of refusals: parents' overloaded schedules (n=2); the patients were deemed too active by their parents, as they engaged in other physical activities multiple times per week (n=4); the patients did not want to come to the hospital for the evaluation (n=2); or the patients did not find the idea of an organized training session interesting (n=3).

Figure 1. Recruitment process flowchart; n represents the number of individuals in the sampling; n_Σ represents the summation of all potential participants at that timepoint.
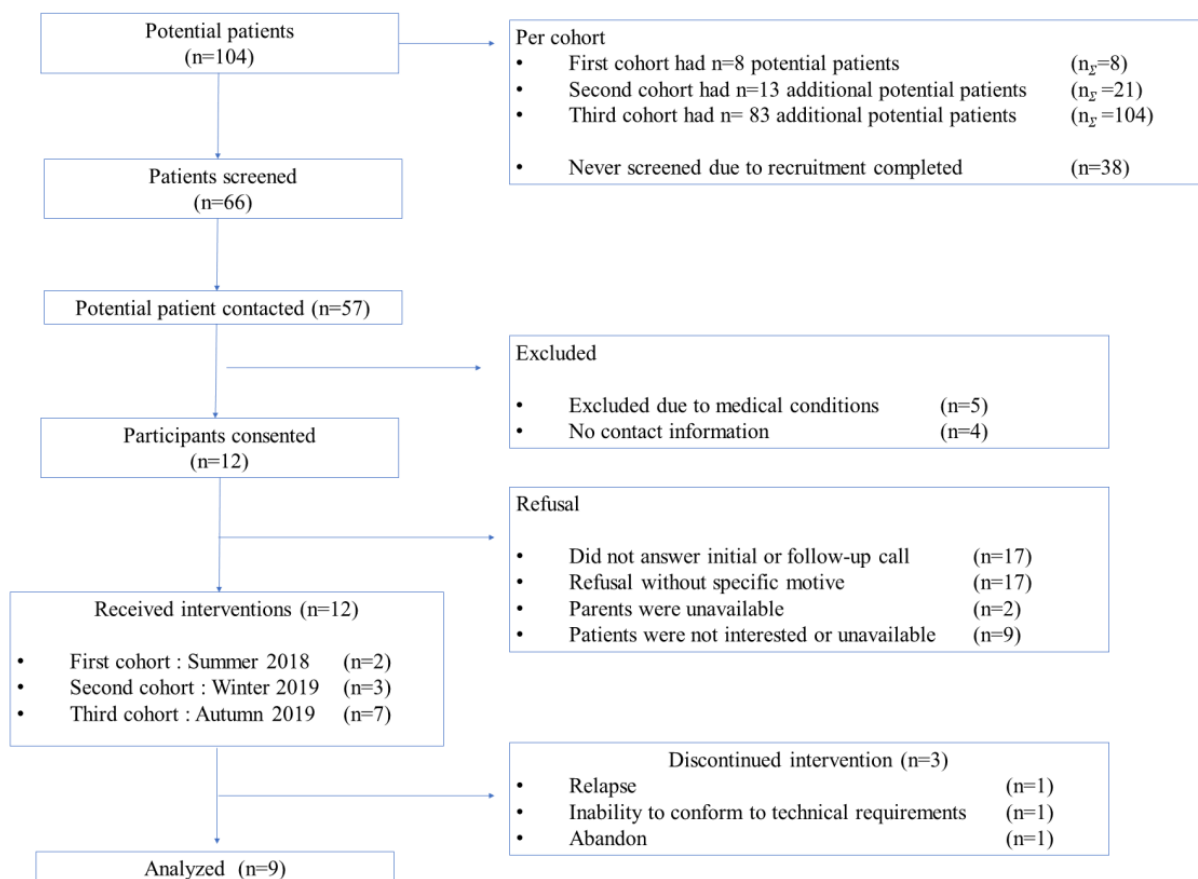
Table 1. Clinical information.

Anthropometric and clinical parameters	Baseline (n=9)	Postintervention (n=9)	Controls (n=9)
Age (years), median (range)	9.17 (8-14.5)	9.5 (8.25-15.1)	9.87 (7.48-14.72)
Sex (female), n (%)	6 (75)	6 (75)	6 (75)
Height (cm), mean (SD)	143.27 (23.63)	145.19 (23.63)	146.03 (17.54)
Weight (kg), mean (SD)	46.92 (24.67)	47.88 (24.92)	40.71 (11.64)
BMI (kg/m^2), mean (SD)	21.58 (6.55)	21.46 (6.53)	18.83 (3.39)
Diagnosis, n (%)			
Acute lymphoblastic leukemia	8 (89)	—[a]	N/A[b]
Lymphoblastic lymphoma	1 (11)	—	N/A
Prognosis, (SR:HR:VHR)[c]	6:2:1	—	N/A
Time since end of treatment (months), mean (SD)	36.67 (16.37)	—	N/A
Recurrence, n (%)	1 (11)	—	N/A
Treatment protocol, n (%)			
DFCI-ALL[d] 2005	2 (22)	—	N/A
DFCI-ALL 2011	7 (77)	—	N/A
Cumulative dose of glucocorticoids			
Dexamethasone, median (range)	352 (256-870)	—	N/A
Prednisone, median (range)	390 (252-2199)	—	N/A
Cranial radiotherapy, n (%)	1 (11)	—	N/A
Duration of hospitalization during treatments (days), mean (SD)	45 (13)	—	N/A
Musculoskeletal comorbidities during treatments, n (%)			
Vertebral fracture	4 (44)	—	N/A
Osteonecrosis	1 (11)	—	N/A
Nonvertebral fracture	2 (22)	—	N/A
Osteoporosis	4 (44)	—	N/A
Low bone mineral density	8 (89)	—	N/A
Received bisphosphonates, n (%)	4 (44)	—	N/A
Cumulative dose of zoledronic acid, median (range)	3.13 (1.70-4.05)	—	N/A
Other comorbidities during treatments, n (%)			
Thrombosis	4 (44)	—	N/A
Neuropathy	1 (11)	—	N/A
Home distance from health care center (round trip; km), median (range)	66 (7-72)	—	N/A

[a]Not reported.

[b]N/A: not applicable.

[c]SR:HR:VHR: standard risk:high risk:very high risk.

[d]DFCI-ALL: Dana-Faber Cancer Institute–acute lymphoblastic leukemia treatment regimen.

Of the 12 enrolled patients, 9 patients completed the 12- to 16-week intervention and had complete pre- and postintervention data sets, representing a 75% completion rate (Figure 1). Of the 12 patients, 3 did not complete the final evaluation because of technical issues (poor internet connection, n=1), relapse (n=1), or dropped out because of lack of interest (n=1). Of the 9 patients who completed the intervention, 5 had 40 potential training sessions and the others had 31, 32, 34, and 38 potential training sessions. Overall, the group's median for adherence rate was 95% (range 70-98; *P*=.04), that is, an average of 33 sessions attended on 37 possible sessions. All participants required adaptations due to pain, on average, for 16 sessions (range 14-27), representing 48% of the training done. Table 2 illustrates the reasons for missing a training session and the overall proportion it represents.

Table 2. Reasons for participants' absences to the exercise sessions (n=35)[a].

Reason of absence	Values, n (%)
Patient acute musculoskeletal pain	6 (17)
Patients' comorbidities or infections (eg, asthma or pneumonia)	8 (23)
Patients' sickness (eg, cold, fever, flu, and so on)	10 (29)
Parents' unavailabilities	3 (8)
Patients' other activities (eg, school-related activities, sports, and so on)	6 (17)
Technical failure	2 (6)

[a]The total of missed sessions is 35 out of 335; the values presented as the absolute number of absence and their relative weights according to their respective reasons for absence.

With regard to the information technology used to receive the telehealth intervention, one family used a desktop computer connected to their television, resulting in a fixed setup; two families used a tablet; and six families used a laptop for interventions. Of the six households that used a laptop, three connected the device to the television to allow for a larger screen view. Mobile technology was also used outside home settings (ie, at the hotel during family vacation: n=2; at the house of family members such as divorced parents, grandparents, uncles, or aunts: n=3; or to benefit from outdoor settings: n=1). The kinesiologist provided most of the sessions within the hospital setting using a fixed system, except for six training sessions delivered outside hospital settings using mobile technology (laptop) for 2 weeks while on conference travel abroad.

The kinesiologist reported four occurrences of mild adverse events over 300 training sessions. The events were intervention related and resulted from falls (n=2) or missteps (n=2). All patients were able to resume training within minutes after the

event had occurred. None of the patients had lasting effects, and it did not prevent patients from participating in any of the following sessions.

Functional Performance and Bone Health

Muscle Parameters

All functional performance parameters are reported in Table 3, except for relative maximal force and power of the lower limb, as illustrated in Figures 2 and 3. Lower limb muscle function showed a significant increase from pre- to postintervention for relative maximal force (11%; Figure 2), in addition to absolute (11%) and relative maximal power (9%; Figure 3). The absolute force data of the lower limbs showed no significant difference between pre- and postintervention. The analyses comparing postintervention mechanographic data of study patients with typically developing controls showed no significant difference for both relative force (P=.76) and relative power (P=.08).

Table 3. Functional outcomes.

Outcome	Baseline evaluation (n=9)	Postintervention evaluation (n=9)	Controls or expected results (n=9)	P value[a]	P value[b]
Mechanographic parameters					
Absolute force (kN)[c]	1.17 (0.96-4.06)	1.60 (1.08-3.72)	1.63 (1.02-2.63)	.10	.73
Absolute power (kW)[c]	0.97 (0.66-3.03)	1.07 (0.72-3.14)	1.57 (0.95-2.73)	*.008* [d]	.73
Hand dynamometer					
Grip test right (kg)	16.6 (8.4)	17.3 (7.7)	___[e]	.50	.16[f]
Grip test left (kg)	14.6 (8.7)	15.6 (7.7)	—	.52	.21[f]
6-minute walking test distance (m)	593 (100)	646 (97)	598 (43)	*.01*	.90

[a]P values of paired-sample t test and Wilcoxon matched-pairs signed-ranked test comparing baseline and postintervention evaluations.

[b]P values of independent-samples t test and independent-samples Mann-Whitney U test comparing postintervention with control data.

[c]Parameters not normally distributed.

[d]Italicized P values denote significance (P<.05).

[e]Not available.

[f]P value of the paired-sample t test of the grip strength Z-scores comparing baseline and postintervention evaluations.

Figure 2. Box and whisker plots of the mechanography results; relative maximal muscle force at baseline, postintervention, and for controls. The "*" indicates paired-sample *t* test comparing baseline and postintervention data, significant at *P*=.05.
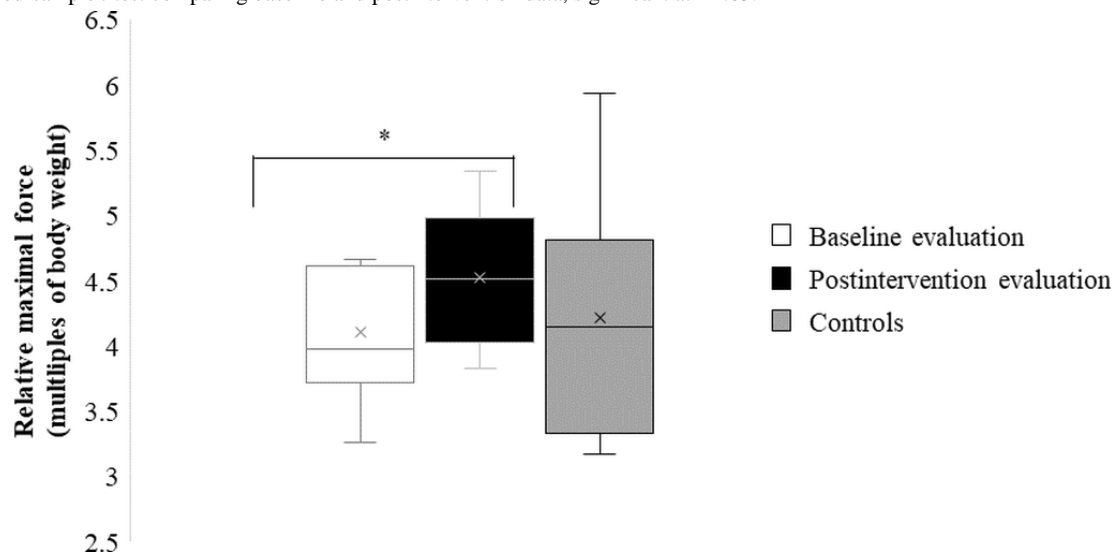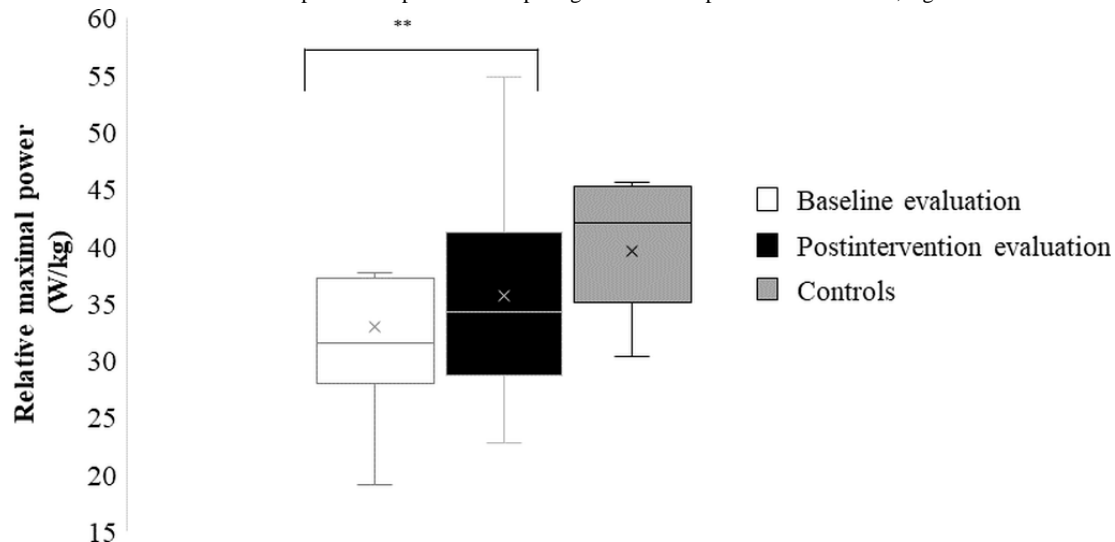

Figure 3. Box and whisker plots of the mechanography results; relative maximal muscle power at baseline, postintervention evaluation, and for sex- and age-matched controls. The "**" indicates paired-sample *t* test comparing baseline and postintervention data, significant at *P*=.002.

Absolute upper limb isometric grip force showed no significant difference between the pre- and postintervention results. Isometric grip force results showed that patients had lower grip force than normal (average *z* score right hand: preintervention −1.06, SD 0.66, *P*=.001; postintervention −0.73, SD 0.94, *P*=.05; and average *z* score left hand: preintervention −1.63, SD 0.86, *P*<.001; postintervention −1.19, SD 0.97, *P*=.006) compared with age and sex reference data. Patients showed a trend toward improvement in isometric grip force from pre- to postintervention (right: 7% and left: 18%), but it did not reach significance (right: *P*=.16 and left: *P*=.21).

Cardiopulmonary Function

Regarding cardiopulmonary function (Table 3), the results of the 6MWT showed a significant increase of 10% in the distance walked from pre- to postintervention. To test whether the increase was clinically significant, a one-sample Wilcoxon signed-rank test analysis showed that the median improvement of 40 m (range 7-159) was significantly different from the threshold of 15 m suggested as the minimal clinically

meaningful difference (*P*=.003) [40]. The comparison between the postintervention average distance walked and the reference values was not significant. The preintervention data were not compared with reference values but would most likely not differ because the preintervention walked distance was within the normal range (593 m walked, SD 107 m vs 598 m, SD 43 m).

