Protocol Title:
Exercise in Radiation Therapy (EXERT)

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If you need help...

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<thead>
<tr>
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<tr>
<td><strong>Office for Research Protections Human Research Protection Program</strong></td>
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1.0 Objectives

1.1 Study Objectives and Endpoints

Aim 1. To determine the acceptability, feasibility, and safety of an exercise intervention among cancer patients receiving radiation therapy. We anticipate that >25% of approached patients will consent to the protocol; >33% of eligible radiation therapy patients who consent will perform the exercise prescribed (based on the response rate from EnACT); and <25% of participants will experience a musculoskeletal impairment (without treatment alterations) and <5% will experience a musculoskeletal injury with symptoms lasting ≥ week or requiring medical attention. Our approach will be to include patients receiving definitive RT; excluding patients at high risk for side effects from combination therapy, including fracture or cardiovascular events.

Aim 2. To discern the clinical outcomes of patients receiving RT+ET. The hypothesis is that adding ET to RT will improve patient reported outcomes and physical functioning. Our approach will be to use standardized questionnaires and assessment tools: patient reported outcomes will be assessed using Common Terminology Criteria for Adverse Events – Patient Reported Outcomes (CTCAE-PROs), loaded onto tablets that patients use in the clinic. Questions will assess global PROs relevant to the ability to tolerate RT, including fatigue, pain, nausea, vomiting; and disease-site-specific PROs, including genitourinary/sexual symptoms for patients receiving pelvic RT. RT dose alterations will be documented. Scores will be compared pre-vs post- RT. We will also use standardized measures already used in EnACT, including grip strength, 30-second chair stand, timed up-and-go, and 4-stage balance. Scores will be compared pre-vs post- RT.

2.0 Background

2.1 Scientific Background and Gaps

In 2018, an estimated 1,735,350 new cases of cancer will be diagnosed in the US. The principal treatment options for cancer include surgery, systemic therapy, and radiation therapy (RT). All treatment options cause toxicity and reductions in quality of life (QOL). International oncologic guidelines recommend exercise therapy (ET) to improve QOL and toxicity associated with the disease and treatment, and to receive the full dose of therapy. To date, most clinical studies of the effect of ET are limited to patients receiving chemotherapy or survivors. Few studies have examined the effect of ET for patients receiving RT. The rationale for the current Exercise Therapy and Radiation Therapy (EXERT) study is that 60% of cancer patients receive RT, and in cancers with a high incidence (e.g. breast, prostate, lung), RT is frequently part of the definitive therapy paradigm. Thus, it is critical to understand if ET may improve patient reported outcomes, including toxicity and quality of life. Our long-term goal is to identify potential synergistic effects of RT and ET on treatment outcomes and short and long-term side effects of cancer patients and identify subgroups of patients likely to gain the most benefit from the combination. The central hypothesis is that the addition of ET to RT improves treatment tolerance, patient reported outcomes and physical function for certain cancers, thereby improving the therapeutic window (Figure 1).

Preliminary data from a sister protocol running at Penn State Cancer Institute, Exercise in All ChemoTherapy (EnACT), demonstrates the infrastructure and support to implement our goals. Of the 139 eligible patients, 108 consented; of these 108, 93 began the study; of these 93, 41 completed, and 37 are still in the study. Thus, acceptability is 67% (108/139), goal >50%; feasibility is 87% (33/38); and dropout rate is 6%. No patients have experienced ET-related injury (goal < 5%). There has been no significant difference in the timed up
and go (11.6 seconds, SD 10.7 pre-therapy vs 10.4 seconds, SD 1.6 post therapy, p=0.15). There has been an improvement in the 30-second chair stand (mean 13 iterations, SD 3.84 pre-therapy vs 14, SD 3.98 post-therapy, p=0.05). For EXERT, we will enroll 50 patients to a single-arm, prospective study of ET among those receiving RT. Patients will be >18 years of age, with any type of cancer, receiving 3-9 weeks of RT. Certified exercise oncology specialists will personalize, prescribe, and guide ET, including twice weekly resistance training (5 exercises, progressing resistance), and walking exercise (building weekly time as tolerated), performed at home, with supervised training at the Exercise Medicine Unit in the cancer institute.

