TCU BURNETT SCHOOL *of* MEDICINE

Creating a Feasible and Reproducible Virtual Exercise Program for Patients Undergoing Neoadjuvant Therapy Prior to Resection of a Primary Gastrointestinal Tumor

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Abstract

Research Question: In patients receiving neoadjuvant therapy prior to a potentially curative resection of a gastrointestinal cancer, is a virtual exercise program better than an in-person exercise program at maintaining health?

Background, Significance, and Rationale for the Question: Neoadjuvant chemotherapy severely decreases a patient's fitness and, consequently, the patient's readiness for surgical resection and adjuvant therapy. Exercise has been found to improve quality of life and decreases adverse events in cancer patients receiving adjuvant chemotherapy and survivorship. The handful of exercise programs available for this population are generally done in-person under close supervision of a cancer exercise trainer. The COVID-19 pandemic initially sparked the need for a virtual option, however; other benefits of going virtual include increased access for those of low SES status, patients without a consistent means of transportation, and those who are immunocompromised.

Materials and Methods: A review of cancer and exercise literature was performed in order to identify and analyze observational literature on exercise's effects on cancer patients during treatment and survivorship. The search was conducted using the PubMed and Academic Search Ultimate databases. Reference lists of identified articles were also reviewed for relevant publications. The databases were searched using the key words "cancer exercise" combined with each of the following terms: "quality of life," "neoadjuvant therapy," "adjuvant therapy," "survivorship," "telehealth" and "physiologic effects."

Results: A virtual cancer exercise was developed with a licensed cancer exercise trainer. This program was adapted from an existing regimen used in-person with patients at Moncrief Cancer Institute. This program covers all current ACSM guidelines. Moreover, an investigative study, designed with statisticians from UT Southwestern was developed. The study was designed to investigate the noninferiority of virtual exercise programs as compared to in-person regimens. This study also includes practical methods for testing patients' fitness prior to surgery.

Conclusions: In conclusion, we propose a valid cancer exercise program that is adapted for use in a virtual platform. Its use in the neoadjuvant setting, will contribute significant knowledge to the field and potentially shift the focus to initiating exercise treatment at the time of diagnosis rather than the typical post treatment settings. An investigative study is also detailed which would test the noninferiority of a virtual exercise program. This objective and practical virtual platform will not only allow for safer environments with immunocompromised patients, but also can also help with adherence, allow for environmental changes such as COVID-19 sequestering, and most importantly make access to these interventions more equitable.

Research Question

In patients receiving neoadjuvant therapy prior to a potentially curative resection of a gastrointestinal cancer, is a virtual exercise program better than an in-person exercise program at maintaining health?

Can a prospective study be made to adequately assess the non-inferiority of a virtual exercise program as compared to an in-person exercise program?

What tests would be most adequate at evaluating fitness prior to surgery for patients with a gastrointestinal cancer receiving neoadjuvant therapy?

Hypothesis: We hypothesize that such patients who receive their exercise regimen training virtually will maintain or improve their fitness and maintain perceived quality of life as well as those who receive such training in person. Moreover, we believe the Stairs Test, Timed-Up-and-Go test, and Karnofsky Performance Status Scale are tools that objectively and feasibly measure a patient's baseline fitness and fitness throughout neoadjuvant therapy. Ultimately, we hypothesize increased overall prognosis for patients starting with the surgical oncologists' decision to move forward with surgical resection as a form of primary treatment. We expect surgeons to correlate an increased patient fitness with an overall favorable outcome during and post-surgery.

Introduction, Significance and Rationale

Introduction

The beneficial impact exercise can have on overall health has long been advocated by many physicians. Susruta, a physician from 600 BCE, was the first to prescribe exercise for his patients.[1] Over two millennia have passed and today we continue to explore the benefits that exercise brings to the healthy and the diseased.