Bone Health

The pre- and postintervention pQCT bone parameter data are shown in Table 4. A significant increase in the following parameters was reported: cortical CSA increased by 4% (14% site; *P*=.001) and 3% (38% site; *P*=.003) and total CSA increased by 2% and 4% at the 14% site (*P*=.01) and 38% site (*P*=.001), respectively. A 6% and 4% increase in SSI was also observed at the 14% site and 38% site (*P*=.001 and *P*=.04), respectively. BMC increased significantly by 4% at the 14% site (*P*=.02) and 38% site (*P*=.003). No other pQCT bone parameters showed significant differences between pre- and postintervention evaluations. To ascertain that changes in bone parameters were associated with exercise training and not

entirely to growth, we performed supplementary bivariate correlations between changes in height and weight and changes in bone parameters. No significant association was found between any growth-associated factors and bone parameters (height vs bone CSA at 14%, P=.36; height vs bone CSA at 38%, P=.28; height vs cortical CSA at 38%, P=.74; body weight vs bone CSA at 14%, P=.75; body weight vs bone CSA at 38%, P=.11; body weight vs cortical CSA at 38%, P=.19), suggesting that changes in bone parameters were associated with the mechanical workload of the exercise interventions rather than with growth itself. The comparison of postintervention bone parameters between patients and paired controls revealed that the only bone parameters that were significantly different from controls at the postintervention evaluation were total CSA at the 4% site, which was 21.2% (P=.01) larger in patients than

in controls, and the SSI at the 14% site, which was 7% (P=.007) greater in patients than in controls. No other bone-related significant differences were observed between patients and controls.

The pQCT analysis showed that muscle density, evaluated at the postintervention assessment, was 5% lower (P=.05) in patients than in typically developing controls. However, muscle density did not change after the intervention.

For the muscle-bone functional unit (Figure 4), there was a significant positive relationship between absolute peak force and BMC at 14% at preintervention (P=.01), at postintervention (P=.004), and for controls (P=.007). The slopes were similar for both patient slopes within 10% of the controls.

Table 4. Bone health parameters assessed with peripheral quantitative computed tomography.

Muscle and bone health parameters	Baseline evaluation	Postintervention evaluation	Controls	P value[a]	P value[b]
Calf muscle (n=8)[c]					
Muscle CSA[d] (mm^2)[e], median (range)	3503 (2687-7222)	3606 (2766-6921)	4618 (2966-6828)	.26	.86
Muscle density (mg/cm^3), mean (SD)	68.7 (4.0)	68.6 (3.3)	71.9 (1.8)	.97	*.05* [f]
Tibia 4% site (n=9)					
Total CSA (mm^2), mean (SD)	819 (325)	830 (332)	675 (227)	.12	*.01*
Total BMC[g] (mg/mm), mean (SD)	234 (99)	239 (103)	207 (58)	.17	.10
Total vBMD[h] (mg/cm^3), mean (SD)	289.46 (37)	289 (32)	312 (31)	.98	.14
Trabecular vBMD (mg/cm^3), mean (SD)	218.92 (38)	216 (38)	212 (19)	.53	.77
Tibia 14% site (n=8)[c]					
Total CSA[e] (mm^2), median (range)	341 (188-517)	349 (194-528)	294 (188-406)	*.01*	.38
Total BMC[e] (mg/mm), median (range)	170 (104-268)	175 (112-272)	188 (111-222)	*.03*	.72
Cortical CSA (mm^2), mean (SD)	120 (44)	124 (44)	133 (34)	*.001*	.68
Cortical vBMD (mg/cm^3), mean (SD)	1000 (32)	1004 (30)	994 (50)	.26	.62
SSI[i] (mm^3), mean (SD)	891 (510)	932 (519)	837 (310)	*.001*	*.007*
Tibia 38% site (n=9)					
Total CSA (mm^2), mean (SD)	292 (116)	301 (116)	282 (85)	*.001*	.47
Total BMC (mg/mm), mean (SD)	222 (78)	229 (79)	233 (62)	*.003*	.89
Cortical CSA (mm^2), mean (SD)	191 (70)	198 (71)	206 (53)	*.003*	.86
Cortical vBMD[e] (mg/cm^3), median (range)	1056 (927-1088)	1045 (930-1096)	1036 (959-1094)	.86	.80
SSI (mm^3), mean (SD)	906 (498)	939 (507)	948 (387)	*.04*	.37

[a]P values of paired-sample t test and Wilcoxon matched-pairs signed-ranked test comparing baseline and postintervention parameters.

[b]P values of independent-samples t test and independent-samples Mann-Whitney U test comparing postintervention data with age- and sex-matched controls' data.

[c]One peripheral quantitative computed tomography scan removed due to movement artifact.

[d]CSA: cross-sectional area.

[e]Parameters not normally distributed.

[f]Italicized values indicates significance of $P<.05$.

[g]BMC: bone mineral content.

[h]vBMD: volumetric bone mineral density.

[i]SSI: stress-strain index.

XSL•FO
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Figure 4. Muscle force and bone strength relationship. Linear correlation between bone mineral content (mg/mm) at the 14% site and muscle force (kN) as a function of the disease status (early-on survivors of acute lymphoblastic leukemia vs age- and sex-matched controls) and testing phase (baseline vs postintervention). Light gray line and white squares depict baseline acute lymphoblastic leukemia data; black line and squares depict postintervention acute lymphoblastic leukemia data. Dark gray line and circles depict age- and sex-matched controls data. Blue line depicts theoretical control muscle-bone relationship.
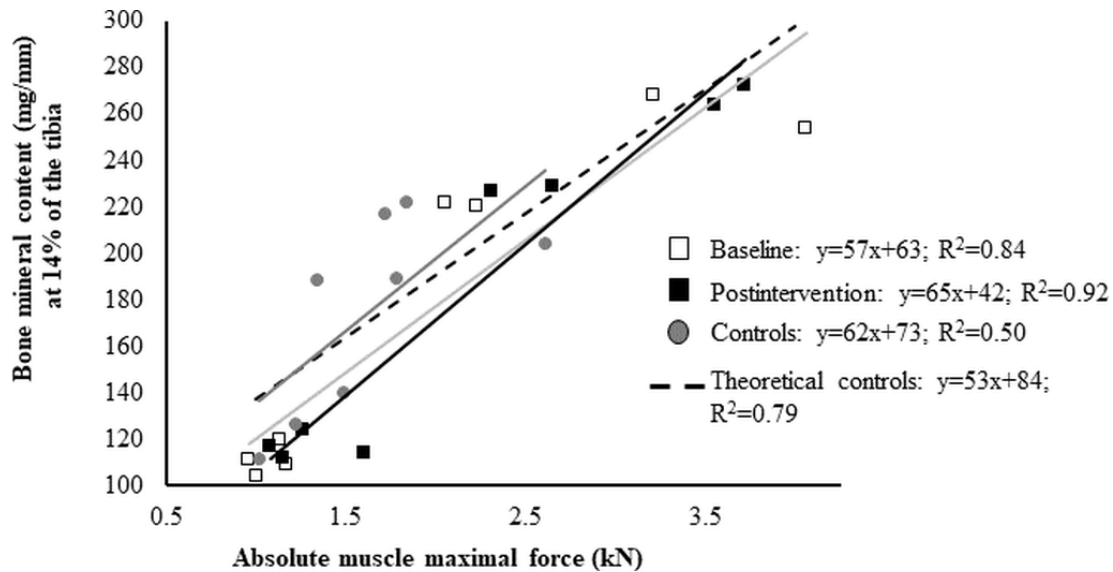
Discussion

Principal Findings

The primary objective of this study was to assess the feasibility of administering a supervised telehealth home-based exercise intervention for early-on survivors of acute lymphoblastic leukemia. The hypothesis was confirmed, and the approach was deemed feasible, as demonstrated by the 75% completion rate and mean adherence rate of 89%. The secondary objective of this study was to explore the benefits of exercise interventions on functional outcomes and bone health parameters. In line with our exploratory hypothesis, an improvement in lower limb muscle function and bone health parameters was observed between pre- and postintervention evaluations.

Feasibility

Compared with an unsupervised home-based exercise intervention, the adherence and completion rates (89% and 75%, respectively) reported in this study are high [15], suggesting that direct supervision contributes to a high adherence rate. These numbers are similar to those reported by Esbenshade et al [20], who reported adherence rates of 81% and completion rates of 71%. This study and a study by Esbenshade et al [20] showed similar improvements in muscle and cardiopulmonary function. In the study by Esbenshade et al [20], direct supervision was not provided, but weekly follow-up phone calls were made. Direct supervision has many advantages that can lead to increased adherence and participation rates [23]. Receiving positive reinforcement [24], improving exercise technique [24], and feeling self-efficient [25] are all benefits associated with increased adherence and, indirectly, health benefits. Another positive impact of supervision is the greater overall volume of exercise achieved during individual sessions, which can be associated with better structured and controlled exercised sessions under supervision compared with no supervision or phone call follow-up [26]. In this study, having

direct supervision might have led to more efficient training because many sessions needed exercise adaptations because of patient pain. Being able to adjust the exercises to avoid pain in real time may have prevented injuries that may have prevented a decrease in participation and adherence rates. According to our data, the high proportion of training that required adaptation for pain management would suggest the need for direct supervision for safety purposes for this specific patient population prone to musculoskeletal-related pain [49,50].

A favorable aspect of the telehealth approach used in this study is that patients showed similar improvement in musculoskeletal and cardiopulmonary functions as in other studies using indirect supervision (phone calls and video recordings of the exercises to be performed) but with lower volume and frequency. In a study by Tanir and Kuguoglu [19], muscle function training was required 3 days per week, 3 times per day, in addition to 3 times per week, once a day of aerobic training, whereas in a study by Esbenshade et al [20], resistance training was required three times per week and aerobic training was required three times per week, for a total training time ranging between 3.5 and 5.25 hours per week. In comparison, the weekly amount of time devoted to training in our study reached a maximum of 2.25 hours (3×45 min). Taken together, this suggests that having a qualified kinesiologist supervising the training sessions improves the efficiency with which the patients are performing the training [26].

Functional Performance and Bone Health

Although this study aimed to evaluate feasibility, it was hypothesized that improvements would be observed for muscle, bone, and cardiopulmonary fitness parameters. Regarding muscle parameters, a previous study in a patient population showing similar muscle weaknesses established [33] the minimal detectable difference to be of 0.42 multiples of body weight for relative force (M2LH test) and 3.19 W/kg for relative power (S2LJ). In this study, and once the patient who relapsed was

removed from the analysis, the improvements were 0.55 multiples of body weight for relative force and 3.05 W/kg for relative power. Notably, all patients showed improvements in these parameters. These results are similar to the reported minimal detectable difference, suggesting clinically relevant improvements in our patients.

In terms of cardiopulmonary fitness, the 6MWT walking distance showed an increase of 53 m from pre- to postintervention. This is more than the 15-m the minimal clinically meaningful difference reported in a previous study evaluating the between-session reproducibility of the 6MWT walking distance [40]. This suggests that the improvement represents true changes rather than the measurement variability.

At the bone level, the mechanostat theory, developed by Frost [51], stipulates that bones adapt to maximal mechanical loading applied from muscle contractions and unfavorable lever arms. In this study, a special emphasis was placed on increasing lower limb muscle force and, indirectly, mechanical loading of patients' bones. The results indicated significant improvements in multiple bone-related parameters, such as BMC and cross-section. Figure 4 shows that the linear relationship associated with muscle force and bone strength parameters was normal in the patient population with acute lymphoblastic leukemia and maintained postintervention. These results suggest that the bone mechanotransduction and modeling process are normal in young early-on survivors of hematological malignancies and that the intervention aimed at increasing muscle force may lead to increased bone strength [44].

Limitations of the Study

In total, two major challenges in the recruitment process were identified: (1) only one-fifth of the patients who were contacted provided informed consent (12/57, 21%) and (2) creating the groups revealed to be difficult, leading to multiple cohorts. Regarding the families that declined participation, the four families that declined because patients were too active were more advanced in their survivorship (>2 years) and returned to their daily living activities before the diagnosis. This suggests that implementing a home-based exercise intervention may be more feasible earlier (1-2 years) than later (3-5 years) in their survivorship. The group approach was also challenging because of two factors: (1) the age range of the participants and (2) the availabilities of families leading to bilingual groups. Owing to difficulty in recruiting patients, the protocol was amended to increase the age range of the study participants from 6 to 10 years to 6 to 18 years. This resulted in one group having two 9-year-old training with a 14-year-old patient, which is not ideal. Québec has a very large proportion of French- and English-speaking population, and both are represented in this study. English- and French-speaking participants had to be grouped together because of family availability constraints, leading to providing bilingual training sessions.

Owing to administrative constraints, the intervention was offered to participants approximately 2 weeks before the start of the interventions. To avoid the challenges mentioned earlier, it is recommended that such interventions for early-on survivors be offered to families during routine checkups, months before their participation. This would provide families sufficient time to organize their schedules to integrate the training intervention with school activities and other obligations. This would also provide the clinician with the opportunity to avoid recruitment pitfalls and the challenges reported earlier.

The positive impact of mobile technology on families' experiences was unforeseen; hence, limited results have been reported. This project was originally designed to be a traditional home-based intervention; however, mobile technology allowed accessibility to the interventions outside the household, favoring everyday life activities versus exercise training balance. As such, families took full opportunity to use their own technologies to train in different environments, such as on their family vacations at the hotel or during family dinners. Without mobile technologies, families would have had to choose between attending training session or their social events. Similarly, the clinician was able to deliver interventions while on a scientific conference travel outside the country over a 2-week period. Nonetheless, the use of personal technologies can be disadvantageous to some families with lower socioeconomic status, which may have limited access to personal technologies and high-speed internet. In this study, no patients declined to participate because of a lack of accessible information technology, but one family was excluded because the available internet connection in their geographical area was too unstable to allow communication and safe exercise supervision.

In terms of health benefits, the results of the intervention are promising, showing improvements in most muscle, cardiopulmonary fitness, and bone measured parameters. However, this study was designed to assess the feasibility of a home-based exercise intervention delivered through telehealth; therefore, it was neither powered nor designed to detect the physiological changes associated with the intervention. In this regard, functional performance and bone health results were analyzed simply and may have statistical artifacts, such as the multiple hypothesis testing effect, because no statistical corrections were applied. Improvements in functional performance and bone health should thus be interpreted with these considerations in mind, despite the fact that improvement was observed in 8 of 9 study participants. Another limitation of this study is that the control group consisted of healthy individuals, rather than early-on survivors who would not receive the intervention. This prevents any conclusion regarding whether the proposed approach provides added benefits compared with the standard of care. The second limitation is associated with the retrospective nature of the control group, which only had data for one time point. This prevented performing adequate statistical analyses comparing the two groups pre- and postintervention. Therefore, any control group comparison should be interpreted in this context.

Conclusions

The results of this study suggest that providing early-on survivors of acute lymphoblastic leukemia with home-based exercise intervention through telehealth is a feasible approach. This approach has multiple advantages, even more so in the context of the current COVID-19 pandemic. Patients with acute lymphoblastic leukemia are usually treated in specialized (tertiary) health care centers located in large cities. As a result,

patients treated at these centers are scattered across large distances, making the implementation of frequent adjunct therapies impossible. Finally, although exploratory in nature, the comparison between pre- and postintervention muscle and bone parameters suggests that the proposed exercise regimen is suitable for inducing musculoskeletal benefits in young early-on survivors of bone marrow–related hematological malignancies.

Acknowledgments

Conflicts of Interest

None declared.

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Abbreviations

6MWT: 6-minute walk test
BMC: bone mineral content
CSA: cross-sectional area
M2LH: multiple two-legged hopping
pQCT: peripheral quantitative computed tomography
SSI: stress-strain index
S2LJ: single two-legged jump
vBMD: volumetric bone mineral density

Original Paper

Cancer Clinicians' Views Regarding an App That Helps Patients With Cancer Meet Their Information Needs: Qualitative Interview Study

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Abstract

Background: Many patients with cancer have unmet information needs during the course of the illness. Smart devices, such as smartphones and tablet computers, provide an opportunity to deliver information to patients remotely. We aim to develop an app intervention to help patients with cancer meet their illness-related information needs in noninpatient settings. In addition to the in-depth exploration of the issues faced by the target users of a potential intervention, it is important to gain an understanding of the context in which the intervention will be used and the potential influences on its adoption. As such, understanding the views of clinicians is key to the successful implementation of this type of app in practice. Additionally, clinicians have an awareness of their patients' needs and can provide further insight into the type of app and features that might be most beneficial.