Methods to improve quality of life in cancer patients
Cancer patients experience a decline in their quality of life (QOL) from their disease and from therapy. Several methods have been attempted at improving QOL, including altering the use of a type of chemotherapy or surgery, using granulocyte colony stimulating factor support, introducing religion and spirituality, and using cognitive behavioral therapy. These interventions have generally been limited because they either focus on altering the prescription of the therapy to treat the cancer (e.g. surgery, chemotherapy), or they likely have no impact on the physiology of the disease and the patient to provide an improvement in outcomes or toxicities (e.g. religion). Exercise therapy (ET) is a complementary treatment that improves QOL, other patient reported outcomes, and surrogates of longevity of cancer patients. Psychologically, moderate ET has been shown to improve fatigue, anxiety, and self-esteem. Moreover, ET has physiologic benefits in that it improves vascular stability, muscle strength, and muscle mass. Thus, ET may be an excellent tool to improve patients’ abilities to tolerate treatment by widening the therapeutic window (Figure 1 above). Several national and international agencies recommend ET for all persons following a cancer diagnosis.

Guidelines for exercise therapy among cancer survivors
However, despite guidance on implementing ET recommendations for cancer patients, ET counseling is still not standard of care in cancer centers across the US, and it is not mentioned in most cancer treatment guidelines for those receiving therapy. Instead, ET has generally been listed as an option for certain cancer survivors, because it has mostly been studies among patients previously treated with systemic therapy (e.g., chemotherapy, hormone therapy) for prostate and breast cancer.

Exercise therapy among cancer patients receiving radiation therapy
About 60% of cancer patients will receive radiation therapy (RT) at some point in their disease course. However, as of 2018, there are no recommendations from the American Society for Radiation Oncology (ASTRO), the European Society for Radiation Oncology (ESTRO), or the National Comprehensive Cancer Network (NCCN) regarding the integration of ET in the treatment regimen for cancer patients receiving RT. The lack of integration into the paradigm of RT for cancer patients is due to several factors: (1) there is limited clinical evidence supporting concurrent RT+ET, and clinicians are concerned that introduction of ET will not be feasible in a clinic; (2) combination therapy may introduce toxicity; (3) clinics lack a dedicated ET unit with supervised support; and (4) combination ET+RT has generally only been attempted across single disease sites (e.g. prostate alone, breast alone). The lack of integration of RT+ET is problematic because clinical and preclinical data suggest that there is synergy between these therapies that improves patient outcomes and toxicities (Figure 2). In the current work, we will show that integration of RT+ET across a diverse range of tumors (Aim 1) is safe, feasible, and has limited toxicity; improves clinical patient reported outcomes (Aim 2).

Clinical evidence supporting radiation therapy + exercise therapy
In the clinical setting, there have been only main disease sites where investigators have studied the interaction of RT and ET: breast and prostate cancer (pink and blue in the figure). In the realm of breast cancer, Lipsett et al performed a systematic review and meta-analysis of trials concurrent RT+ET. Among 9 studies, ET reduced the development of fatigue vs standard care (standardized mean difference, -0.46, 95% confidence interval, -0.79 to 0.14). Similarly, Taaffe et al performed a randomized controlled trial of prostate cancer patients receiving androgen
deprivation therapy, randomized to 6 months of supervised exercise followed by a 6 month home-based maintenance program, or to printed physical activity educational material. Those in the supervised exercise arm had improved muscle performance and body composition, including lean and fat mass, and appendicular skeletal muscle. These studies suggest that RT+ET is acceptable and feasible for both male and female patients; a study for many cancer patients receiving RT is warranted.

Although these clinical data are encouraging, there are several unknown factors about ET+RT. For example, patient acceptability and feasibility have not been characterized outside of prostate and breast cancer. Further, ET+RT may be better tolerated by patients in certain disease sites compared to others; the impact of ET+RT to reduce toxicities may be more pronounced in disease sites that where treatments have a relatively narrow therapeutic window. Additionally, the exercise intervention type may play a role in acceptability and patient reported outcomes.