In 2002, the American Cancer Society recommended regular exercise to reduce the risk of cancer.[2] In 2007, the American College of Sports Medicine and other prominent associations led a global initiative aimed to assemble healthcare workers and educators worldwide to promote the use of exercise to deter illness.[1] The association between cancer and fitness, however, has been overlooked, at least when compared to common chronic diseases such as coronary artery disease or diabetes mellitus. Subsequently, a field of research has evolved which aims at elucidating *all the facets* of oncology and exercise. These include understanding changes in the tumor microenvironment as a result of exercise and elucidating the preventative effects of exercise on cancer related cognitive impairment, or chemo brain.

Medical oncologists, radiation oncologists, cancer surgeons, and patients often partner together in deciding the next best step for surgical resection of a primary solid tumor. Surgery is the primary curative treatment for most localized solid organ cancers. In this potentially curative setting, additional radiation or chemotherapy is called adjuvant treatment. Adjuvant therapy is delivered to decrease the likelihood of cancer progression or recurrence. Adjuvant chemotherapy or radiation treatments are administered after surgery. Chemotherapy and/or radiation administered prior to a surgery is called neoadjuvant treatment and is given to reduce the size of a tumor before surgical resection to help ensure total resection with negative margins as well as to help clear any cancer cells that may have metastasized.[3]

Chemotherapy has historically been known for its adverse effects. These adverse effects often have a negative impact on the patient's quality of life.[3] Muscle atrophy and a decline in strength are often seen.[3] The decrease in overall fitness seen in patients undergoing neoadjuvant therapy can have a negative impact on the patient's surgical eligibility and prognosis. Adding an exercise regimen in the neoadjuvant phase of treatment could possibly reverse these adverse effects and improve operative eligibility and quality of life.

The world is becoming increasingly digital and even exercise can be delivered via a virtual platform. Fitness apps such as Runkeeper have become popular among smartphone users in order to improve their current lifestyles. One study found that a virtual platform could lead to improved diet, physical activity and a decrease in sedentary behaviors.[4] Thus, the delivery of a digital exercise regimen for cancer patients undergoing neoadjuvant chemotherapy is also feasible.

During the Spring of 2020, the COVID-19 pandemic has changed the culture of medicine. Concerns about multiple facets of care such as physical distancing, protection of patients and staff, shortage of personal protective equipment (PPE) and the Medicare emphasis on telehealth has served to radically improve the infrastructure of all aspects of medical care. Not only is the hardware software improved, but the provider and patient expectations have changed and allowed for an acceptance of virtual care that was not present prior to the pandemic.

Significance

Across the globe, cancer that derives from the gastrointestinal (GI) tract continues to be among the five most common cancers in both men and women.[5] Furthermore, GI cancers including those in the stomach and liver are the most common cause of cancer deaths in men[5] and colorectal cancer is the

third most common cause of death in women.[5] According to the American Cancer Society, when grouped, gastrointestinal cancers are the most common and second leading cause of death in the US.[6] Moreover, the incidence of individuals under the age of 50 years old with GI cancer saw a 22% increase from the years 1995 to 2013.[6] The wide collection of tumors found in the GI system are vastly distinctive, yet, surgical resection remains the primary treatment for these cancers.[7]
Neoadjuvant therapy has been used in multiple types of GI cancers to reduce tumor size, thus, improving post-surgical overall survival.[8] Nevertheless, neoadjuvant treatment is connected to surgical mortality and morbidity in those patients with prominent toxic effects.[8] Neoadjuvant chemotherapy is often given in cycles that can last anywhere from 2 to 6 months and can lead to significant decreases in patient fitness. Specifically, neoadjuvant chemotherapy has been shown to cause a substantial reduction in oxygen uptake at the lactate threshold as well as at peak.[9] Cardiopulmonary exercise testing, or CPET was established as a way of assessing the patient's ability to meet the increased oxygen demand of major surgery.[10] Generally, a patient with an oxygen uptake at peak less than 11 ml/min/kg is deemed to have a higher risk of surgical complications including death.[10]
The introduction of an exercise regimen for patients undergoing neoadjuvant therapy has been found to be safe and feasible.[3,11,12] Furthermore, combining exercise and neoadjuvant therapy has resulted in improved aerobic fitness, strength, and quality of life for patients.[3] Exercise regimens varied from aerobic to anaerobic, as well as those that focused on cardio or resistance training.