Objective: This study aims to explore cancer clinicians' views on this type of intervention and whether they would support the use of an app in cancer care. Specifically, the perceived acceptability of an app used in consultations, useful app features, the potential benefits and disadvantages of an app, and barriers to app use were explored.

Methods: A total of 20 qualitative, semistructured interviews were conducted with 22 clinicians from urological, colorectal, breast, or gynecological cancer clinics across 2 hospitals in South Wales. The interviews were audio recorded, transcribed, and analyzed using thematic analysis.

Results: Clinicians felt that it would be acceptable for patients to use such an app in noninpatient settings, including during consultations. The benefits of this type of app were anticipated to be a more informed patient, an increased sense of control for patients, better doctor-patient communication, and a more efficient and effective consultation. In contrast, an increase in clinicians' workload and poorer communication in consultations, which depended on the included app features, were identified as potential disadvantages. The anticipated barriers to app use included patients' age and prior experience with smart technology, their access to smart devices, the confidentiality of information, and an avoidant coping approach to their condition.

Conclusions: This study suggests that clinicians should support their patients in using an app to help them meet their information needs both at home and during consultations. This study highlights some of the potential barriers for this type of intervention in practice, which could be minimized during the intervention design process.

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Introduction

Most patients with cancer now largely manage their condition at home with less regular supervision by clinicians, which requires them to take a more active role in their treatment and survivorship [1,2]. To become a more activated patient and to manage the changes in daily life that come with cancer, patients require relevant and accurate information [3], and patients generally want as much information as possible about their condition [4]. However, recent studies conducted in Europe and the United States over the last 5 years have reported high rates of unmet information needs among patients with cancer [5-7]. In addition to limiting patients' ability to participate in their care, unmet information needs are also associated with a lower quality of life, the loss of control over one's life, increased anxiety and depression, and dissatisfaction with care [5,8-11].

Smart technology, including smartphones and tablet computers, has the potential to support the shift in cancer care to community settings and help patients meet their information needs by facilitating the delivery of information-based interventions to patients at home. However, a recent systematic review of the use of mobile devices to support patients with cancer with their information needs identified that available mobile interventions are mainly limited to helping patients with their treatment- or symptom-related information needs [12]. The authors concluded that more comprehensive interventions are required for patients managing the wider aspects of their condition in noninpatient settings.

This paper reports part of a series of studies documenting the systematic development of an app to help patients with cancer to meet their illness-related information needs [12,13], which followed the Medical Research Council (MRC) framework for the development of complex interventions in health care [14] and the person-based approach to enhance the acceptability and feasibility of such interventions [15]. A systematic review of the use of mobile devices to help patients with cancer meet their information needs reported that the vast majority of interventions aimed to improve the monitoring and management of treatment-related symptoms [12]. There were no interventions designed to meet patients' full range of cancer-related information needs; more comprehensive interventions are required for patients to meet their information needs when managing their condition in noninpatient settings. Qualitative interviews were then conducted with a sample of patients with cancer to explore their views and preferences for a potential app to help them meet their illness-related information needs [13]. Suggestions for app features indicated the need for an app that supports patients to gather the key information that they need from their clinicians during time-constrained consultations, facilitates understanding, collates large amounts of information regarding available services, and helps patients navigate them. The anticipated benefits of this type of app included a more informed patient, improved quality of life, reduced anxiety, and increased confidence to participate in their care, which appeared to outweigh the potential disadvantages, such as potentially increased anxiety and distraction in consultations. Finally, patients anticipated that potential barriers to app use could be previous experience with smart technology, access to smart devices and the internet, an avoidant coping approach to their condition, and concerns about security and confidentiality of personal information.

In addition to an in-depth exploration of the issues faced by the target users of a potential intervention, it is important to gain an understanding of the context in which it will be used and the potential influences on the intervention [15,16]. As patients with cancer desire an app that would facilitate information gathering, exchange, and understanding during and between consultations with their clinicians [13], it is important to explore clinicians' perceptions of the acceptability of this type of app to provide an opportunity to identify and minimize the potential barriers to its implementation in a clinical context [16,17]. In addition, clinicians have a potential role in encouraging the uptake of an app for patients with cancer following a diagnosis, as patients value the opinions of their clinicians and trust them as a source of reliable information [18,19]. Therefore, the support of clinicians will be key to the successful implementation of such interventions in practice [16].

The primary aim of the study reported in this paper is to explore clinicians' views on the acceptability of an app for patients with cancer, including whether clinicians would support the use of an app in cancer care. Views on information exchange in consultations, useful app features, and the potential benefits and disadvantages of, and barriers to, app use were also explored.

Methods

Overview

Semistructured interviews were conducted with cancer clinicians at their clinics between June 2014 and November 2014. Participants were interviewed for this study before a qualitative interview study was conducted with a sample of patients with cancer [13]. Given that patients with cancer still report unmet information needs in recent years [5-7], it is prudent to continue with the development of interventions to support them and publish data that will help to build the evidence base in this field. National Health Service (NHS) ethical approval and R&D approval were granted (approval number: 14/WA/0066). Semistructured interviews were chosen because they enable a more personal and in-depth response from individuals compared with quantitative methods [20]. This method also allows participants the freedom to raise other relevant issues [19].

Participants

We aimed to recruit a varied sample of clinicians to enable divergent views to emerge [20]. Cancer clinicians were recruited from colorectal, urological, breast, and gynecological cancer clinics within the University Hospital Wales and Velindre Hospital (a specialist cancer hospital) in South Wales, United Kingdom. These 4 cancer clinics were chosen because they have a variety of clinicians who deal with some of the most common cancers [21]. A decision was made to include a varied sample, including consultant surgeons, consultant oncologists, cancer nurse specialists (CNSs), and trainee clinicians (both medical and nursing).

Recruitment

Clinical leads were identified and contacted so that the lead author (RR) could attend multidisciplinary team (MDT) meetings at each of the cancer clinics to present the study and invite clinicians to participate. Interested clinicians were emailed an information pack containing an invitation letter, information sheet, and reply form. It was not possible to attend an MDT meeting in all cancer clinics. In these circumstances, the lead clinician was asked to email their colleagues to invite clinical colleagues to participate in the study and to contact RR if they were interested. As a result of this recruitment method, the response rate could not be determined.

Procedure

Face-to-face interviews were conducted with interested participants at the clinicians' place of work. The interview was treated confidently, and only the research group had access to anonymized data. Clinicians provided written consent at the time of the interview and completed a demographic questionnaire that allowed us to describe the characteristics of our sample. Interviews were audio recorded, transcribed verbatim, and anonymized.

Interview Topic Guide

Relevant literature informed the development of a semistructured interview topic guide [12]. The topics included information provision in consultations, experience with smart technology in consultations, perceived acceptability of an app intervention, perceived benefits and disadvantages of, barriers to app use, and useful app features for patients with cancer. At the beginning of the interviews, participants were told that an app could help with a wide range of things, such as patients' information needs, communication in consultations, adherence to medication, and social support. Multimedia Appendix 1 provides a topic guide.

Analysis

Participants were interviewed until the research team felt that data saturation was reached, sometimes referred to as the point of information redundancy. Although the concept of data saturation can be considered problematic in qualitative research [22], we considered this to have occurred when no new refinements to codes were made for at least three interviews. Data were managed using the qualitative analysis software package NVivo 10 (QSR International). Thematic analysis was selected to analyze interview transcripts, as this helps to provide insights by moving from a broad reading of the data to the conceptualization of codes and themes, followed by their interpretation [22]. The approach used was not considered purely inductive nor deductive but instead a blend of both approaches [22]. Each transcript was read several times to achieve familiarity by noting meanings and patterns. Initial codes were generated from each data item, and mind maps were created to identify the links between codes and possible overarching themes. Codes were then organized into meaningful subthemes and main overarching themes that captured the essence of the codes associated with them. Themes were reviewed and refined by reviewing each data item within a theme to ensure coherence.

RR, a doctoral student, collected and analyzed the data. A total of 5 transcripts were independently analyzed by a second author (FW) to allow collaborative discussion about the data and facilitate the interpretation of findings. Both authors maintained an awareness of how their personal characteristics and values may have influenced the data collection or analysis. For example, RR and FW are not medically trained and thus may not fully understand the clinical implications of the data. Participants knew that RR was also interviewing other cancer clinicians, possibly from the same clinic or hospital. Therefore, RR was aware of how this might have influenced participants' trust and openness during the interviews and made every effort to build rapport and trust before the interview and to make the participants feel comfortable and at ease. RR assured participants that the interviews were confidential and that their views and opinions would not be discussed with other clinicians or their patients.

Results

Overview

In total, 20 interviews were conducted with 22 clinicians between June 2014 and November 2014. A total of 4 CNSs chose to be interviewed in pairs stating time constraints in the clinic; however, the remaining clinicians participated in individual interviews. The average length of the interviews was 27 minutes (range 20-39 min).

Sample Characteristics

Participant characteristics are presented in Table 1. Of 22 clinicians, 12 (55%) were female and 10 (45%) were male. Overall, 36% (8/22) of the participants were CNSs, 23% (5/22) were consultant oncologists, 14% (3/22) were consultant surgeons, 23% (5/22) were trainee surgeon or oncologists, and 4% (1/22) were palliative care clinician. Of 22 clinicians, 7 (32%) were from urological cancer clinics, 6 (27%) were from colorectal cancer clinics, 5 (23%) were from gynecological cancer clinics, 3 (14%) were from breast cancer clinics, and 1 (4%) working in palliative care across subspecialities. All participants reported that they owned a smartphone or tablet computer.

Table 1. Sample characteristics.

ID (code)	Occupation	Cancer clinic
P1 (Onc[a])	Oncologist	Gynecology
P2 (Onc)	Oncologist	Breast
P3 (Onc)	Oncologist	Breast
P4 (PCC[b])	Palliative care clinician	All types
P5 (CNS[c])	Cancer nurse specialist	Breast
P6 (TOnc[d])	Trainee oncologist	Gynecology
P7 (CNS)	Cancer nurse specialist	Gynecology
P8 (CNS)	Cancer nurse specialist	Gynecology
P9 (CNS)	Cancer nurse specialist	Colorectal
P10 (CNS)	Cancer nurse specialist	Colorectal
P11 (Sur[e])	Surgeon	Colorectal
P12 (Onc)	Oncologist	Colorectal
P13 (TSur[f])	Trainee surgeon	Colorectal
P14 (Onc)	Oncologist	Gynecology
P15 (TSur)	Trainee surgeon	Urology
P16 (Sur)	Surgeon	Colorectal
P17 (TSur)	Trainee surgeon	Urology
P18 (CNS)	Cancer nurse specialist	Urology
P19 (Sur)	Surgeon	Urology
P20 (CNS)	Cancer nurse specialist	Urology
P21 (CNS)	Cancer nurse specialist	Urology
P22 (TSur)	Trainee surgeon	Urology

[a]Onc: oncologist.

[b]PCC: palliative care clinician.

[c]CNS: cancer nurse specialist.

[d]TOnc: trainee oncologist.

[e]Sur: surgeon.

[f]TSur: trainee surgeon.

Interview Themes

From the interviews, 4 key themes were identified: (1) anticipated acceptability, (2) suggested app features, (3) anticipated benefits of app use, and (4) potential disadvantages or anticipated barriers to app use. Participants are identified with "P" followed by their identification number and the abbreviations of occupations listed in Table 1 (eg, P1 [Onc] is Participant 1, oncologist).

Theme 1: Anticipated Acceptability

Most clinicians reported that they do not currently use smart technology with their patients in consultations; however, 2 clinicians used apps to assist in explaining a patient's condition to them. Most clinicians anticipated that it would be acceptable for patients to use a cancer app in consultations, reporting that patients already bring printed information or written question lists and that some use their smartphones to make notes during consultations:

> *Patients bring bits of paper, articles, all sorts of things. I mean, I think the patient population is changing...it's just a screen with information on it really isn't it? So I think, you know, the delivery is not critical...patients write things down quite a lot now. I think if patients did something on the app as opposed to the writing it down, I don't think it makes any difference.* [P19, surgeon]

In contrast, 2 participants suggested that some older clinicians might perceive patients' use of an app in consultations to be socially unacceptable and would resist the use of this type of technology in consultations. However, none of the senior clinicians in this study reported this to be an issue:

There are still, I'm sure the older clinicians...they might, they might have a big resistance to it. [P22, trainee surgeon]

Theme 2: Suggested App Features

Clinicians suggested including the types of information most commonly requested by patients in consultations in an app for patients, such as information on the types of cancers and investigations, treatment options and side effects, cancer symptoms, recovery, and potential long-term effects:

> *...Things like why the investigations have been carried out, why we need to carry out extra tests, information about treatments, possible side effects and what psychological support is out there...and probably information on how to look after yourself as well. I mean smoking cessation, diet, stuff like that. Because a lot of patients ask that.* [P21, cancer nurse specialist]

Clinicians suggested including links to credible cancer information websites to signpost patients to reliable information, as they were aware that patients can often struggle to find reliable information outside of consultations, particularly on the internet:

> *I think if the patients are getting good information, so you know if this app is directing them to the right websites and everything...lots of patients go on the Internet and Google breast cancer and you get millions of hits back and they don't know what is good information and what is bad information, so I think if this [the app] is going to point them in the right direction, clinicians would be up for that totally.* [P5, cancer nurse specialist]

Some clinicians felt that an app could also help patients to organize their care and suggested linking the app to the calendar feature on a smart device to remind patients of upcoming appointments. A medication log for patients to record their medication was also suggested by some clinicians:

> *I mean, I really like the idea of prompts and the diary and reminders, I mean patients forget, so maybe a day in advance to just remind them and then it reduces our DNAs [Did Not Attend]. Or a week before, "Have you asked your boss for that time off? Have you booked transport?" Or something like that. You get text messages for your bank appointments don't you? Why not for your cancer appointments?...So act maybe as a diary manager.* [P13, trainee surgeon]

Clinicians suggested a feature that could store contact details to enable patients to contact their clinicians quickly where required, as they explained that patients often forget their designated nurse or consultant or lose their contact details:

> *The name of the clinicians that are looking after them, half the time they can't remember contact details for their clinicians. That would be really useful. Summary of, you know, this is your diagnosis, this is your consultant, this is the number, the name of the nurse specialist, this is the name of the stoma nurse, these are their contact details, these are their email*

addresses, this is the secretary's number. [P13, trainee surgeon]

Many clinicians discussed that patients forget to ask questions in consultations and that this can lead to unmet information needs. Therefore, a question prompt list (QPL) feature was suggested to remind patients to ask important questions during consultations:

> *Many patients come and say to us, at the initial the shock of the diagnosis, they can't think about anything else. So if they can formulate some questions, they won't forget to ask, and they can keep their smartphone in front of the consultation, and keep ticking the boxes. That um, that'll be useful actually for them, so they don't forget anything.* [P15, trainee surgeon]

Many clinicians reported that they often use anatomical diagrams or images in consultations to help patients understand the information they are given, such as diagrams showing the location of the cancer and how operations will be performed. As a result, clinicians suggested an app feature that includes anatomical diagrams and images that could be used by clinicians to facilitate communication of information to patients in consultations:

> *Having pictures really helps...trying to explain what we are trying to do in terms of the operation as well, sometimes having a diagram actually makes a difference. And there are some apps where you could then look at your staging pictorially, that might be helpful to include in an app.* [P14, oncologist]

Clinicians also suggested including app features that would increase patients' awareness of, and access to, patient support, as they explained that clinicians often forget or do not have time to provide this type of information. Suggestions included contact numbers of cancer charities and information on psychological support, such as support groups:

> *Erm, relevant information on how to find help, you know how to get extra support like erm, like a forum...or group support...or MacMillan numbers, Tenovus Cancer Care numbers.* [P18, cancer nurse specialist]

> *Um, local support groups...as well as national groups. I think more of the supportive side that perhaps we...we can't really spend a huge amount of time on. Because I think we're quite good at treating the disease and talking about the scientific part of the disease but it's the, like the supportive aspect that we can't provide enough time for, that I think would be of greatest benefit to a patient.* [P17, trainee surgeon]