Preclinical evidence supporting radiation therapy + exercise therapy

The improvement in the therapeutic window is likely secondary to a left-shift of the tumor control probability curve (i.e. making RT more effective in killing cancer cells), or secondary to a right-shift of the normal tissue complication probability curve (i.e. making patients less likely to experience toxicity from therapy). The shift in either curve is secondary to a physiologic mechanism, and understanding this mechanism will advance our understanding of cancer therapy.

In the preclinical setting, combination RT+ET is postulated to improve outcomes and toxicities for many cancer patients, as they affect the endocrine system, myokine release, autonomic function, immune function, the extracellular tumoral microenvironment, and neurocognitive function. For example, with respect to the endocrine system, ET causes systemic epinephrine production, interleukin (IL)-6 secretion, and mobilization of cytotoxic immune cells that may infiltrate the tumor. Similarly, ET stimulates epinephrine-dependent Hippo YAP signaling, decreasing cancer cell seeding and formation of metastases. Thus, combination of ET and RT may be beneficial for patients who have metastatic disease. After several weeks of ET, there is a decrease in pro-inflammatory markers (e.g., C-reactive protein [CRP], tumor necrosis factor [TNF]-α, IL-6), which are associated with chronic toxicity (e.g., fibrosis) from RT. ET improves and treats certain comorbidities (e.g., diabetes), which increase toxicity of RT; thus, a study combining RT and ET may also decrease toxicities in patients.

ET reduces systemic adiposity, thereby decreasing systemic estrogen, which is a growth stimulus for certain cancers expressing the estrogen receptor (e.g., breast). Further, over weeks, ET increases systemic muscle mass. Maintenance of muscle mass is most important in (1) patients with swallowing dysfunction, including those with pancreatic cancer, esophageal cancer, stomach cancer, head and neck cancer; (2) cancers creating muscle-wasting hormones (parathyroid hormone-related protein [PTHrP] and myostatin), as seen in colon and lung cancer; and (3) patients receiving systemic treatments that cause sarcopenia, including androgen deprivation and chemotherapy. Prevention of sarcopenia decreases the risk of perioperative complications with neoadjuvant RT. Thus, there is potential synergy of RT and ET to improve tolerance of patients receiving combined modality therapy.

ET increases autonomic stimulation, pulse, and blood pressure, and causes mild hyperthermia. Subsequently, there is an increase in natural killer (NK) cell and cytotoxic T-cell trafficking, which are important in cancer cell killing after RT. Further, RT and hyperthermia act synergistically: RT causes DNA damage, while hyperthermia causes damage to proteins. ET has also been shown to increase blood vessel diameter and reduce hypoxia. DNA damage caused by RT is contingent on oxygenation, and an improvement in tumoral oxygenation would be expected to increase cancer killing. Taken together, these data suggest that combination RT and ET would be synergistic in treatment of cancer of the pancreas, endometrium, cervix, soft tissue (sarcomas), and brain, which are all hypoxic and are sometimes also treated with hyperthermia.

With respect to the immune system, ET and RT both independently increase myokines, including IL-6, IL-7, and IL-5. These myokines cause NK and T-cell proliferation, differentiation, maturation, infiltration of tumor and RT also independently increase peritumoral release of TNF-α, which induces macrophage activation towards a pro-inflammatory or classically-activated (M1) phenotype and enhances myeloid cell recruitment, causing increased anti-tumoral response and decreased chronic tissue injury. Similarly, ET and RT independently cause an increase in IL-1β, which subsequently causes CD8+ T-cell accumulation, and accumulation of monocytes and M1 macrophages. ET also causes conversion of M1 macrophages to M2 macrophages, which may have increased activity against various cancers. Additionally, ET decreases immunosuppressive factors, including lactate and lactate dehydrogenase. Taken together, these results suggest that RT and ET would have synergistic anti-tumoral effects in tumors that are immunogenic, including melanoma, renal cell carcinoma, hepatocellular carcinoma, non-small cell lung cancer,
gastroesophageal carcinoma, cervical carcinoma, Hodgkin lymphoma, and colorectal carcinoma. Notably, patients with these cancers have typically been excluded from trials evaluating RT + ET.