Rationale

The effects of exercise in cancer patients have been studied extensively in the setting of primary and adjuvant therapy. However, there has been little investigation into the relationship between exercise and neoadjuvant therapy. Further analysis is needed to assess the benefits of exercise in patients undergoing neoadjuvant chemotherapy. A systematic review published in 2016 indicated that there were insufficient controlled trials to draw a reliable conclusion.[11] Patients receiving neoadjuvant therapy are doing so to improve the outcome of their definitive therapy. If patients suffer greatly from adverse effects, then their chances of receiving or surviving the primary treatment are greatly diminished.
This study aims to add to the existing literature by providing a reproducible, conclusive exercise regimen that help preserve or improve performance status and quality of life using clinically relevant straight forward measurements. Given the recent changing medical culture and increasing technical capabilities, this study also aims to provide that regime in a virtual effective format that will lead to not only further clinical trials evaluating the efficacy of exercise in cancer therapy, but also provide a therapeutic tool to improve patient care in the post COVID-19 era.

Materials and Methods

General Details and Resources

A review of cancer and exercise literature was performed in order to identify and analyze observational literature on exercise's effects on cancer patients during treatment and survivorship. The search was conducted using the PubMed and Academic Search Ultimate databases. Reference lists of identified articles were also reviewed for relevant publications. The databases were searched using the key words "cancer exercise" combined with each of the following terms: "quality of life," "neoadjuvant therapy," "adjuvant therapy," "survivorship," "telehealth" and "physiologic effects." Additionally, the exercise program was developed with a licensed cancer exercise trainer from UT Southwestern's Moncrief Cancer institute. Similarly, a statistician was consulted when designing the study that would adequately test for noninferiority of a virtual exercise program.

Results

Virtual Exercise Program
A virtual exercise program was curated by a Cancer Exercise Trainer at Moncrief Cancer Institute. Patient's differing baseline fitness, exercise equipment and safety were considered when developing the program. The training program consists of twice weekly supervised aerobic, resistance, flexibility, balance and agility exercises of approximately 75 minutes each. Individual fitness and strength capacity as well as learning style are used to personalize the program.