Theme 3: Anticipated Benefits of App Use

Clinicians anticipated several potential benefits of an app that would help patients meet their information needs. The most commonly anticipated benefit of an app was a more informed patient. Clinicians suggested that an app could provide patients with a better understanding of cancer before consultations, which would enable them to have a more detailed discussion. In turn,

clinicians expected that a more informed patient might develop more questions to ask:

> I think it would have benefits in that the patient would be more prepared and therefore understand more about their own disease before their consultations, which would help. It may be that they ask more questions as a result of it. [P21, cancer nurse specialist]

A minority of clinicians also anticipated that patients' increased knowledge could lead to an increased sense of control over their lives by being able to plan ahead, which, in turn, might reduce their anxiety:

> What do you think the benefits would be in the long term for patients? [Interviewer]

> It just gives them more control, um I think when they feel more control that helps them because it's their lack of control, their lack of being able to plan, things just happening around them, and at least if you know what's happening, so many patients come in and say, "Even though you kind've given me bad news, I feel better leaving than I did coming because I know what's happening and I know you've got a plan." [P1, oncologist]

Clinicians anticipated that this type of app could also improve communication between patients and clinicians during consultations. It was thought that a QPL feature could act as an agenda for the consultation and, in turn, facilitate a more structured discussion while encouraging patients to communicate their concerns:

> The first steps I think you need to take are fairly simple and that's things like frequently asked questions...The app can be introduced, obviously, at various different stages, but certainly prior to the second visit, if they download the app and they have been on to answer those, ask those questions,...common questions that are asked...frequently asked questions, they may want to go through those before they then come back and see you a second time, or even the first time. [P12, oncologist]

> Well I think clearer communication actually, knowing you're following the patient's agenda and what their problems are enables you to, you know, clarify things quicker, and to answer questions better. [P4, palliative care clinician]

Clinicians suggested that this might improve the efficiency of the consultation and increase clinicians' confidence that they have met the patients' information needs:

> Hopefully it could form a very clear structure for a consultation which, you know, means it's probably more time efficient. Consultations can be quite long sometimes, particularly when you're trying to get the complex situation across, so I think there are benefits in terms of time. [P11, surgeon]

Theme 4: Potential Disadvantages of and Barriers to App Use

On the other hand, a minority of clinicians were concerned that an app for patients could potentially increase their workload and the length of consultations if it encourages patients to contact clinicians (via a contacts feature) or ask questions in consultations (via a QPL feature). However, clinicians believed that the many potential advantages of such an app would outweigh this potential disadvantage:

> It could potentially slow down consultations, we have to bear that in mind. But I think in the end of you have a quality consultation, in the end it probably speeds things up overall. As well as improves the quality of that consultation. [P12, oncologist]

A small number of clinicians were also concerned that an app might hinder communication during consultations by distracting patients, who may then miss information. Similarly, some clinicians felt that app use during consultations could potentially reduce patients' nonverbal communication, which is used by clinicians to assess whether patients have understood the information:

> If it doesn't divert the consultation...because they are constantly looking at the app, and they won't be able to listen to what we say, and they may even miss it. So I presume that's the downside of it actually...I personally don't like um, somebody sitting in front of me and they're just on the smartphone ticking boxes, not listening to what I say, because a lot of it...face to face, eye contact on the person, and from the eye contact I can see whether the patient has understood it or not. [P15, trainee surgeon]

Clinicians anticipated several potential barriers to the use of this type of app in practice. The main anticipated barriers were patients' age and prior experience with smart technology, where many clinicians believed that many older patients lacked the knowledge and experience to be able to use, or want to use, an app. In addition, clinicians expected that some older patients might have problems with physically using an app because of poor eyesight and/or dexterity:

> I think in general, and it is a vast generalization, cancer patients tend to be older patients and the older patients tend not to be able, quite so versed, in using apps and all that sort of stuff. So I think at the moment you might not get a great uptake. Give it ten years and I think yeah, I think everyone will be using it and the people who are in their sixties, seventies now, who are then going on to get cancer in their eighties and things...it'll be very useful for. [P22, trainee surgeon]

> You have the very practical problems with patients of this age group because their eyesight is often poor, their dexterity might not be that good, you know on an iPhone rather than an iPad. [P13, trainee surgeon]

Some clinicians were concerned that the cost of a smart device would be a barrier for some older patients who do not currently

have access to one. However, clinicians expected that these patients could gain access to a device via their family or friends:

> *It would be sort of potentially be a barrier you know for the older ones who may not have the equipment or want the equipment but then again may have family members that would be willing.* [P20, cancer nurse specialist]

Some clinicians were concerned about the confidentiality of patients' information on an app, particularly due to cancer being a sensitive topic:

> *I think storage of information, sensitive information is the main issue. If they have a smartphone or, you know, a tablet device that isn't locked then potentially if you put sensitive information on it, it could be easy to view, so you might need to put a password onto the app.* [P14, oncologist]

Finally, some clinicians indicated that a minority of patients appear to have an avoidant coping approach to their illness and so do not wish to have extensive information. As such, clinicians anticipated that this type of patient would not want to use this type of app:

> *One thing I guess I would say is that you're always going to get the patient that will do everything, and you're always going to get the patient that will do nothing. There are those patients that will use everything and everything that they can access they will do...and others won't, you know?* [P5, cancer nurse specialist]

Discussion

Principal Findings

To our knowledge, this is the first study to explore the views of cancer clinicians regarding the development of a novel app intervention to help patients with cancer to meet their illness-related information needs in noninpatient settings. The primary aim of this study is to understand clinicians' views on the value of this type of intervention, the type of app that they anticipate to be most useful for patients, and whether clinicians would support the use of an app in clinical practice. Overall, clinicians felt it would be acceptable for patients to use such an app to support their information needs, including consultations. Clinicians' awareness of the barriers to information exchange during, and outside of, consultations with patients were reflected in the type of app features they suggested. The benefits of this type of app were anticipated to be a more informed patient, an increased sense of control for patients, better doctor-patient communication, and a more efficient and effective consultation. In contrast, an increase in clinicians' workload and poorer communication in consultations, which depended on the included app features, were identified as potential disadvantages, although clinicians believed that these would be outweighed by the benefits. The anticipated barriers to app use included patients' age and prior experience with smart technology, access to smart devices, confidentiality of information, and an avoidant coping approach to their condition. Overall, the views of

clinicians largely mirror the views of patients with cancer on this type of intervention [13].

Most clinicians reported that they had not previously used an app to assist them with patients in consultations; however, all clinicians owned a smart device and were familiar with this technology. This finding is likely because of the lack of availability of patient-facing apps that are reliable and developed by researchers or health organizations [23,24], as an increasing number of clinicians use apps for a wide variety of work-related tasks [25]. Importantly, clinicians appeared to be supportive of the development of an app to help patients meet their information needs. This finding is consistent with previous studies that reported clinicians' positive perceptions and expectations for mobile interventions for other chronic health conditions [26-28].

Clinicians' suggestions for app features reflected their awareness of barriers to information exchange during and outside of consultations with patients with cancer. First, clinicians suggested app features that would help patients to better self-manage their condition by providing detailed information about their cancer. This type of information might help prevent unnecessary hospitalizations [29]. Clinicians also suggested links to reliable websites to help patients source accurate information. As the internet is now a common health information resource, studies have highlighted the importance of guiding patients to filter accurate health information [30,31]. This could help avoid patients becoming unnecessarily anxious and prolonging consultations with their clinicians, leaving room for more informed discussions. Clinicians also suggested additional app features that were not thought of by patients themselves in our previous qualitative study [13], including a feature to help them organize their care, such as appointment reminders, a medication log, and a feature to store clinicians' contact details.

Second, clinicians suggested app features to enable patients with cancer to overcome barriers to communication in consultations, such as a QPL to help patients remember to ask important questions. Clinicians felt that this type of feature would help patients to make their information needs clear to the clinician, instead of passively relying on the clinician to relay information. It is important for patients to voice their concerns and provide relevant information for their clinicians in order for clinicians to formulate the correct diagnosis and prescribe or amend treatment for patients [32]. Clinicians also suggested a feature to assist *them* in imparting information to patients more effectively using diagrams or images; however, this feature might be better placed in a clinician-facing, rather than patient-facing, app.

Third, clinicians felt that an app could help with raising awareness of, and signposting patients to, cancer support services, such as contact numbers for cancer charities or information on support groups, which they felt would be beneficial for patients. This finding is supported by previous studies on the benefits of social support during cancer [33]. Clinicians explained that they were not often able to impart this information because of limited time in consultations; thus, this presents an example of how technology can help to relieve

pressure on the NHS services and help to meet information needs of patients with cancer.

The most commonly anticipated outcome of this type of intervention was a more informed patient, which is consistent with patient expectations [13]. Clinicians further highlighted the benefits that they themselves might receive as a result of using a patient-facing app, including a more structured and efficient consultation. However, although some previous studies on the use of paper-based QPLs in cancer consultations have reported a decrease in consultation length, the evidence is generally mixed [34,35]. Indeed, some clinicians were concerned that this type of app could lead to an increased workload if the app increased patient contact and question-asking. Some previous studies on clinicians' perceptions of their involvement in mobile symptom-monitoring interventions for patients with cancer have reported that increased workloads and technical issues were problematic in clinical practice [17,36,37]. However, these interventions were used equally by clinicians and patients, whereas a patient-facing app that is used independently of the clinician would limit the potential impact on clinicians' workloads. In addition, clinicians in this study believed that the advantage of an improved consultation might outweigh the potential increase in workload. Subsequently, studies of digital and paper-based patient-facing interventions that are used *during* allocated consultation times have been found to be acceptable by clinicians [38,39].

A number of clinicians in our study were concerned that an app might hinder communication during consultations by distracting patients and that some older clinicians might be particularly resistant to this change in consultations. These findings are unsurprising, as previous studies have reported that some clinicians perceive the use of a smartphone in clinical settings to be unprofessional because of the association of mobile phones with poor quality social contact [40,41]. However, as stated earlier, previous studies have shown that digital interventions that are used by patients in consultations are acceptable by clinicians in practice [38,39]. In addition, senior clinicians were interviewed for this study and found the idea of an app for patients with cancer to be acceptable.

Other potential barriers to app use identified by clinicians included patients' age and experience with smart technology, access to smart technology and the internet, and confidentiality of patients' medical information, which were also concerns of patients with cancer [13] and clinicians of previous studies of mobile interventions for chronic health conditions [26-28]. However, clinicians recognized that patients' age and prior experience with smart technology is only a temporary potential barrier and an app that would not require the input of sensitive information might circumvent concerns of confidentiality.

Implications

This study presents novel findings on the views of cancer clinicians regarding the development of an app for patients with cancer, including the potential outcomes and benefits of this type of intervention. In line with the MRC framework [14] and person-based approach [15] for the development of complex interventions in health care, these findings can be used, in combination with the findings from our patient study [13], to

develop intervention objectives and inform the selection of app features. For example, based on clinicians' views reported in this study, and in support of patients' views, the objectives of the intervention might be to facilitate the development of patients' understanding and self-management of their condition, and it is anticipated that this could be achieved by including app features that enable patients to (1) better self-manage their condition by sourcing accurate information outside of consultations and improving the organization of their care through the use of reminders and logs, (2) overcome barriers to communication in consultations by encouraging question-asking and participation in their care, and (3) identify and access cancer support services that will provide further information and support where needed (such as psychological support). This study identified the potential benefits of a patient-facing app for the clinicians themselves and the potential disadvantages of, and barriers to, this type of app. These findings can be considered during app design to optimize its uptake, usability, and usefulness [15]. For example, clinicians were concerned that patients could be distracted in consultations, so an objective would be to design an app that will only be referred to briefly in consultations but not actively used throughout. Similarly, to circumvent some clinicians' concerns about the confidentiality of information, a further objective would be to design an app that does not require the input of sensitive information.

Limitations

A varied sample of clinicians, including a variety of roles, settings, patient types, and career lengths as well as a balance of both genders, is a strength of this study. However, there were several limitations to consider. It was not possible to calculate the response rate for this study nor to collect the key characteristics of those who declined to participate. In addition, all clinicians were smart technology owners. Therefore, the sample may not be representative of the general population of clinicians and may have included those with more favorable perceptions of an app than those who chose not to participate. However, statistics suggest that ownership of smart technology among clinicians is common, where up to 90% of health care professionals own a smart device, and new technologies will continue to be integrated into health care services [42,43]. Joint interviews with 4 clinicians may have prevented these participants from discussing important issues that they might have talked about in a separate interview; however, most interviews were conducted individually at length.

Providing examples of types of app features that could be used by patients with cancer before beginning the interview might have influenced some participants' responses because of social desirability. The risk of this bias was minimized as the interviewer explained that all opinions were valued, both positive and negative, to develop an app that would be most useful for future patients.

Finally, participants were asked to reflect on a hypothetical scenario in which an app could be available for patients in the future. Participants were also asked to anticipate *the potential* benefits and disadvantages of, and barriers to, a hypothetical app. As a result, the data are not necessarily grounded in

concrete experience and therefore may not translate into engagement.

Conclusions

To our knowledge, this study is the first to explore the views of cancer clinicians regarding an app that aims to help patients with cancer meet their illness-related information needs in noninpatient settings. Clinicians appear to be supportive of the development of an app and its use in consultations and suggested the types of app features that they anticipate to be useful for patients; specifically, an app that would enable patients to better self-manage their condition, overcome barriers to communication in consultations, and identify and access cancer support services. The potential outcomes of this type of intervention were highlighted, including the benefits for both the patients and clinicians, and the potential benefits of this type of intervention appeared to outweigh clinicians' few minor concerns.

Authors' Contributions

RR, PK, KB, and FW were responsible for the concept, design, and conduct of the study. RR was responsible for data collection and analysis as well as for manuscript preparation. FW was responsible for double coding a subset of the interview data. FW, PK, and KB reviewed the manuscript drafts for intellectual content. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Clinician topic guide.
[DOCX File , 16 KB - cancer_v7i2e23671_app1.docx]

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Abbreviations

CNS: cancer nurse specialist
MDT: multidisciplinary team
MRC: Medical Research Council
NHS: National Health Service
QPL: question prompt list

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Original Paper

Data Integration to Improve Real-world Health Outcomes Research for Non–Small Cell Lung Cancer in the United States: Descriptive and Qualitative Exploration

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Abstract

Background: The integration of data from disparate sources could help alleviate data insufficiency in real-world studies and compensate for the inadequacies of single data sources and short-duration, small sample size studies while improving the utility of data for research.

Objective: This study aims to describe and evaluate a process of integrating data from several complementary sources to conduct health outcomes research in patients with non–small cell lung cancer (NSCLC). The integrated data set is also used to describe patient demographics, clinical characteristics, treatment patterns, and mortality rates.

Methods: This retrospective cohort study integrated data from 4 sources: administrative claims from the HealthCore Integrated Research Database, clinical data from a Cancer Care Quality Program (CCQP), clinical data from abstracted medical records (MRs), and mortality data from the US Social Security Administration. Patients with lung cancer who initiated second-line (2L) therapy between November 01, 2015, and April 13, 2018, were identified in the claims and CCQP data. Eligible patients were 18 years or older and received atezolizumab, docetaxel, erlotinib, nivolumab, pembrolizumab, pemetrexed, or ramucirumab in the 2L setting. The main analysis cohort included patients with claims data and data from at least one additional data source (CCQP or MR). Patients without integrated data (claims only) were reported separately. Descriptive and univariate statistics were reported.

Results: Data integration resulted in a main analysis cohort of 2195 patients with NSCLC; 2106 patients had CCQP and 407 patients had MR data. The claims-only cohort included 931 eligible patients. For the main analysis cohort, the mean age was 62.1 (SD 9.27) years, 48.56% (1066/2195) were female, the median length of follow-up was 6.8 months, and for 37.77% (829/2195), death was observed. For the claims-only cohort, the mean age was 66.6 (SD 12.69) years, 52.1% (485/931) were female, the median length of follow-up was 8.6 months, and for 29.3% (273/931), death was observed. The most frequent 2L treatment was immunotherapy (1094/2195, 49.84%), followed by platinum-based regimens (472/2195, 21.50%) and single-agent chemotherapy (441/2195, 20.09%); mean duration of 2L therapy was 5.6 (SD 4.9, median 4) months. We describe challenges and learnings from the data integration process, and the benefits of the integrated data set, which includes a richer set of clinical and outcome data to supplement the utilization metrics available in administrative claims.