With respect to **neurocognitive function**, ET improves short term memory and processing.\(^75\)\(^-\)\(^77\) Preservation of neurocognitive function may be most important to those receiving RT to the brain.\(^78\)\(^-\)\(^80\) Demonstration of a positive impact of ET would be important given the relative failure of other neuroprotective treatments available for these patients: (1) the use of RT + memantine has not been shown to preserve neurocognitive function; and (2) the use of hippocampal-sparing RT is still investigational. Thus, combination RT and ET could serve as a new therapy to preserve neurocognitive function for patients with cancers of the **central nervous system** among **all cancer patients**.

As of 2018, there have been no studies focusing on combination of exercise therapy and RT for all cancer patients. Herein, we capitalize on the ability of our center to assess the synergy of RT and exercise therapy. In my analysis of the Surveillance, Epidemiology, and End Results database, I showed that patients with cancers of the **liver, ovary, gallbladder, pancreas, esophagus, cervix, head and neck, lung, and nervous system** have had limited improvement in outcomes from the 1970s to the 2010s.\(^81\) These patients are in dire need of novel treatment approaches, and combination RT + exercise therapy may be the ideal low-cost strategy. The long-term goal is to identify potential synergistic effects of RT and exercise therapy on the outcomes of cancer patients to design better interventions and identify subgroups of patients likely to gain the most benefit from the combination. The central hypothesis is that the combination of radiation therapy and exercise therapy is an acceptable, feasible and safe treatment approach for cancer patients that decreases toxicity and improves survival, thereby **increasing the therapeutic ratio**. Exercise therapy will become a standard co-treatment that is integrated in the guidelines set forth by ASTRO, ESTRO, and the NCCN.
<table>
<thead>
<tr>
<th>Effect</th>
<th>Physiologic effects of exercise therapy (approximate time after event)</th>
<th>Physiologic effects of RT</th>
<th>Biologic effects of combined therapy</th>
<th>Cancers or normal tissue most affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systemic endocrine</td>
<td></td>
<td></td>
<td>NK and T-cell proliferation, differentiation, maturation, infiltration of tumor</td>
<td>Multiple cancers</td>
</tr>
<tr>
<td>Acute systemic epinephrine production, IL-6 secretion, mobilization of cytotoxic immune cells</td>
<td>Increased in minutes&lt;sup&gt;10&lt;/sup&gt; Negligible / unknown</td>
<td>Negligible / unknown</td>
<td>Possible interaction through abscopal response</td>
<td>Metastatic cancers, particularly those where local RT may be effective in metastatic disease&lt;sup&gt;22&lt;/sup&gt;</td>
</tr>
<tr>
<td>Long-term changes in pro-inflammatory markers (e.g. CRP, TNF-α, IL-6)</td>
<td>Decreased in weeks&lt;sup&gt;29,34&lt;/sup&gt; Typically negligible</td>
<td>Typically negligible</td>
<td>Decreased toxicities in normal tissues.</td>
<td>Normal tissue</td>
</tr>
<tr>
<td>Comorbid conditions (e.g. diabetes)</td>
<td>Improved in weeks</td>
<td>Negligible; however, worse RT toxicity with comorbidities&lt;sup&gt;33&lt;/sup&gt; Negligible; however, worse RT toxicity with comorbidities&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Decreased growth stimulus for cancer cells, synergistic with tumoral RT effects</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Decreased from lower adiposity&lt;sup&gt;34&lt;/sup&gt; Negligible / unknown</td>
<td>Decreased / unknown</td>
<td>Decreased growth stimulus for cancer cells, synergistic with tumoral RT effects</td>