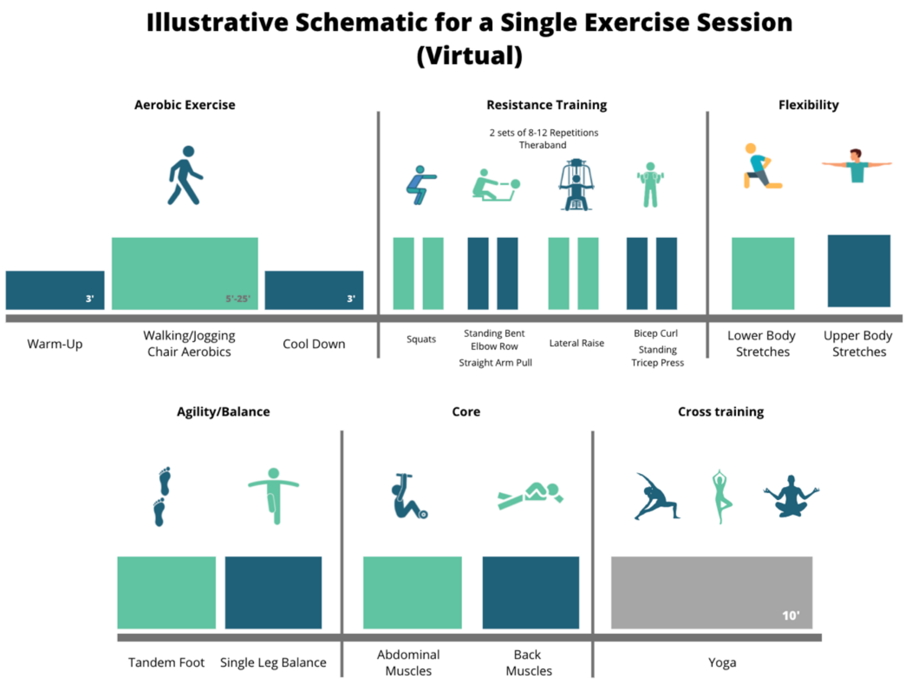

Figure 1Virtual Exercise Program

Session Overview:

Aerobic

- 3 minutes warm up-walking or jogging in place
- Followed 5-25 minutes of low-impact cardiovascular exercise and a 3-minute cool down.
    - Based on personal ability and equipment available at home.
    - Following cancer exercise trainer through a variety of movements and gauge perceived exertion.

Resistance

- Training is comprised on exercises to work major muscle groups.
- Progressing to two sets of 8-12 repetitions per major muscle groups.
- The resistance program generally includes exercises using body weight and resistance bands (TheraBands). Unless additional equipment is available at home such as

dumbbells. Often, household items can be used to add resistance during certain exercises.

- For clients unable to stand comfortably or safely, seated or supine exercises may be substituted and will be addressed by the CET.
- Strength programs are adapted and progressed based on the patient's abilities and goals.
- The standard **strength** protocol includes:
    - Squats (quadriceps, hamstrings, glutes)
    - Standing Bent Elbow Row (lats, posterior delts, biceps)
    - Straight Arm Pull (lats, posterior delts)
    - Lateral Raise (mid deltoids)
    - Bicep Curls (biceps)
    - Standing Triceps Press (triceps)
- As able, clients are progressed to compound strength exercises to address motor issues such as balance, agility, core, and functional movement.

Flexibility, Balance, Core, and Agility

- **Flexibility**
    - Full Body Flexibility Program
- **Balance**
    - Tandem Stance
    - Single Leg Stance
    - Slow Motion March
- **Core**
    - Abdominal Bracing
    - Abdominal bracing with marching legs
    - Double Leg Lift
    - Bridge
    - Dead Bug
    - Seated Hinge
- **Yoga**
    - can be included in the session when time permits and based on patient abilities/needs. It can be done seated, standing, prone, quadruped or supine positions.

Prospective Study Design

Subject Identification

Patients that meet the following criteria will be identified. Inclusion criteria will be used in identifying potential subjects for the study. The target patient population will be 18 to 75 years of age, diagnosed with gastrointestinal cancer, in need of neoadjuvant therapy prior to surgery. Patients will be excluded if they have completed more than two weeks of neoadjuvant therapy without being enrolled or have received systemic cancer treatment in the past year.

The subjects will be separated into two groups: patients with in-person exercise protocol (IPEP), and patients with a virtual exercise protocol (VEP). The first group of patients will have access to the gym facilities on the MCI campus and personal training from a Cancer Exercise trainer. The second group will only have access to the exercise protocol developed via a virtual platform. Additionally, they will not have access to the gym facility on the hospital campus.

Additionally, characteristics for secondary groups within the above-mentioned primary groups will be identified. Biological sex, age range, BMI, comorbidities and Social Economic Status, or SES, will be used to evaluate possible trends within these secondary groups. However, patients will not undergo additional stratification due to limitations with number of study participants.

Prospective Primary Endpoint Data Collection and Basic Recording

Patients meeting study inclusion criteria and IPEP and VEP group criteria will be included in this portion of the study. Upon identification, each subject will be evaluated prospectively, from date of enrollment to three months post-surgery to examine neoadjuvant therapy completion, patient assessment for surgery, complications post-surgery, and adjuvant therapy enrollment.