Conclusions: The management of patients with NSCLC requires care from a multidisciplinary team, leading to a lack of a single aggregated data source in real-world settings. The availability of integrated clinical data from MRs, health plan claims, and other sources of clinical care may improve the ability to assess emerging treatments.

Introduction

Background

Real-world health outcomes research is often challenged by data insufficiency resulting from studies using a single data source and/or short durations [1-3]. For example, medical records (MRs) generally do not contain details of care outside of the point of service of the single health care provider, claims data contain few variables related to clinical outcomes, and registries often do not contain complete longitudinal data [4-7]. The integration of clinical data from different sources such as MRs [8], disease registries, or quality initiatives with large administrative claims repositories has been shown to increase the volume and quality of available data [9-12]. For example, integrated data allow the inclusion of important clinical factors when analyzing health care utilization and costs, as recorded in claims [13]. Such integrated observational data sets have also been used to generate predictive algorithms to better identify patients with cancer [14-17] and their disease characteristics [18-20].

Lung cancer is the second most common cancer in the United States, with approximately 230,000 new diagnoses in 2020 [21]. It is the leading cause of cancer-related deaths in the United States, projected at 136,000 in 2020 [22]. Non–small cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancer cases [23]. Treatment modalities for advanced and/or metastatic NSCLC include radiotherapy, chemotherapy, targeted therapy, or a combination therapy [24]. Over the last few years, second-line (2L) treatment options have expanded rapidly with the introduction of immune checkpoint and epidermal growth factor receptor inhibitors and associated predictive biomarkers [25].

Treatment sequencing in the setting of NSCLC is not well characterized, largely because of the sparseness of applicable studies, which tend to be limited by inadequate data. This study was designed based on the rationale that a combination of retrospective data from multiple sources, such as MRs, administrative claims, and care quality initiatives, would provide a solid foundation for observing and characterizing real-world treatment outcomes at a lower cost than a traditional site-based prospective approach.

Objectives

The central objective of this study is to create an integrated database from several complementary sources and to assess the feasibility and effectiveness of these integrated observational data for health outcomes research. Patient characteristics and outcomes were described to evaluate the enrichment attained through integration. This analysis presents a descriptive summary of the final study cohort that was obtained for the study.

Methods

Study Design

RESOUNDS (Real-World Treatment Sequences and Outcomes Among Patients With Non-Small Cell Lung Cancer) was a retrospective, observational cohort study that integrated data from 4 sources: administrative claims from the HealthCore Integrated Research Database (HIRD), clinical data from a quality initiative called the Cancer Care Quality Program (CCQP), clinical data extracted from patients' MRs obtained from treating providers, and all-cause mortality data from the Death Master File of the US Social Security Administration. Details of the RESOUNDS study design and each of these data sources have been published previously [26]. The study protocol was approved by the New England Institutional Review Board before the commencement of data collection activities. This study was conducted in full compliance with the relevant provisions of the Health Insurance Portability and Accountability Act.

Patient Identification

Patients diagnosed with lung cancer who initiated 2L therapy between November 01, 2015, and April 13, 2018, were identified in the HIRD and CCQP data. Patients were required to receive 1 of the following 2L therapies alone or in combination: atezolizumab, docetaxel, erlotinib, nivolumab, pembrolizumab, pemetrexed, or ramucirumab. This subset of the original set of therapies listed in the protocol [26] was selected based on treatment guidelines and observed frequency of use during the study period, to ensure sufficient sample sizes to evaluate treatment patterns. Patients aged under 18 years at the start of 2L therapy were excluded. Due to the absence of specific International Classification of Diseases, Ninth and Tenth Revision, Clinical Modification codes for NSCLC, cancer type was confirmed via CCQP or MR data. Follow-up for all-cause death events was conducted through March 31, 2019.

Integrated Database Development

Patients were first identified in the CCQP data, where information on the type of lung cancer (NSCLC or not) was available, and information for patients with a record of 2L therapies of interest was retained. All cancer stages were included in the analyses. Second, lung cancer diagnosis and treatment claims were used to identify patients with 2L treatment in the HIRD. Patients who also had claims for other primary cancers were retained. All patients identified in the CCQP data were also included in the HIRD sample; patients who appeared in the HIRD but not the CCQP were retained. Third, copies of MRs were obtained from selected patients' 2L prescribers (focusing on oncologists, as identified in the HIRD) and screened for qualification (presence of evidence for NSCLC and that the index treatment was used as therapy for NSCLC). Regulatory and operational requirements for inclusion in this process consisted of patients having a fully insured status (vs administrative services only) and presence of complete contact

information for the 2L prescriber. Once obtained and screened, clinical information was abstracted from each record by trained health information management technicians using a standardized form. The target sample size for MR abstraction was 398 patients, based on the expected feasible accrual over the 2.5-year patient identification period.

Data from each source were accumulated in 3 consecutive waves to continuously build the database. After each MR abstraction wave was complete, the claims and CCQP data were refreshed to the most current date at that point to obtain additional follow-up outcomes. The integrated data were used to establish the main analysis cohort, consisting of patients with both claims and either CCQP or MR data (or both). Eligible patients from the HIRD who did not appear in the CCQP and for whom no MRs were obtained were included in the claims-only cohort (these patients could have any type and stage of lung cancer).

Patient Characteristics and Outcomes

Demographic and clinical characteristics, treatment patterns, and survival outcomes were recorded. Baseline was defined as the 6 months before the index date (start of 2L therapy). The Quan-Charlson Comorbidity Index (QCI) was calculated, excluding lung cancer and metastatic carcinoma [27]. A patient was considered to be on the same line of therapy until new agents were added (except for maintenance and platinum agent switching), a gap of >90 days between treatments, end of follow-up, or (for 2L and higher) discontinuation. The percentage of patients flagged as deceased (for all causes) was calculated using a combination of the Death Master File, a hospitalization discharge code of *deceased* from claims, and mortality recorded from the health plan enrollment files.

Statistical Analysis

Univariate statistics including means, SDs, and medians for continuous variables and relative frequencies and percentages for categorical variables were reported. No hypothesis testing was performed. Statistical analysis was performed using SAS version 9.3 (SAS Institute Inc).

Results

Data Integration and Patient Selection

Following data integration, the main analysis cohort consisted of 2195 patients. All patients had claims data, 2106 patients had CCQP data, and 407 patients had MR data (Table 1).

Approximately 47.14% (997/2115) of patients fulfilled regulatory and operational requirements for their MRs to be requested from their 2L-prescribing providers; for 54.5% (543/997) of those, the records were obtained. A large number of MRs were not obtained as outreach was stopped after the planned sample size (n=398) was achieved; others could not be obtained because the provider did not have a record of the particular patient or because of inability to contact the provider. Among the obtained records, the most frequent reason for exclusion was the absence of confirmation of NSCLC (43/543, 7.9% of the obtained records). The claims-only cohort comprised 931 patients. Table 2 details what variables were obtained from which source.

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Table 1. Patient selection.

Criteria	First wave sample (patients, n)	Second wave sample[a] (patients, n)	Third wave sample (patients, n)	Final sample[b] (patients, n)
Step A: Patients identified from CCQP[c]				
Step 1: Patients with non–small cell lung cancer	295	760	1428	__[d]
Step 2: From step A1, patients with 2L[e] therapy[f]	174	469	863	—
Step B: Patients identified from claims				
Step 1: Patients with lung cancer claim before start of first-line therapy	640	1058	2187	—
Step 2: From step B1, patients with 2L therapy	368	600	1127	—
Step C: Combined patients from CCQP and claims				
Step 1: From A2 and B2, unique patients with 2L therapy	423	756	1732	2115
Step D: Patients considered for MR[g] review				
Step 1: Patients used for MR outreach	149	279	718	997
Step 2: Number of patient MRs obtained	102	194	349	543
Step 3: Number of failed MRs[h]	15	20	45	65
Step 4: Not used (target had been met previously)	—	—	62	62
Step 5: Final MRs used	87	174	242	416
Step E: Main analysis cohort (patients with claims and either CCQP or MR data)	272	791	1446	2195[i]
Step 1: Patients with CCQP data	223	748	1399	2106
Step 2: Patients with MR data	85	168	239	407
Step F: Claims-only cohort (patients with claims data only, no CCQP or MR data)	377	243	659	931[i]

[a]Second wave included all patients from the first wave.

[b]The final sample removed duplicates that were included in >1 wave. For those patients, information from the most recent wave was used for analysis.

[c]CCQP: Cancer Care Quality Program.

[d]Not available.

[e]2L: second-line therapy.

[f]2L medications of interest included atezolizumab, docetaxel, erlotinib, nivolumab, pembrolizumab, pemetrexed, or ramucirumab.

[g]MR: medical record.

[h]Medical records excluded due to one or more of the following: no documentation of lung cancer, no documentation of non–small cell lung cancer, and patient mismatch (missing or unmatched name, sex, or date of birth; wrong timeframe; inconsistent clinical information).

[i]These are the final sample sizes for the 2 cohorts of interest.

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Table 2. Variable sourcing by database type.

Variable	HealthCore Integrated Research Database (claims)	Cancer Care Quality Program	Medical record
Length of follow-up	✓[a]	—[b]	—
Age	✓	—	✓
Gender	✓	—	✓
Health plan type	✓	—	—
Geographic region of patient residence	✓	—	—
Race/ethnicity	—	—	✓
Weight, height, and BMI	—	—	✓
Histology	—	✓	✓
Staging	Y[c]	✓	✓
Treating physician specialty	✓	—	—
Smoking status	—	—	✓
Performance status (Eastern Cooperative Oncology Group)	—	✓	✓
Comorbidities	✓ (Quan-Charlson Comorbidity Index, secondary cancers)	—	—
Mortality	Z[d]	—	—

[a]Indicates variable was sourced from the data set listed in the column header.

[b]Variable was not sourced from the data set listed in the column header.

[c]Indicates the presence of claims for metastatic disease.

[d]This was based on the Death Master File data from the US Social Security Administration.

Demographic Characteristics at Baseline

In the main analysis cohort, mean age was 62.1 (SD 9.27) years and 48.56% (1066/2195) were female (Table 3), whereas in the claims-only cohort, mean age was 66.6 (SD 12.69) years and 52.1% (485/931) were female. More than two-thirds (1498/2195, 68.25%) of the main analysis cohort were from the Midwest and South, and 23.01% (505/2195) had Medicare Advantage or Supplemental and Part D coverage. In the claims-only cohort, patients were almost equally distributed across the West, Midwest, and South, with a smaller proportion (164/931, 17.6%) from the Northeast; almost half (457/931, 49.1%) had Medicare Advantage coverage. Treating physician specialty based on claims listed oncologists for 67.52% (1482/2195) of the main analysis population and for 30.7% (286/931) of the claims-only sample; this difference is by design as only patients whose 2L-prescribing providers were listed as oncologists were included in the MR phase. Among the 407 patients with MR data, 45.7% (186/407) were White, 3.7% (15/407) were Black, 3.2% (13/407) were other races, and 47.4% (193/407) had no race information. Race was not available in patients without MRs.

Table 3. Demographic characteristics at baseline (on or close to second-line therapy initiation date).

Variables	Main analysis cohort (n=2195)	Claims-only cohort (n=931)
Age at second-line therapy initiation (years), mean (SD)	62.1 (9.27)	66.6 (12.69)
Age categories (years), n (%)		
18-39	22 (1.0)	33 (3.5)
40-64	1509 (68.7)	343 (36.8)
65-74	412 (18.8)	278 (29.9)
≥75	252 (11.5)	277 (29.8)
Female, n (%)	1066 (48.6)	485 (52.1)
Health plan type, n (%)		
Health maintenance organization	769 (35.0)	225 (24.2)
Preferred provider organization	1126 (51.3)	628 (67.5)
Consumer-driven health plan	300 (13.7)	78 (8.4)
Medicare Advantage[a], n (%)	505 (23.0)	457 (49.1)
Affordable Care Act exchange plan, n (%)	550 (25.1)	106 (11.4)
Geographic region of patient, n (%)		
Northeast	344 (15.7)	164 (17.6)
Midwest	815 (37.1)	262 (28.1)
South	683 (31.1)	274 (29.4)
West	353 (16.1)	231 (24.8)
Treating physician specialty, n (%)		
Oncology	1482 (67.5)	286 (30.7)
Pulmonary medicine	34 (1.5)	18 (1.9)
Primary care provider	77 (3.5)	36 (3.9)
Other	481 (21.9)	133 (14.3)
Missing	121 (5.5)	458 (49.2)

[a]Includes Supplemental and Part D plans.

Clinical Characteristics at Baseline

In the main analysis cohort, the mean QCI was 1.6 (SD 1.59). The most frequent comorbidities were dyspnea (1417/2195, 64.56%), chronic pulmonary disease (1125/2195, 51.25%), hypertension (1073/2195, 48.88%), anemia (880/2195, 40.09%), and dyslipidemia (792/2195, 36.08%; Table 4). More than half of the main analysis cohort (1224/2195, 55.76%) had claims for additional or secondary malignancies and 79.41% (1743/2195) had claims for metastatic disease. In the claims-only cohort, the mean QCI was 1.8 (SD 1.69). The most frequently occurring comorbidities were hypertension (565/931, 60.7%), dyspnea (542/931, 58.2%), and dyslipidemia (403/931, 43.3%). Almost three-quarters (681/931, 73.1%) had codes for other malignancies and 67.9% (632/931) had codes for metastatic disease.

In the main analysis cohort, additional clinical information was available via CCQP and/or MRs (Table 5). Among the 407 patients with MR data, 59.2% (241/407) were former smokers, 16.5% (67/407) were current smokers, 14.3% (58/407) were never smokers, and 10.1% (41/407) had no documentation. Height and weight were available for the majority (341/407, 83.8% height; 371/407, 91.2% weight) of patients; mean BMI was 26.1 (SD 6.36). The most common cancer histology was adenocarcinoma (271/407, 66.6%); for most of the remainder, histology was not documented. Metastasis was noted in MRs for 95.1% (387/407) of the patients, most commonly to the lymph nodes (289/407, 71.0%). Eastern Cooperative Oncology Group (ECOG) performance status was available for 96.26% (2113/2195) of the sample, and an ECOG score ≥2 was observed in 21.20% (448/2113) of patients.

Table 4. Clinical characteristics from claims at baseline (over 6 months before second-line therapy initiation date).

Variables	Main analysis cohort (n=2195)	Claims-only cohort (n=931)
QCI[a], mean (SD)	1.6 (1.59)	1.8 (1.69)
QCI categories, n (%)		
0	570 (26.0)	230 (24.7)
1	705 (32.1)	271 (29.1)
2	414 (18.9)	185 (19.9)
3-5	444 (20.2)	212 (22.8)
6+	62 (2.8)	33 (3.5)
QCI comorbidities, n (%)		
Myocardial infarction	112 (5.1)	46 (4.9)
Congestive heart failure	195 (8.9)	111 (11.9)
Peripheral vascular disease	357 (16.3)	186 (20.0)
Cerebrovascular disease	255 (11.6)	100 (10.7)
Dementia	18 (0.8)	10 (1.1)
Chronic pulmonary disease	1125 (51.2)	390 (41.9)
Connective tissue/rheumatic disease	57 (2.6)	32 (3.4)
Peptic ulcer disease	31 (1.4)	13 (1.4)
Mild liver disease	421 (19.2)	162 (17.4)
Moderate or severe liver disease	10 (0.5)	<10[b]
Paraplegia and hemiplegia	50 (2.3)	<10[b]
Renal disease	172 (7.8)	127 (13.6)
Diabetes with chronic complications	96 (4.4)	75 (8.1)
Diabetes without chronic complications	380 (17.3)	211 (22.7)
Malignancy (excluding lung cancer)	1224 (55.8)	681 (73.1)
Metastatic carcinoma	1743 (79.4)	632 (67.9)
AIDS/HIV	<10[b]	<10[b]
Other comorbidities of interest, n (%)		
Anemia (any)	880 (40.1)	376 (40.4)
Anemia due to chemotherapy	323 (14.7)	92 (9.9)
Asthma	166 (7.6)	88 (9.5)
Cardiac dysrhythmias	375 (17.1)	199 (21.4)
Coronary heart disease	410 (18.7)	209 (22.4)
Depression	338 (15.4)	139 (14.9)
Dyslipidemia	792 (36.1)	402 (43.2)
Dyspnea	1417 (64.6)	542 (58.2)
Hypertension	1073 (48.9)	565 (60.7)
Idiopathic fibrosis of the lung	15 (0.7)	<10[b]
Interstitial lung disease	29 (1.3)	<10[b]
Peripheral vascular disease	361 (16.4)	187 (20.1)
Pneumonia	508 (23.1)	151 (16.2)
Pneumonitis	29 (1.3)	16 (1.7)
Pulmonary fibrosis	112 (5.1)	<10[b]

Variables	Main analysis cohort (n=2195)	Claims-only cohort (n=931)
Stroke	255 (11.6)	100 (10.7)
Thyroid disease	272 (12.4)	165 (17.7)
Tuberculosis	<10[b]	<10[b]

[a]QCI: Quan-Charlson Comorbidity Index.