<td>Breast cancer</td>
</tr>
<tr>
<td>Testosterone</td>
<td>Decreased with fitness&lt;sup&gt;35&lt;/sup&gt; Negligible / unknown</td>
<td>Decreased / unknown</td>
<td>Decreased growth stimulus for cancer cells, synergistic with tumoral RT effects</td>
<td>Prostate cancer</td>
</tr>
<tr>
<td>Fat mass</td>
<td>Decreased in weeks&lt;sup&gt;36&lt;/sup&gt; Negligible direct. However, weight gain after therapy in certain cancers (prostate, breast)&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Negligible direct. However, weight gain after therapy in certain cancers (prostate, breast)&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Decreased growth stimulus for cancer cells. Decreased ability of cancer cells to repair DNA. Effects synergistic with tumoral RT effects.</td>
<td>Multiple cancers (especially prostate, breast); normal tissue</td>
</tr>
<tr>
<td>Insulin, IGF1 production</td>
<td>Increased in body within minutes; concurrent reductions in circulating levels&lt;sup&gt;34,35,36,37&lt;/sup&gt; Negligible / unknown</td>
<td>Negligible / unknown</td>
<td>Decreased growth stimulus for cancer cells. Decreased ability of cancer cells to repair DNA. Effects synergistic with tumoral RT effects.</td>
<td>Multiple cancers</td>
</tr>
<tr>
<td>Leptin</td>
<td>Decreased in weeks&lt;sup&gt;36,37&lt;/sup&gt; Negligible / unknown</td>
<td>Decreased / unknown</td>
<td>Decreased growth stimulus for cancer cells. Decreased ability of cancer cells to repair DNA. Effects synergistic with tumoral RT effects.</td>
<td>Multiple cancers (especially prostate, breast); normal tissue</td>
</tr>
<tr>
<td>Muscle / myokines</td>
<td></td>
<td></td>
<td>Prevention of sarcopenia/cachexia, which has high incidence in certain cancers. Decreased risk of perioperative complications&lt;sup&gt;45&lt;/sup&gt; Important in (1) patients with swallowing dysfunction: pancreatic cancer, esophageal cancer, stomach cancer, head and neck cancer; (2) cancers creating muscle-wasting hormone (PTHrP&lt;sup&gt;50&lt;/sup&gt;, myostatin&lt;sup&gt;51&lt;/sup&gt;): colon, lung; (3) treatment causing sarcopenia: ADT, chemo&lt;sup&gt;59-42&lt;/sup&gt;</td>
<td>Muscle tissue.</td>
</tr>
<tr>
<td>Muscle mass</td>
<td>Increased in weeks&lt;sup&gt;35,36&lt;/sup&gt; Negligible / unknown direct effect. However, decreased with certain treatments (e.g. chemo-RT, ADT)</td>
<td>Negligible / unknown direct effect. However, decreased with certain treatments (e.g. chemo-RT, ADT)</td>
<td>Possible prevention of loss of function</td>
<td>Muscle tissue.</td>
</tr>
<tr>
<td>IL-6, IL-7, IL-15</td>
<td>Increased in minutes&lt;sup&gt;38&lt;/sup&gt; Increased&lt;sup&gt;57&lt;/sup&gt; Increased&lt;sup&gt;57&lt;/sup&gt;</td>
<td>Increased&lt;sup&gt;57&lt;/sup&gt;</td>
<td>NK and T-cell proliferation, differentiation, maturation, infiltration of tumor. Increase immune response Antagonize TGF-β and Wnt signaling</td>
<td>Multiple cancers (especially melanoma).</td>
</tr>
<tr>
<td>Oncostatin M</td>
<td>Increased&lt;sup&gt;46&lt;/sup&gt;</td>
<td>Decreases cancer cell viability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPARC</td>
<td>Increased&lt;sup&gt;47&lt;/sup&gt;</td>
<td>Decreases tumorigenesis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone</td>
<td></td>
<td></td>
<td>Possible prevention of loss of function</td>
<td>Multiple cancers (especially prostate, breast); normal tissue prevention of fracture</td>
</tr>
<tr>
<td>Bone mineral density</td>
<td>Increased in weeks</td>
<td>Negligible / unknown; loss of density in irradiated area Negligible / unknown; loss of density in irradiated area</td>
<td></td>
<td></td>
</tr>
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</table>