A baseline fitness level will be established upon enrollment and prior to any exercise intervention. The following primary and secondary endpoints will be measured and recorded.

I. Physiologic Endpoints for Exercise Protocol Efficacy

Patients' fitness overall will be assessed using the *Timed Up and Go* test, Stairs Test, and Karnosfky Performance Status Scale. These tests were chosen because of they are easily reproduced in a clinical setting. Furthermore, they assess the following domains of fitness: aerobics, resistance, agility, balance, and posture. Patients will be tested by Lisa Ross and data will be recorded. The patient's Karnosfky score will be obtained from the EHR.

II. Serious Adverse events

Additionally, the EHR will be analyzed for direct adverse events that led to a postponed or cancelled surgery. Metrics for this endpoint will fall under one of the following categories: death, verified disease progression, medically unfit for surgery, or local tumor invasion to nearby structures preventing radical resection.

III. Patient Quality of Life

The patient's quality of life will be assessed using the FACT-G survey. The survey will be administered at three time points during the exercise protocol and neoadjuvant therapy. Once at the initial exercise session, then again at the midpoint of their neoadjuvant therapy, and finally at the end of their neoadjuvant therapy. Paper surveys will be handed out at the appropriate exercise session and will be returned prior to the patient leaving.

Prospective Secondary Endpoint Data Collection and Basic Recording

IV. Occurrence of other Adverse Events

The EHR will be analyzed for the occurrence of other adverse events that do not directly postpone or cancel surgery. Metrics will include the following categories: non-scheduled preoperative hospitalization, dose reduction, and postponement of neoadjuvant therapy.

V. Perioperative Complications

The following perioperative complications, should they occur, will be gathered from the EHR: Discovery of occult tumor invasion, wound complications, pulmonary complications (Pneumonia, Unplanned reintubation, Pulmonary embolism), cardiovascular complications (cardiac arrest, MI, blood transfusions), and infections (sepsis, UTI). Perioperative complications will be monitored 90 days out from operation.

Identification of Survey Subjects

All patients enrolled in the study will be encouraged to participate and answer surveys. Subjects must fully answer the survey at every timepoint that it is collected. The survey will be available in different languages for patients that might not be fluent English readers.

Patient Quality of Life Survey Recruitment

Patients that meet the inclusion criteria and participate in the surveys will be given a paper survey during scheduled exercise sessions. There will be two scheduled exercise sessions where the survey will be administered. The first survey will be administered at the first exercise session, and this can be before or after starting neoadjuvant therapy. The second time the survey is administered during an exercise session that correlates with the midpoint of neoadjuvant therapy. The survey will then be administered prior to surgery and post-surgery for a total of four collection points

Statistical Analysis of Survey Responses

In order to quantitively describe the data acquired from the FACT-G, descriptive analyses will be calculated for both the IPEP and VEP groups. Descriptive analyses calculated will be used to compare differences over time for overall FACT-G score, as well as its individual domains. ANOVA will also be used because of the repeated measure over time. It is hypothesized that score will increase with time from baseline. Finally, the two groups will be compared to each other.

Statistical Analysis of Demographic and Clinical Characteristics

Descriptive analyses (counts, percentages, means, t-tests/chi-square) will be used to quantify and compare patient characteristics. Similarly, ANOVA will be used to compare differences on all performance measures over time.

Power, Sample Size, and Statistical Analysis for Primary and Secondary Endpoints

The primary endpoint of the power and sample size calculation will be the mean difference in the three primary outcomes between IPEP and VEP patients. IPEP AND VEP groups will be measured at three different time points thus ANOVA will be used for statistical analysis. We expect a sample size of 80 but no less than 78, half in group IPEP and half in VEP. We will need at least 0.8 power to detect a medium effect size (0.5) according to this sample size.