[b]Values <10 have not been reported for patient confidentiality.

Table 5. Clinical characteristics from Cancer Care Quality Program and/or medical records at baseline (on or close to second-line therapy initiation date).

Variables	Main analysis cohort
Information from MRs[a]; valid N=407	
Smoking status, n (%)	
Current smoker	67 (16.5)
Former smoker	241 (59.2)
Never smoker	58 (14.3)
Not documented	41 (10.1)
Presence of number of years smoked, n (%)	201 (49.4)
Number of years smoked, mean (SD)	36.1 (13.48)
Presence of weight, n (%)	371 (91.2)
Weight (pounds), mean (SD)	165.0 (44.48)
Presence of height, n (%)	341 (83.8)
Height (inches), mean (SD)	66.5 (3.88)
Presence of BMI, n (%)	339 (83.3)
BMI, mean (SD)	26.1 (6.36)
Histology, n (%)	
Adenocarcinoma	271 (66.6)
Large-cell carcinoma	9 (2.2)
Bronchioloalveolar carcinoma	2 (0.5)
Mixed	3 (0.7)
Unspecified nonsquamous	2 (0.5)
Other	4 (1.0)
Unknown/not documented	116 (28.5)
Presence of metastasis, n (%)	387 (95.1)
Lymph nodes (thoracic region)	289 (71.0)
Supraclavicular nodes	87 (21.4)
Superior mediastinal nodes	201 (49.4)
Aortic nodes	64 (15.7)
Inferior mediastinal nodes	132 (32.4)
Hilar, lobar, and/or (sub)segmental nodes	199 (48.9)
Bone	190 (46.7)
Other respiratory systems (not trachea)	163 (40.0)
Brain	121 (29.7)
Liver	72 (17.7)
Adrenal gland	59 (14.5)
Number of metastases sites, mean (SD)	3.2 (1.90)
Information from Cancer Care Quality Program and/or MRs; valid N=2195	
Eastern Cooperative Oncology Group performance status, n (%)	2113 (96.26)
0	464 (21.96)
1	1201 (56.84)
2	364 (17.23)
3	74 (3.50)

Variables	Main analysis cohort
4	10 (0.47)
5	0 (0)
TNM[b] stage classification, n (%)	2146 (97.77)
0	0 (0)
1	<10
2	32 (1.49)
3	167 (7.78)
4	1935 (90.17)
Unknown or not documented	<10

[a]MR: medical record.

[b]TNM: tumor/lymph nodes/metastasis cancer staging system.

Length of Follow-Up and Mortality

The mean length of follow-up in months was 7.9 (SD 5.77) for the main analysis cohort (median 6.8) and 9.1 (SD 6.06) for the claims-only cohort (median 8.6). Death (for all causes) was observed in 37.77% (829/2195) of the main analysis cohort and 29.3% (273/931) of the claims-only cohort.

Treatment Patterns

Among the 1974 patients with first-line (1L) treatment information, 69.50% (1372/1974) used platinum-based regimens, 37.69% (744/1974) used pemetrexed-containing regimens, and 16.51% (326/1974) used single-agent chemotherapy (treatment groups are not mutually exclusive; Table 6). The mean duration of 1L therapy was 128 (median 90) days; 56.84% (1122/1974) switched to 2L therapy with a gap ≤90 days and 43.16% (852/1974) had a gap of >90 days before initiating 2L. The most frequent 2L treatment was immunotherapy (1094/2195, 49.84%), followed by platinum-based regimens (472/2195, 21.50%). The mean duration of 2L therapy was 169 (median 121) days; this variable was right-censored due to loss of follow-up. For patients with third- and/or fourth-line therapy (n=731 and 265, respectively), platinum-based regimens were used most frequently (418/731, 57.2% of third-line patients and 139/265, 52.5% of fourth-line patients), and 21.6% (158/731) of third-line patients and 20.4% (54/265) of fourth-line patients also used immunotherapy. Among the 269 patients who received radiation therapy after the initial diagnosis of NSCLC, 46.1% (124/269) patients received radiation therapy as a palliative treatment.

Table 6. Treatment patterns from Cancer Care Quality Program and claims, measured from the initiation of first-line treatment to the end of follow-up.

Therapy	Main analysis cohort (N=2195)
1L[a] therapy, n (%)	1974 (89.9)
Chemotherapy, n (%)	
Platinum-based regimen	1372 (69.5)
Nonplatinum-based regimen	90 (4.6)
Pemetrexed-containing regimen	744 (37.7)
Single-agent chemotherapy	326 (16.5)
Immunotherapy, n (%)	
PD-1/PD-(L)1[b] inhibitor–containing regimen	241 (12.2)
Targeted therapy, n (%)	
EGFR[c] TKIs[d]-containing regimen	98 (5.0)
EGFR mAb[e]-containing regimen	11 (0.6)
VEGF[f] mAb-containing regimen	308 (15.6)
ALK[g] inhibitor	21 (1.1)
Duration of time (days) between initial lung cancer diagnosis and 1L treatment, mean (SD)	134.6 (380.98)
Duration (days) of 1L therapy, mean (SD)[h]	127.7 (142.75)
Treatment change, n (%)	
Gap of ≤90 days before 2L[i]	1122 (56.8)
Gap of >90 days before 2L	852 (43.2)
2L therapy, n (%)	2195 (100.0)
Chemotherapy	
Platinum-based regimen	472 (21.5)
Nonplatinum-based regimen	221 (10.1)
Pemetrexed-containing regimen	344 (15.7)
Single-agent chemotherapy	441 (20.1)
Immunotherapy	
PD-1/PD-L1 inhibitor–containing regimen	1094 (49.8)
Targeted therapy	
EGFR TKIs-containing regimen	36 (1.6)
EGFR mAb-containing regimen	10 (0.5)
VEGF mAb-containing regimen	141 (6.4)
ALK inhibitor	<10[j]
Duration (days) of 2L therapy, mean (SD)[k]	168.6 (148.4)
Radiation therapy following initial diagnosis of non-small cell lung cancer, n (%)	269 (12.3)
Intent of radiation therapy, n (%)	
Curative	21 (7.8)
Palliative	124 (46.1)
Both curative and palliative (separate instances)	15 (5.6)
Unknown	109 (40.5)

[a]1L: first-line therapy.

[b]PD-(L)1: programmed death-(ligand) 1.

[c]EGFR: epidermal growth factor receptor.

[d]TKI: tyrosine kinase inhibitor.

[e]mAb: monoclonal antibodies.

[f]VEGF: vascular endothelial growth factor.

[g]ALK: anaplastic lymphoma kinase.

[h]Median 90.0.

[i]2L: second-line therapy.

[j]Values <10 have not been reported for patient confidentiality.

[k]Median 121.0.

Discussion

Principal Findings

This study combined 3 data sources for the analysis of real-world outcomes in patients with NSCLC, conducting data integration on a large scale across disparate but complementary sources. It was designed to simulate a prospective observational study by identifying patients upfront within large preexisting databases and then following them within the data set to examine outcomes. One of the potential strengths of this approach is the development of a database that includes demographic, clinical, and health care resource utilization data that can more accurately assess health outcomes.

The use of big data from multiple sources, such as health plan enrollment, disease registries, and scanned image repositories, among others, is becoming more important for the accurate determination of patient outcomes, particularly in the setting of NSCLC [28-31]. With the current availability of a wide range of newer, more effective systemic therapies, including several novel biologic agents, the use of diverse provider, institutional, and registry databases is increasingly necessary to evaluate outcomes due to the gaps in administrative claims data alone [32-35]. As treatments in oncology have improved, patients with lung cancer are living longer with the ability to personalize care with novel targeted therapies. This approach, coupled with more effective treatment, means that treatment strategies are increasingly complex, and factors influencing these strategies and their resultant outcomes are not fully identifiable in administrative claims data. As a result, the effective evaluation of treatment outcomes increasingly draws on data from multiple sources across lines of treatment, providers, and institutions.

Real-world evidence (RWE), which is largely derived from big health care data, has increasingly been driven by important technological advances, including machine learning, natural language processing improvements in electronic medical systems, and the ability to link clinical and health claims data in private and public systems [9]. As RWE grows and gains value, especially for pragmatic clinical trials (PCTs), the traditional gold standard of a randomized clinical trial (RCT) is facing major hurdles: low recruitment rates, small patient populations, long durations, and high costs. This evolving environment, along with growing interest in PCTs, is increasing the importance of big data and RWE as a complement to RCTs [36,37].

Furthermore, a bigger role for RWE is developing in decision making across the health care system, including regulators, payers, providers, and patients. Part of the reason is that although RCTs have internal validity, which is essential for safety and efficacy determinations, results from clinical studies may have limited external validity. At the same time, RWE studies using big data are able to explore key clinical questions that are outside the scope of RCTs. Such studies are well suited for investigations seeking safety and effectiveness outcomes data for broader target populations. This is especially valuable for the evaluation of fast-tracked medical products, which typically gain regulatory approval based on limited data. In addition, large RWE studies are invaluable in detecting the side effects of treatments over longer periods. Other circumstances in which RWE is valuable include exploration of rare diseases, assessing the impact of treatment adherence, when rapid retrospective results are needed, comparing multiple treatments that have not been explored in trials, and focusing on population subsets of interest, given more heterogeneity and larger population sizes in real-world data compared with clinical trials [36-38].

Due to the frequency of onset of NSCLC later in life, our study sample included patients with an average age greater than 60 years, with females constituting about half of the study population, which is consistent with other real-world US outcomes studies that examined patients with NSCLC [39-48]. All prior studies, to our knowledge, that focused on the United States used 1 or 2 of the following data sources: administrative claims, registry data, or MR. Limitations of these studies fall into 2 categories: (1) missing data on potential confounders and/or outcomes of interest (eg, claims data can assess utilization outcomes but lack disease characteristics; MR data have a rich set of clinical characteristics but lack longitudinality and utilization or cost data) and (2) limited generalizability (eg, the SEER-Medicare linked data in the United States capture claims and cancer registry data only for patients aged 65 years or older).

The ability of our study to integrate data across 3 sources to create a cohort of NSCLC patients with rich clinical and economic data offers an important addition to the comparatively small body of data on the performance of data integration methods and the determination of health outcomes based on these data for patients with NSCLC. To the extent that our study sample reflects the larger national population affected by lung cancer and with commercial insurance, these data could be instructive for a range of decisions made by multiple health care stakeholders including providers and patients requiring insights into the allocation of resources and overall disease management that cannot be completely ascertained from a single data source alone. One example would be the interaction of biomarker testing, treatment choice, and health outcomes. Integrated data

sets such as RESOUNDS that can be refreshed regularly also offer many opportunities for future research, such as treatment sequencing, disease progression, and health care resource utilization and costs.

Data Integration Challenges

Our study also highlighted some challenges in the creation, maintenance, and analysis of large integrated data sets. Integration of data sets in the midst of a rapid shift in the treatment landscape (such as the introduction of immune checkpoint inhibitors for oncology) may impact the value of data sets that are large and deep, but that include periods of time that are no longer relevant to current standards of care. The maintenance of these data sets requires constant refresh and update, so that the periods of interest to the investigator can be current and available for analysis. The wealth of data available in MRs presents challenges in identifying the trade-offs between generating a limited set of relevant but reasonably quickly available data versus a broader set of data that is potentially available but more difficult to obtain and prepare for analysis. Methods of data integration and data extraction may be improved with machine learning or natural language processing to reduce the manual extraction via data collection forms that was used in this study. Patient sample sizes available for analysis diminish when multiple data sources are required. Finally, there were specific data integration challenges in our study that resulted in additional effort needed by the project team to understand and address (eg, the estimated 2L therapy start date for a given patient sometimes differed between the data sources, plan enrollment changes entailed patients leaving or entering the data set multiple times, and conflicts between data sources for a given variable had to be resolved).

Study Limitations

Results based on integrated data must also be viewed with some limitations. The data quality and content will depend on the underlying data selected for integration. Specific to the data used for this project, limitations include the following: CCQP data were collected at the time of the prior authorization request,

not at diagnosis. CCQP offers incentives to physicians for treating according to evidence-based guidelines created by the health plan, which could have influenced treatment choices. MR data may be underreported or missing due to vague, incomplete, or illegible entries; the inability to locate the required information; or missing patient files. ECOG performance status, a standard data item in cancer trials, is not always assessed in real-world patient care settings (in our study, this variable was available for 96.26% (2113/2195) of the sample, mostly from the CCQP), and information on race/ethnicity is often missing in claims data. Similarly, tumor growth and progression information is collected in various formats and levels of detail outside of a clinical trial setting. As a result, some of our research questions of interest had underpopulated data. Efforts by payers to tie provider reimbursement to the collection of key data points, for example, through quality improvement initiatives, may over time alleviate some of the missing data issues. Data collected during MR abstraction may have measurement errors linked to inconsistent coding, transcription, and data transfer errors. The typical limitations of claims data also apply. For example, a diagnosis code on a medical claim (eg, for secondary malignancies) does not guarantee the presence of a disease. Similarly, a claim for a prescription fill does not indicate that the medication was consumed or taken as prescribed. The generalizability of claims-based results is confined to similarly insured populations (eg, commercial, US-based in this study).

Conclusions

The care of patients with NSCLC requires a range of resources in a variety of settings in the real world. NSCLC and other forms of cancer are increasingly being managed like chronic diseases with a broad range of increasingly effective treatments. The assessment of real-world data to evaluate outcomes among patients with NSCLC will require the integration of a broad range of clinical data with health plan claims data. Overcoming data integration and completeness challenges will allow better informed decision making by all stakeholders of the health care system.

Conflicts of Interest

MG is an employee of HealthCore, Inc, an independent research organization that received funding from Eli Lilly and Company for the conduct of this study. CM, KW, ZC, and LH are employees and stockholders of Eli Lilly and Company. GC was an employee of Eli Lilly and Company at the time the study was conducted. LW was an employee of HealthCore at the time the study was conducted.

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Abbreviations

1L: first-line
2L: second-line
CCQP: Cancer Care Quality Program
ECOG: Eastern Cooperative Oncology Group
HIRD: HealthCore Integrated Research Database
MR: medical record
NSCLC: non–small cell lung cancer
QCI: Quan-Charlson Comorbidity Index
RCT: randomized clinical trial
RESOUNDS: Real-World Treatment Sequences and Outcomes Among Patients With Non-Small Cell Lung Cancer
RWE: real-world evidence

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<u>Original Paper</u>

Clinicopathological Criteria Predictive of Recurrence Following Bacillus Calmette-Guérin Therapy Initiation in Non–Muscle-Invasive Bladder Cancer: Retrospective Cohort Study

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Abstract

Background: Bacillus Calmette-Guérin (BCG) is currently the most clinically effective intravesical treatment for non–muscle-invasive bladder cancer (NMIBC), particularly for patients with high-risk NMIBC such as those with carcinoma in situ. BCG treatments could be optimized to improve patient safety and conserve supply by predicting BCG efficacy based on tumor characteristics or clinicopathological criteria.

Objective: The aim of this study is to assess the ability of specific clinicopathological criteria to predict tumor recurrence in patients with NMIBC who received BCG therapy along various treatment timelines.