Table 1. Interaction between exercise therapy and radiation therapy on various body systems and cancers
| Neuro-cognitive | Improved cognition  & Decreased with brain RT. & Decreased with brain RT. & Prevention of cognitive decline, depression, suicide & Multiple cancers (especially those of brain) |
|----------------|----------------------|----------------------|----------------------|----------------------|

| Extracellular tumoral microenvironment | Increased in minutes; concurrent reductions in circulating levels & Increased in minutes & Induce macrophage activation towards a pro-inflammatory (M1) phenotype and enhance myeloid cell recruitment. Increased anti-tumoral response; decreased chronic tissue injury & Multiple cancers |
|----------------|----------------------|----------------------|----------------------|----------------------|

| Tumor growth kinetics | Decreased melanoma, lung, colon, breast, HCC, head and neck & Decreased, short/long-term & Decreased, short/long-term & Multiple cancers |
|----------------|----------------------|----------------------|----------------------|----------------------|

| Cellular energy stress | Induces stress, higher susceptibility to fasting, caloric restriction, RT in minutes & Increased & Increased & Higher susceptibility to damage & Multiple cancers |
|----------------|----------------------|----------------------|----------------------|----------------------|

| Peptide pools and mTOR activation | Decreased in minutes & Decreased in seconds-minutes & Decreased cell growth & Increased IL-15 production, NK cell production, tumor cell recognition; synergistic effects with stress & Multiple cancers |
|----------------|----------------------|----------------------|----------------------|----------------------|

| AMPK | Increased in organs and tumors & Activated in seconds & Improvement in normal tissue repair. Initiates DNA damage repair. Activates ATM. Inhibits mTOR to inhibit protein translation. & Multiple tumors and normal tissues |
|----------------|----------------------|----------------------|----------------------|----------------------|

| Fas production | Increased in minutes, lasting weeks & Increased in minutes, lasting weeks & Promotion of tumor death pathways & Multiple cancers |
|----------------|----------------------|----------------------|----------------------|----------------------|

<table>
<thead>
<tr>
<th>MHC-1</th>
<th>Up-regulation in</th>
<th>Up-regulation in</th>
<th>Increased immune recognition</th>
<th>Multiple cancers</th>
</tr>
</thead>
</table>
2.1.4 Premise for current trial
As of 2018, there are no studies evaluating the impact of exercise therapy and radiation therapy among all patients with cancer. Thus, we plan a single group, pre-post intervention study to capture the effects of an exercise intervention on the average radiation therapy patient.

2.2 Previous Data

**International**
Previously published work on exercise interventions among all cancer patients revealed few injuries, no adverse effects of exercise during radiation therapy on relative dose intensity, and improvements in fatigue, pain, fitness, physical function, symptom scales, quality of life, depression, and anxiety. However, these studies generally recruited fewer than 15% of the patient pool originally targeted for recruitment. Further, comparison of patient characteristics of those who entered these studies reveals that study participants tend to be younger, healthier, and have lower stage cancer, to be better educated, and to reflect less distress from their diagnosis. As such, it may not be surprising to note that it has been challenging to translate these results into clinical practice. The overarching goal of this protocol is to gather the necessary data to undertake a program of research in the area of dissemination and implementation science to translate the RCT evidence base on exercise during radiation therapy into clinical practice.

**Penn State Cancer Institute**
Table 2 details the patients treated at Penn State Cancer Institute in FY 2016. Each month, 80 patients (standard deviation, 9) start a course of definitive radiation therapy in the Department of Radiation Oncology. Each day, there is an average of 52 patients on treatment (SD, 4). Roughly half of these patients have an ECOG status of 0-2 and would be eligible for the current protocol. Thus, we estimate that roughly 20-40 patients could be eligible for EXERT per month.