Fitness Tests

Stairs Test

Test Procedures

1. Steps taken were to be of constant rhythm throughout the whole duration of the test.
2. Only one step at a time whilst running was not allowed
3. Not allowed to stop at any point during the climb or use the side-railings for support
4. Investigator will accompany each subject on his or her climb to ensure that subjects followed the protocol accordingly and for patient's safety

Data Collected

- Age:
- BMI:
- time of the climb (CT, in seconds):
- heart rate at the end of the climb (HRend, in beats•min-1):

Vo2 Calculations from Data

For males:

VO2max (ml•kg-1•min-1) = 133 - 0.273 (Age) - 0.672 (BMI) - 0.236 (CT) - 0.232 (HRend)

For females:

VO2max (ml•kg-1•min-1) = 66.69 - 0.135 (Age) - 0.249 (BMI) - 0.128 (CT) - 0.021 (HRend)

Timed Up and Go Test

The test requires the subject to rise from a chair, walk approximately 10 feet at a comfortable pace to a mark placed on the floor, turn around at the 10 feet mark, walk back to the starting point, and return to sitting in the chair.

Karnofsky Performance Scale

Value	Level of functional capacity	Definition
100	Normal, no complaints, no evidence of disease	Able to carry on normal activity and to work; no special care needed
90	Able to carry on normal activity, minor signs or symptoms of disease	
80	Normal activity with effort, some signs or symptoms of disease	
70	Cares for self, unable to carry on normal activity or to do active work	Unable to work; able to live at home and care for most personal needs; various degrees of assistance needed
60	Requires occasional assistance but is able to care for most needs	
50	Requires considerable assistance and frequent medical care	
40	Disabled, requires special care and assistance	Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly
30	Severely disabled, hospitalization is indicated although death is not imminent	
20	Hospitalization is necessary, very sick, active supportive treatment necessary	
10	Moribund, fatal processes progressing rapidly	
0	Dead	

Discussion

The American Cancer Society (ACS) and American College of Sports Medicine (ACSM) have always been at the forefront of cancer exercise. There was a time when a cancer diagnosis came with the recommendation that patients rest as much as possible and avoid physical activity. However, in 2019, a roundtable was assembled by ACSM, including NCI and ACS representation, among others. This panel analyzed exercise data related to cancer patients' prevention, treatment, and survival. The meeting led to an exercise prescription for these patient populations, as seen in figure 2. The virtual program

Effects of Exercise on Health-Related Outcomes in Those with Cancer

What can exercise do?

- **Prevention of 7 common cancers***
  Dose: 2018 Physical Activity Guidelines for Americans: 150-300 min/week moderate or 75-150 min/week vigorous aerobic exercise
- **Survival of 3 common cancers****
  Dose: Exact dose of physical activity needed to reduce cancer-specific or all-cause mortality is not yet known; Overall more activity appears to lead to better risk reduction

*bladder, breast, colon, endometrial, esophageal, kidney and stomach cancers
**breast, colon and prostate cancers