Methods: A total of 1331 patients (stage Ta, T1, or carcinoma in situ) who underwent transurethral resection of a bladder tumor between 2006 and 2017 were included. Univariate analysis, including laboratory tests (eg, complete blood panels, creatinine levels, and hemoglobin A_{1c} levels) within 180 days of BCG therapy initiation, medications, and clinical and demographic variables to assess their ability to predict NMIBC recurrence, was completed. This was followed by multivariate regression that included the elements of the Club Urológico Español de Tratamiento Oncológico (CUETO) scoring model and variables that were significant predictors of recurrence in univariate analysis.

Results: BCG was administered to 183 patients classified as intermediate or high risk, and 76 (41.5%) experienced disease recurrence. An abnormal neutrophil-to-lymphocyte ratio measured within 180 days of induction BCG therapy was a significant predictor (P=.047) of future cancer recurrence and was a stronger predictor than the CUETO score or the individual variables included in the CUETO scoring model through multivariate analysis.

Conclusions: An abnormal neutrophil-to-lymphocyte ratio within 180 days of BCG therapy initiation is predictive of recurrence and could be suggestive of additional or alternative interventions.

Introduction

Background and Significance

Bacillus Calmette-Guérin (BCG) is currently the most clinically effective intravesical treatment for non–muscle-invasive bladder cancer (NMIBC), particularly for patients with high-risk NMIBC such as those with carcinoma in situ (CIS). Unfortunately, recent manufacturing insufficiencies have resulted in a worldwide, health-threatening BCG shortage [1-4]. Optimizing the limited supply by identifying patients who could benefit the most from

BCG treatment is essential from a public health perspective because the percentage of patients with NMIBC who fail BCG treatment has been reported to be as high as 40% [5]. BCG optimization could also improve patient safety by reducing BCG treatments that have a low probability of improving clinical outcomes [6]. The incidence of BCG-related adverse effects is considerable—nearly 70% of the patients with NMIBC in a large, randomized controlled trial experienced local or systemic complications, including a long-term risk of treatment sequelae that can develop years after BCG therapy initiation [7,8]. In an era of BCG shortage, a prediction model that could predict NMIBC recurrence following BCG therapy initiation (ie, BCG failure) could support both public health and precision medicine. A risk-adapted approach for BCG maintenance therapy could continue to minimize treatment-related toxicity and optimize cost-effectiveness regardless of BCG availability in the future [4].

The heterogeneous risk of cancer recurrence and progression in patients with NMIBC has led to the investigation of a wide range of methods and factors for predicting a patient's prognosis, including the Club Urológico Español de Tratamiento Oncológico (CUETO) scoring model, which was designed for patients treated with BCG, and European Organization for Research and Treatment of Cancer nomograms [9]. Although the CUETO scoring model and European Organization for Research and Treatment of Cancer nomograms are the most widely used predictive models to date, their accuracy is inconsistent, and the search continues to find better clinical, pathological, genetic, or demographic prognostic features, alone or in combination [10-12]. In studies with patients who received BCG treatment, the findings suggest that recurrence and disease progression may be predicted by indicators of health (eg, BMI) and measures of inflammation (eg, an elevated neutrophil-to-lymphocyte ratio) [13-16]. Other novel prognostic measures for BCG recipients include immunological or cytokine-based markers (eg, urinary fluorescence in situ hybridization testing and urinary cytokine-based nomograms), protein-based biomarkers (eg, ezrin), and gene-based biomarkers (eg, quantifying mutations in DNA damage repair genes) [8].

Objective

Debate and uncertainty persist regarding the potential of various clinical risk factors. The overarching goal of this study is to identify and validate easily employable risk factors that predict BCG failure. Although immunological or cytokine-based markers, protein-based biomarkers, and gene-based biomarkers show potential, they require extra expenditure and testing because they are not collected in the normal course of clinical care. In contrast, clinicopathological criteria are often captured as part of the clinical workflow and are thus actionable at the time that treatment decisions are being made. The aim of this study, therefore, is to assess the ability of commonly used clinicopathological criteria or medications to predict recurrence in patients with NMIBC who were treated with intravesical BCG.

Methods

Recruitment

We conducted a retrospective cohort analysis following institutional review board (IRB) approval. From 2006 to 2017, a total of 1331 patients underwent transurethral resection (TUR) of a bladder tumor that was clinically staged as non–muscle invasive. Patients received care within a community health care system in the Midwest that includes 17 different hospitals dispersed across a wide geographic area that spans rural, suburban, and urban locations. Data captured during the normal course of clinical care were extracted and collated retrospectively from the cancer registry (ie, patient demographics, cancer diagnosis, recurrence, and treatment) and electronic health records (EHRs; ie, surgery and pathology reports, medication orders, laboratory tests, procedure codes, and billing diagnoses). We used a hybrid data extraction and preparation pipeline incorporating automated, semiautomated, and manual techniques. A detailed description of the pipeline can be found in our previous study [17]. This study was performed in compliance with the World Medical Association Declaration of Helsinki on Ethical Principles for Medical Research Involving Human Subjects and was reviewed and approved by the IRB. The IRB waived the requirement for informed consent because of the low risks of the study.

We included patients with NMIBC and a primary or recurrent diagnosis of Ta or T1 urothelial carcinoma or CIS per the American Joint Committee on Cancer tumor size, node involvement, and metastasis system [18]. Patients were excluded from the study if they had metastatic urothelial carcinoma. Patient follow-up continued from the initial TUR (index TUR) until recurrence, progression (ie, ≥stage T2), cystectomy, death, or last known bladder cancer–directed treatment (ie, cystourethroscopy, TUR, urologist visit, BCG instillation, chemotherapy instillation, or urine cytology test). Only patients newly diagnosed with NMIBC on the index TUR were enrolled into this study.

Measures

Recurrence following the index TUR was the primary outcome of interest in this study. Recurrence was defined as cancer returning more than 6 weeks after the index TUR. In contrast, a TUR occurring 2-6 weeks after the index TUR was defined as a Re-TUR (ie, a second-look TUR) instead of a recurrence. Progression, in this study, was defined as cancer upstaging to ≥stage T2 or patients requiring cystectomy. Bladder cancer recurrence and progression were identified using pathology reports and the dates of the events listed in the cancer registry. The date of decease was also captured in the cancer registry. The BCG instillation date was extracted from (1) procedure billing data, (2) medication administration records, (3) medication order records (ie, prescription), or (4) extracted from a free-text chemotherapy field in the cancer registry data.

Pathology reports were reviewed to determine tumor stage, size, quantity, and grade for each TUR. The tumor stage recorded was the highest stage confirmed by the pathologist. Tumor grade was captured in, or converted to, the 2004 World Health Organization grading system. Tumor size was stratified into

small (≤3 cm) or large (>3 cm). CIS and lymphovascular invasion were extracted from the cancer registry. The study cohort is exclusively composed of patients with a primary cancer diagnosis; therefore, all patients with a prior incidence of NMIBC were excluded. Variant histology was extracted from the pathology reports, although all patients with variant histology in the data were staged T2 or higher in their index TUR and, thus, were excluded from the study. High-grade prostatic urethral involvement occurs when the cancer preferentially invades the prostatic urethra before the bladder muscle and was extracted from the pathology reports. Age was calculated based on the difference between the date of the index TUR and date of birth and was extracted from the cancer registry (along with sex).

Several clinical characteristics associated with the efficacy of BCG treatment were extracted from the EHR, including white blood cell, lymphocyte, neutrophil, monocyte, and platelet counts and levels of creatinine and hemoglobin A_{1c} (Table 1). The derived neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio were computed based on the EHR data. We investigated three different time frames corresponding to pre-TUR, 180 days after TUR, and beyond 180 days after TUR (Multimedia Appendix 1). The pre-TUR timeframe corresponds to prior risks. A +1- to +180-day after TUR time frame covers the induction BCG and early maintenance BCG treatments. The delta in laboratory values was calculated to further evaluate whether a change in the patients' baseline clinical characteristics following BCG treatment demonstrated any clinical relevance in predicting recurrence (Multimedia Appendix 1). Patients who received BCG did not have an estimated glomerular filtration rate or tuberculosis status noted for the purposes of this study.

Table 1. Clinicopathological criteria or medication definitions.

Type and clinicopathological criterion or medication	Description
Binary	
BCG[a] instillation	First instillation of BCG documented 0-90 days after TUR[b]
Epirubicin	Epirubicin use documented 0-90 days after TUR
Tuberculostatic agents	Use of isoniazid isonicotinylhydrazide, rifampicin, rifambutin, fluoroquinolones (ofloxacin, ciprofloxacin, levofloxacin, and moxifloxacin), ethambutol, clarithromycin, aminoglycosides (gentamicin, amikacin, tobramycin, kanamycin, and neomycin), or doxycycline documented –30 to 90 days of induction BCG (index to median day of BCG administration if no BCG)
Spasmolytics or anticholinergics	Use of spasmolytics: oxybutynin documented –30 to 90 days of induction BCG (index to median day of BCG administration if no BCG)
Antiphlogistics	Use of antiphlogistics: fluticasone documented –30 to 90 days of induction BCG (index to median day of BCG administration if no BCG)
Topical steroids	Use of local topical steroids: betamethasone, clobetasol, diflorasone, fluocinoide, halobetasol, amcinonide, desoximetasone, propionate, triamcinolone, fluocinolone, hydrocortisone, desonide, alclometasone, and mometasone documented –30 to 90 days of induction BCG (index to median day of BCG administration if no BCG)
Nonsteroidal anti-inflammatory drugs	Use of nonsteroidal anti-inflammatory drugs: aspirin, ibuprofen, naproxen, nabumetone, celecoxib, diclofenac, etodolac, indomethacin, ketoprofen, ketorolac, and piroxicam documented –30 to 90 days of induction BCG (index to median day of BCG administration if no BCG)
Numeric	
General description	• Most recent (laboratory test) occurring 1-180 days after induction BCG computed 14 days before the next event (ie, TUR but not Re-TUR[c], recurrence, progression, or death) • Difference between the most recent (laboratory test) occurring 1-180 days after induction BCG computed 14 days before next event and the most recent (laboratory test) occurring 90-0 days before induction BCG (index to median day of BCG administration if no BCG)
Lymphocyte count (normal: 20%-40% differential)	N/A[d]
Neutrophil count (normal: 55%-70% differential)	N/A
Monocyte count (normal: 2%-8% differential)	N/A
Platelet count (K/μL)	N/A
White blood cell count (K/μL)	N/A
Creatinine level (mg/dL)	N/A
Hemoglobin A_{1c} (mmol/mol)	N/A
Computed percentage	
General description	• Most recent (laboratory test) occurring 1-180 days after induction BCG computed 14 days before the next event (ie, TUR but not Re-TUR, recurrence, progression, or death) • Difference between the most recent (laboratory test) occurring 1-180 days after induction BCG computed 14 days before next event and the most recent (laboratory test) occurring 90-0 days before induction BCG (index to median day of BCG administration if no BCG)
Derived neutrophil-to-lymphocyte ratio	N/A
Platelet-to-lymphocyte ratio	N/A

[a]BCG: bacillus Calmette-Guérin.

[b]TUR: transurethral resection of a bladder tumor.

[c]Re-TUR: second-look transurethral resection of a bladder tumor.

[d]N/A: not applicable.

We additionally extracted medication information from the EHR for drugs that potentially interact with BCG, such as epirubicin (Table 1). Several medications that are used to prevent or manage BCG-associated adverse effects were extracted from medication administration and prescription data, including tuberculostatic agents, spasmolytics or

anticholinergics, antiphlogistics, local topical steroids, cranberry supplements, and nonsteroidal anti-inflammatory drugs (Table 1) [19]. Patients who received BCG did not have documented use of cranberry supplements, and more contemporary medications such as pembrolizumab or atezolizumab were not available in the data during the time frame of this study [20]. The CUETO scoring model includes the variables of age, gender, number of tumors, tumor stage, grade, and presence of concomitant CIS. We investigated each variable included in the CUETO scoring model to determine if these risk factors were predictive of NMIBC recurrence in this cohort. We also investigated additional risk factors that have been previously demonstrated to predict NMIBC recurrence in the setting of BCG therapy such as perioperative chemotherapy agents, race, and diabetes (Multimedia Appendix 1) [21].

Statistical Analysis

The 2016 American Urological Association (AUA) risk guidelines for recurrence were used to stratify each index TUR as low, medium, or high risk [22]. This stratification was used to describe cohort characteristics and BCG use. TURs identified as low risk were excluded from the remainder of the analysis because BCG was less likely to be clinically necessary or efficacious for these patients and thus rarely administered. Summary statistics were calculated using R version 3.5.2 (The R Foundation for Statistical Computing) and grouped by BCG use. The CUETO risk stratification tables for predicting recurrence were used as a multivariate measure of BCG efficacy because the CUETO scoring model was designed to consider BCG use as opposed to other NMIBC predictive models [9,23].

We used the Mann-Whitney U test—using the Wilcox test function in the stats package (version 1.8.12) in R—to compare patients who received BCG and were designated as intermediate to high risk for recurrence and BCG failure. Variables with a Mann-Whitney U value of <0.1 were considered candidates for multivariate logistic regression. Various combinations of multivariate logistic regression were tested using the generalized linear model function in the stats package in R, and the one with the highest area under the receiver operating characteristic curve was selected.

Results

Of the 1331 patients, 855 (64.24%) were intermediate to high risk according to the 2016 AUA guidelines, among whom 183 (21.4%) received an induction course of BCG (Figure 1; Table 2). Of the patients classified as intermediate to high risk who lost to follow-up (Figure 1), only 38 had a last check-in within 180 days of the index TUR (13 lost in less than 30 days; 8 lost between day 31 and day 60; 4 lost between day 61 and day 90; 6 lost between day 91 and day 120; and 7 lost between day 121 and day 180). In this cohort of 1331 patients with NMIBC, 105 (7.8%) progressed; however, all but the 5 included in Figure 1 followed at least one NMIBC recurrence event. The mean and median dates of BCG administration were 88 and 89 days, respectively, after the index TUR. White blood cell, monocyte and neutrophil counts as well as neutrophil-to-lymphocyte ratio measured between 1 and 180 days after BCG instillation were predictive of cancer recurrence in patients classified as intermediate and high risk who received BCG following an initial TUR (Table 3; Multimedia Appendix 1).

Figure 1. Patient flowchart. AUA: American Urological Association; BCG: bacillus Calmette-Guérin; TUR: transurethral resection of a bladder tumor.
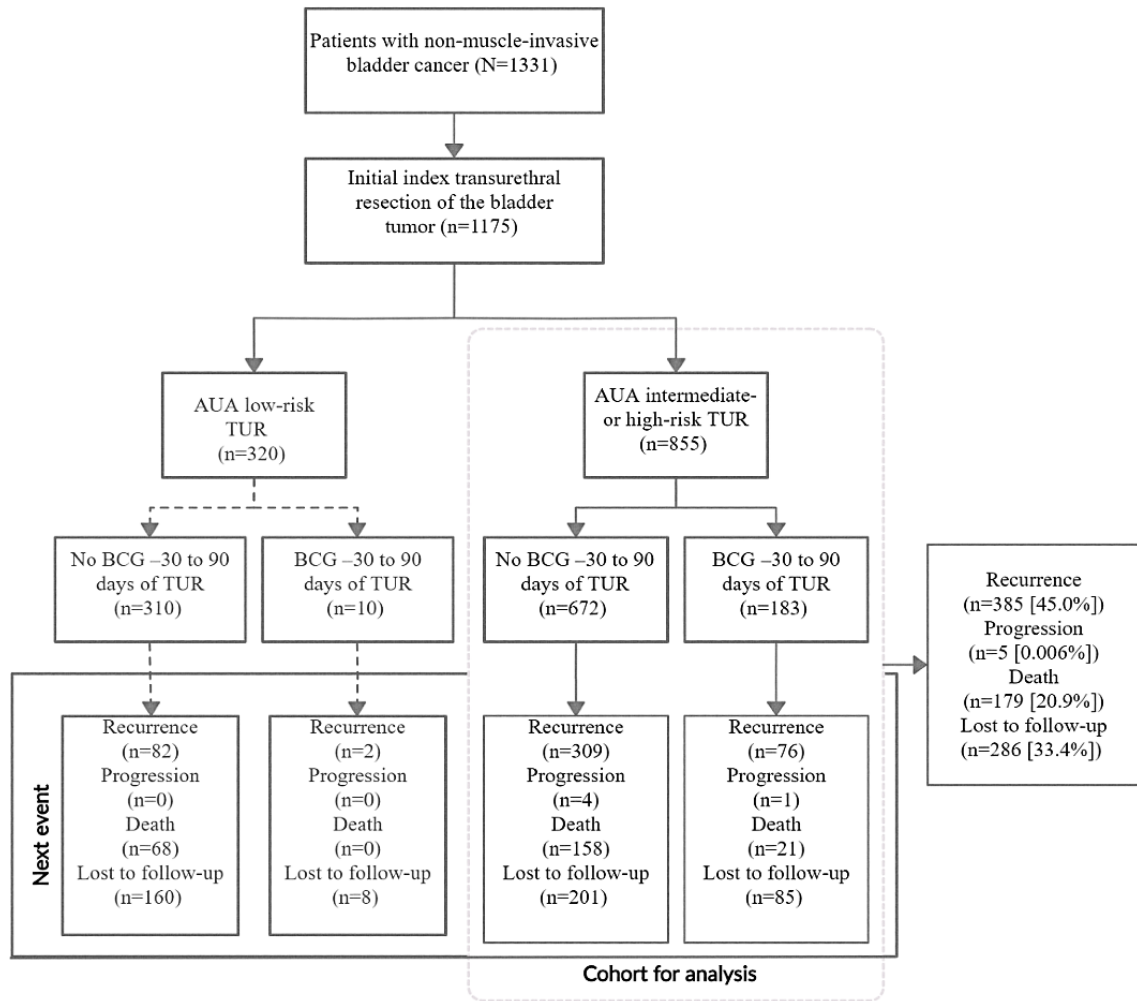
Table 2. Next event and cohort characteristics at the initial transurethral resection of the bladder tumor by bacillus Calmette-Guérin status.