Outcome	Aerobic Only	Resistance Only	Combination (Aerobic + Resistance)
Strong Evidence	Dose	Dose	Dose
Cancer-related fatigue	**3x**/week for **30** min per session of moderate intensity	**2x**/week of **2** sets of **12-15** reps for major muscle groups at moderate intensity	**3x**/week for **30** min per session of moderate aerobic exercise, plus **2x**/week of resistance training 2 sets of 12-15 reps for major muscle groups at moderate intensity
Health-related quality of life	**2-3x**/week for **30-60** min per session of moderate to vigorous	**2x**/week of **2** sets of **8-15** reps for major muscle groups at a moderate to vigorous intensity	**2-3x**/week for **20-30** min per session of moderate aerobic exercise plus **2x**/week of resistance training **2** sets of **8-15** reps for major muscle groups at moderate to vigorous intensity
Physical Function	**3x**/week for **30-60** min per session of moderate to vigorous	**2-3x**/week of **2** sets of **8-12** reps for major muscle groups at moderate to vigorous intensity	**3x**/week for **20-40** min per session of moderate to vigorous aerobic exercise, plus **2-3x**/week of resistance training **2** sets of **8-12** reps for major muscle group at moderate to vigorous intensity
Anxiety	**3x**/week for **30-60** min per session of moderate to vigorous	Insufficient evidence	**2-3x**/week for **20-40** min of moderate to vigorous aerobic exercise plus **2x**/week of resistance training of **2** sets, **8-12** reps for major muscle groups at moderate to vigorous intensity
Depression	**3x**/week for **30-60** min per session of moderate to vigorous	Insufficient evidence	**2-3x**/week for **20-40** min of moderate to vigorous aerobic exercise plus **2x**/week of resistance training of **2** sets, **8-12** reps for major muscle groups at moderate to vigorous intensity
Lymphedema	Insufficient evidence	**2-3x**/week of progressive, supervised program for major muscle groups does not exacerbate lymphedema	Insufficient evidence
Moderate Evidence			
Bone health	Insufficient evidence	**2-3x**/week of moderate to vigorous resistance training plus high impact training (sufficient to generate ground reaction force of **3-4** time body weight) for at least **12** months	Insufficient evidence
Sleep	**3-4x**/week for **30-40** min per session of moderate intensity	Insufficient evidence	Insufficient evidence

Citation: bit.ly/cancer_exercise_guidelines

Figure 2 ACSM Cancer Exercise Guidelines

above is a modification of an existing in-person program at Moncrief Cancer Institute. Moncrief is home to the Harold C. Simmons Comprehensive Cancer Center, the only NCI-designated center in North Texas. Functioning under UT Southwestern, Lisa Ross has a state-of-the-art gym facility where she sees and adapts exercise programs for patients with various primary cancers and survivors. The initial study was geared towards investigating the beneficial effects of an in-person program exercise program on patients receiving neoadjuvant therapy prior to resection. We hypothesized that patients would have fewer complications and reduced delays for their primary treatment, surgery. However, the pandemic disrupted many aspects of life but especially healthcare.

As Lisa Ross transitioned to a virtual platform for her patients, we worked to see if an equivalent exercise program could be made. The resulting program followed current exercise guidelines, as seen in figure 2, and also focused on flexibility, agility, core strength, and balance. Although the patient's workout material at home can be minimal, resistance training can be done using various household products. For example, they used a milk jug with different water levels to simulate different weights. Additionally, patients who had previously worked with the CET also had access to TheraBands, which produce resistance through elastic recoil. Despite being creative for certain patients, most exercise sessions were successful. The MCI transitioned to Zoom to deliver these exercise sessions at home. Although patients are recommended to keep active, it is essential for patient safety that a CET supervise these sessions. Moreover, modifying the program in real-time is crucial, as overexerting and under-exerting are no benefit to the patient. Zoom's encryption also made it an ideal platform for protecting patient health information during this pivotal time.

Having a virtual exercise program is beneficial for a multitude of reasons. As we saw during the pandemic, this was useful in helping patients avoid unnecessary exposure to harmful pathogens. This is especially important in a cancer population undergoing therapy, as most treatments can lead to an immunocompromised state. As patients progress through treatment with this expected outcome, they can be transitioned from in-person to virtual, thus decreasing the risk for adverse effects such as sepsis. Moreover, a cancer diagnosis comes with a substantial financial burden and often for patients of low SES backgrounds. With patients often needing help making it to infusion appointments, the addition of another in-person appointment a week for exercise can be burdensome. Having the ability to take this Zoom session from a computer or even a smartphone at home makes it more feasible. Some institutions may even lend tablets with cellular capabilities to patients without access. Overall, this transition allows for more equitable access to much-needed services for this patient population.