Characteristic	Received BCG[a] (n=183), n (%)	No BCG (n=672), n (%)	P value
Sex (male)	143 (78.1)	507 (75.5)	.45
White	175 (95.6)	652 (97)	.35
African American	6 (3.3)	14 (2.1)	.34
Hispanic ethnicity	3 (1.6)	9 (1.3)	.73
Other ethnicity	2 (1.1)	6 (0.9)	.68
Stage Ta	81 (44.3)	433 (64.4)	<.001
Stage T1	104 (56.8)	241 (35.7)	<.001
Low grade	34 (18.6)	320 (47.6)	<.001
High grade	149 (81.4)	354 (52.7)	<.001
Carcinoma in situ	99 (54.1)	99 (14.7)	<.001
Re-TUR[b]	32 (17.5)	63 (9.4)	.002
Mitomycin[c]	33 (18)	44 (6.5)	<.001
Cisplatin[c]	1 (0.5)	2 (0.3)	.51
Gemcitabine[c]	0 (0)	2 (0.3)	.99
Recurrence	76 (41.5)	309 (45.9)	.28
Progression	1 (0.5)	4 (0.6)	.99
Death	21 (11.5)	158 (23.5)	<.001

[a]BCG: bacillus Calmette-Guérin.

[b]Re-TUR: second-look transurethral resection of a bladder tumor.

[c]Chemotherapy agent used –30 to 90 days of initial index transurethral resection of the bladder tumor. There were no records of the use of lenalidomide, thiotepa, valrubicin, atezolizumab, and pembrolizumab.

Table 3. Club Urológico Español de Tratamiento Oncológico scoring model or statistically significant clinicopathological criteria in univariate analysis among patients with intermediate- or high-risk non–muscle-invasive bladder cancer who received bacillus Calmette-Guérin (N=183) +1 to 180 days after induction.

Clinicopathological criterion	Missing[a], n (%)	Recurrence (Mann-Whitney U test)
Neutrophil count	73 (60.1)	0.009
Derived neutrophil-to-lymphocyte ratio	73 (60.1)	0.03
CUETO[b], continuous	182 (99.5)	0.10
CUETO, categorical[c]	182 (99.5)	0.07
CUETO, gender	182 (99.5)	0.61
CUETO, number of tumors	182 (99.5)	0.05
CUETO, CIS[d]	182 (99.5)	0.33
CUETO, high-grade tumor	182 (99.5)	0.34
CUETO, age	183 (0)	0.75

[a]We have complete data for CUETO and age (N=183), and 0% of the data are missing. For other CUETO, we have data for 182 patients, and the data are 99.5% complete. We have 60.1% of data (from 73 patients) for neutrophil count within that time span, with 39.9% not having a recorded lab test for this in the timespan.

[b]CUETO: Club Urológico Español de Tratamiento Oncológico.

[c]CUETO, categorical: ≤4, 0 points; 5 or 6, 1 point; 7-9, 2 points; and ≥10, 3 points.

[d]CIS: carcinoma in situ.

A univariate model with only a neutrophil-to-lymphocyte ratio of +1 to 180 days after BCG induction had an area under the receiver operating characteristic curve of 64.55% (Figure 2).

Neither the CUETO scoring model nor any of its elements were found to be significant in univariate analysis in this cohort (Table 3) or when used as components in multivariate analysis

with the neutrophil-to-lymphocyte ratio of +1 to 180 days after   BCG induction (Table 4).

Figure 2. Area under the receiver operating characteristic curve for recurrence prediction. Time span: 1-180 days after bacillus Calmette-Guérin induction. CUETO: Club Urológico Español de Tratamiento Oncológico; Neutrophil: neutrophil count (differential); Lymphocyte: lymphocyte count (differential); Neutrophil Lymphocyte: derived neutrophil-to-lymphocyte ratio.
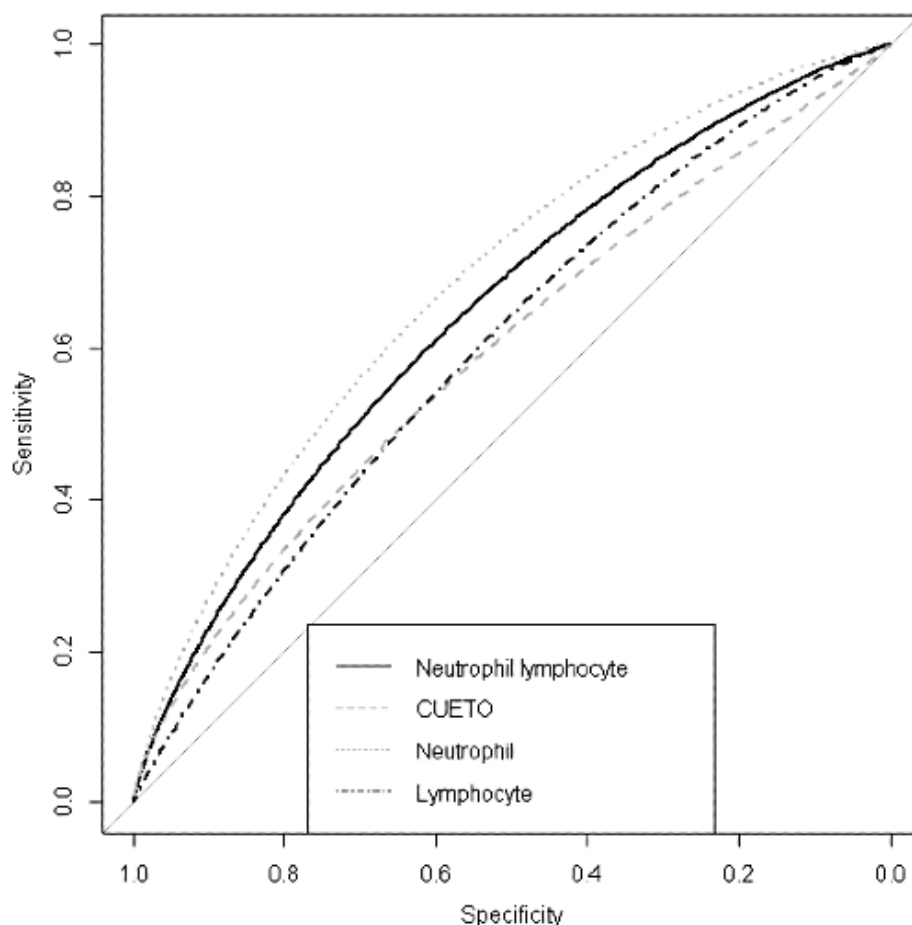

Table 4. Coefficients from multivariate regression with Club Urológico Español de Tratamiento Oncológico scoring model elements.

Coefficients	Estimate	SE	t test (df)	P value
(Intercept)	0.64586	0.18476	3.496 (66)	<.001
Gender	0.02581	0.04944	0.522 (175)	.60
Number of tumors	0.0927	0.08056	1.151 (175)	.25
Carcinoma in situ	–0.02382	0.07126	–0.334 (175)	.74
High-grade tumor	–0.07384	0.05686	–1.299 (175)	.20
Age	–0.12589	0.07109	–1.771 (175)	.08
Neutrophil-to-lymphocyte ratio	0.03017	0.01492	2.022 (66)	.047

Discussion

Principal Findings

Our main finding was that in patients with intermediate- or high-risk NMIBC who received BCG, the neutrophil-to-lymphocyte ratio measured between +1 and 180 days after BCG instillation was predictive of subsequent BCG failure. Early detection of BCG failure could prevent metastatic NMIBC progression by intervening earlier in tumor development. In addition, in the era of BCG shortages around the country, if patients elect to switch to BCG-salvage regimes,

early detection of BCG failure would also preserve BCG supply for the patients who truly need it. In this study, we evaluated whether common clinicopathological variables might be predictive of BCG failure in patients with elevated risk. BCG failure is broadly categorized as refractory, relapsing (ie, recurrence), unresponsive, and intolerant cases [24-26]. However, we did not have information on BCG intolerance and, therefore, did not include this information in our analysis. These results suggest that white blood cell, monocyte, and neutrophil counts as well as the neutrophil-to-lymphocyte ratio measured between 1 and 180 days after BCG instillation were as predictive of cancer recurrence in patients classified as intermediate and

high risk who received BCG following an initial TUR while adjusting for the CUETO score. This suggests that monitoring blood panels is useful in the first 6 months after BCG instillation to evaluate whether BCG failure is likely to occur. In addition, neutrophil count alone, when measured within 180 days of BCG instillation, provides predictive performance equivalent to that of monocyte count, neutrophil-to-lymphocyte ratio, or combinations of these variables.

For patients who undergo BCG therapy, the CUETO risk model was designed to predict the probability of cancer recurrence and progression. However, in this cohort, the CUETO score was not a statistically significant differentiator for predicting recurrence after patients classified as low risk (AUA risk guidelines) were excluded from the cohort. This could be due to the poor generalizability of the CUETO scoring model. When external data were previously applied to these scores, the CUETO scoring model overestimated disease recurrence and demonstrated a poor ability to predict recurrence [10-12]. Perhaps, most importantly, these results show that even when the CUETO elements were included in the multivariate analysis, the neutrophil-to-lymphocyte ratio remains a robust predictor. This provides preliminary evidence that in a diverse cohort of patients with NMIBC treated with BCG, the neutrophil-to-lymphocyte ratio could help guide treatment decision making, particularly for NMIBC surveillance. If patients with elevated risk demonstrate a neutrophil-to-lymphocyte ratio indicative of BCG failure, they might benefit from more frequent cystoscopy, enhanced cystoscopy techniques, or additional imaging procedures. This is similar to current AUA guideline recommendations for patients with high-risk disease who show positive cytology during surveillance [22]. Additional prospective studies are warranted to determine the predictive power of the neutrophil-to-lymphocyte ratio in a large randomized sample of patients with NMIBC.

The clinicopathological criteria—neutrophils and lymphocytes—are consistent with those in the study by Vartolomei et al [15]; however, the time frame of measurement differs, which deserves further investigation. As BCG is known to be immunostimulatory, markers of net functional immunity, such as the neutrophil-to-lymphocyte ratio, are affected by its use. Although these markers of net functional immunity are nonmodifiable, they can be useful clinically to predict the failure of the BCG treatment strategy by informing the clinician that recurrence is likely, and another clinical intervention is required.

A second course of BCG induction may be reasonable for refractory or relapsing cases because approximately 25%-50% of these patients will respond to this subsequent induction [24-27]. We concur with Zamboni et al [10] that the completeness of BCG schedules may be useful to include in future models for optimizing BCG use across the entire course, rather than just the induction. Future studies with sufficient power to capture data for all subclassifications of BCG failure (particularly progression) or following a second course of BCG induction may provide additional insights into predicting BCG efficacy.

Our data sets only contain data for patients before the halt in the production of the Connaught BCG strain by Sanofi Pasteur, thus precluding any impact analysis, although we expect that these effects are likely more recent than the 2017 stoppage, and we are unaware of the date corresponding to when stockpiles of that strain became unavailable [3,28]. Several clinical recommendations on how to manage patients with NMIBC when BCG supplies are low can be found in the clinical literature [1,2]. Patients at increased risk for BCG failure could undergo additional surveillance, receive maintenance intravesical chemotherapy in addition to induction BCG, or become candidates for timely cystectomy. Given the poor generalizability of the CUETO scoring model in the literature [10-12], external validation of these results is warranted before recommending additional expenditure on complete blood panels that are requested outside of the current standard of care.

Continuous monitoring of a patient's clinicopathological criteria for the duration of NMIBC treatment to predict future recurrence events is a unique aspect of this study. Another unique aspect was to account for differences in markers of net functional immunity (eg, neutrophil count and lymphocyte count) over time, effectively evaluating whether the changes are predictive. Although the changes in neutrophil count were significant in univariate analysis (Table 3), the value of the neutrophil count at +1 to 180 days after BCG induction was sufficient to account for this change in the multivariate analysis. The temporality of when things are measured with respect to an event (eg, BCG induction) is important when considering risk factors because the time period from –90 to 0 days before BCG induction and >180 days after BCG induction were not found to be predictive of recurrence when considering these clinicopathological criteria (Multimedia Appendix 1).

Limitations

Prior research by Tazeh et al [29] suggests that race-specific differences should be considered when interpreting the neutrophil-to-lymphocyte ratio at the time of TUR. However, the study population lacks sufficient diversity to thoroughly investigate this finding [29]. As only data from one health system were included, these statistics may not generalize elsewhere without adaptation to the local institution's EHR. The disadvantage of a retrospective cohort design is that data may be incomplete or inadequately captured in the available medical record data [30]. For example, BCG dose information was scarce in these data because only a portion of the records was associated with pharmaceutical records, and the proportion of patients with a known lower dose (eg, a one-third dose) was too small for a subgroup analysis to be performed. Outside of a clinical trial, it is unlikely that missing data would be collected more frequently in future clinical workflows without changes to meaningful use requirements or documentation guidelines; thus, the statistics are more robust when applied to typical clinical environments. The consumption of steroids or the presence of an infection or thromboembolism, any of which may affect the neutrophil-to-lymphocyte ratio, were not considered in this study. Smoking status, which has been shown to predict recurrence [31,32], was also not considered because our retrospective data lacked completeness and granularity of smoking status.

Conclusions

In patients with intermediate- or high-risk NMIBC who received BCG, the neutrophil-to-lymphocyte ratio measured between +1 and 180 days after BCG instillation was predictive of subsequent BCG failure. In conjunction with existing risk stratification scores such as the CUETO score, the neutrophil-to-lymphocyte ratio could be used to predict BCG failure. Patients at increased risk for BCG failure could undergo additional surveillance, receiving maintenance intravesical chemotherapy instead of BCG, thereby preserving limited BCG supplies, or be considered for timely cystectomy. Additional retrospective and prospective studies are needed to validate these findings.

Authors' Contributions

All authors provided substantial contributions to the conception and design of this work, its data analysis and interpretation, and helped draft and revise the manuscript. All authors are accountable for the integrity of this study. JP, JW, and K Ravvaz had access to all of the data. TD and K Richards did not have access to the data.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional statistical analysis at different time points.
[DOCX File , 78 KB - cancer_v7i2e25800_app1.docx]

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Abbreviations

AUA: American Urological Association
BCG: bacillus Calmette-Guérin
CIS: carcinoma in situ
CUETO: Club Urológico Español de Tratamiento Oncológico
EHR: electronic health record
IRB: institutional review board
NMIBC: non–muscle-invasive bladder cancer
TUR: transurethral resection of a bladder tumor

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