A prospective study was created and detailed in the results section. This study was created to test the non-inferiority of a virtual platform as compared to an in-person one. The study would specifically look at patients between the ages of 18 and 75 diagnosed with a gastrointestinal cancer needing neoadjuvant therapy before resection. This study would also help us understand the effects of exercise on patients receiving neoadjuvant therapy, a specific cancer population that has not been studied heavily. The two study groups would undergo the same basic exercise program tailored to their present activity levels. Although patients would be starting with different capabilities and fitness, it is their progression through the program as chemotherapy is started that is most important. As we know from previous research and the 2019 ACSM panel recommendations: some of the benefits of exercise are undisputable, such as increased quality of life and reduction in cancer-related fatigue. While our study design gauges some of those important aspects, we also wanted to see if exercise could preserve time for surgery, i.e., primary therapy. Chemotherapy's adverse effects on the body might leave patients unfit for surgery leading to a poor prognosis.

Fitness for surgery can be challenging to deduce in a patient with cancer. The current gold standard for assessing fitness is by performing a cardiopulmonary exercise test, CPET. However, performing CPETs can be costly, time-consuming, and not routinely done by most surgeons. We wanted to include three tests in this study that could help identify patient fitness for surgery. Most importantly, we wanted these tests to be easily reproducible in any clinical environment. The first measure is the patient's Karnofsky Score, a standard way of assessing performance status, thus, quantifying the patient's general well-being and activities of daily living. An easy-to-use tool, this can be done by the physicians or nursing team on staff. The Timed Up and Go test is another previously validated test; however, more generally used in the geriatric population. Using this test not only gives us an understanding of the patient's fitness but can tell us if a patient's response time, agility, and balance are improving with exercise. This test is routinely performed in internal medicine clinics and can be performed by most medical staff members. The last test we chose, the Stairs Test, is not only functional but has been used in the past by surgeons to assess fitness. This would allow for both a subjective and objective assessment of the patient's fitness. As described in the results section, a patient's time-to-climb, and other patient data can be plugged into a formula to calculate VO2 max. VO2 max is a central component of CPET and a well-established marker for fitness.

Future Direction

Cancer exercise is undoubtedly a growing field. There is much to parse out from understanding the physiologic effect exercise can have on a tumor microenvironment to understanding its role as a treatment adjunct. Our study has seen many changes, but we believe the current design aims to answer many important questions. For starters, it looks specifically at patients undergoing neoadjuvant therapy but also assess the validity of delivering these programs via a virtual platform. We believe the study is adequately designed with our only issue having been recruitment. We suggest following the study design but conducting it as a multi-center study. Our study required many modifications, but we believe the current design answers many important questions and leads to others. It suggests a standardized virtual supervised exercise platform in the neoadjuvant setting. We suggest further validation against live patients as suggested in our initial study. We suggest therapeutic and diagnostic exercise tolerance testing throughout the course of the disease from the time of diagnosis, through their treatment and beyond.

Conclusion

In conclusion, we propose a valid cancer exercise program exists that can be adapted for use in a virtual platform. Its use in the neoadjuvant setting, contributes significant knowledge to the field and shift the focus to initiating exercise treatment at the time of diagnosis rather than the typical post treatment settings The exercise program designed incorporated all ACSM's cancer exercise guidelines. Moreover, it was still a safe option for patients as they were supervised during each session. A virtual platform not only allows for safer environments with immunocompromised patients, but it can also help with adherence, and makes access more equitable. Moreover, following the study design contributes significant knowledge to the field and shifts the focus from commonly studied areas of exercise during survivorship or adjuvant therapy. The investigative study made with Moncrief Cancer Institute experts aims to prove the noninferiority of exercise programs delivered online. This data will also establish functional tests that can assess patient's fitness for surgery; thus, allowing for a more standardized approach by surgical oncologists.

Compliance

The investigative study to examine the virtual exercise program versus in-person will be subject to the IRB and the study will need IRB approval as well as the investigators needing to complete Human Subjects training.

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