<table>
<thead>
<tr>
<th>Month</th>
<th>High dose rate brachytherapy procedures</th>
<th>New Starts</th>
<th>Total body irradiation</th>
<th>Stereotactic</th>
<th>Intensity modulated</th>
<th>Standard Total</th>
<th>Average Daily Patient Load</th>
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</thead>
<tbody>
<tr>
<td>July</td>
<td>19</td>
<td>72</td>
<td>8</td>
<td>23</td>
<td>481</td>
<td>616</td>
<td>1120</td>
</tr>
<tr>
<td>August</td>
<td>0</td>
<td>61</td>
<td>1</td>
<td>13</td>
<td>334</td>
<td>575</td>
<td>922</td>
</tr>
<tr>
<td>September</td>
<td>0</td>
<td>72</td>
<td>6</td>
<td>23</td>
<td>277</td>
<td>753</td>
<td>1053</td>
</tr>
</tbody>
</table>

Table 2. Patients receiving treatment in the Department of Radiation Oncology at Penn State Cancer Institute.
2.3 Study Rationale

The slow maturation process from exercise research to clinically integrated cancer programming is similar to that experienced in cardiac rehabilitation. Challenges to knowledge translation in this field of exercise oncology persist and require strategic approaches to ensure that exercise programming is approached in a manner that is widely acceptable to patients and their clinicians. Therefore, we seek to conduct a safety and feasibility study to assess patient interest in exercise, adherence to exercise during radiation therapy, and logistics of operating an exercise intervention program in the department. We hope to gather data that will lead to externally funded dissemination and implementation research grants on the benefits of exercise during radiation therapy. A new exercise facility has been built within the 2nd floor in the Penn State Cancer Institute in anticipation of this protocol.

3.0 Inclusion and Exclusion Criteria

3.1 Inclusion Criteria for cancer patients
- Males and females ≥18 years of age
- Fluent in written and spoken English
- Must be able to provide and understand informed consent
- Must have an ECOG PS of ≤ 2
- Diagnosed with a malignancy
• Cancer patients (stage 1-4)
• Treatment to primary site or metastatic disease
• Scheduled to receive radiation therapy at Penn State Cancer Institute
• Absence of absolute contraindications for exercise according to the American Heart Association (see below)
• Primary attending oncologist approval
• Receiving treatment as an outpatient

3.2 **Exclusion Criteria for cancer patients**
• Receiving radiation therapy at a location other than Penn State Cancer Institute
• Not fluent in written and spoken English
• Evidence in the medical record of an absolute contraindication for exercise
• Cardiac exclusion criteria:
  o Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system
  o History of acute coronary syndromes (including myocardial infarction and unstable angina), coronary angioplasty or stenting within the past 6 months prior to the start of radiation therapy
  o Uncontrolled arrhythmias; patients with rate controlled atrial fibrillation for >1 month prior to start of radiation therapy may be eligible
  o syncope
  o acute myocarditis, pericarditis, or endocarditis
  o acute pulmonary embolus or pulmonary infarction
  o thrombosis of lower extremities
  o suspected dissecting aneurysm
  o pulmonary edema
  o respiratory failure
  o acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise
  o mental impairment leading to inability to cooperate
• Pregnant women
• In-patient receiving radiation therapy for a radiation emergency (e.g. cord compression, SVC syndrome, brain metastases)
• High risk of fracture or spine instability (Mirels score ≥7, SINS ≥7)
• Children (the protocol will only include individuals 18 and older)

3.3 **Early Withdrawal of Subjects**

3.3.1. **Criteria for removal from study**
Subject consent withdrawal for any reason; consent process will ensure that patients understand this does not mean radiation therapy would stop.
Development of contraindication(s) to exercise training.
Worsening physical condition that indicates medical requirement of stopping exercise (as determined by treating oncologist).

3.3.2. **Follow-up for withdrawn subjects**
No follow up for withdrawn subjects. The patients will continue with their usual follow-up recommendations per standard of care.
4.0 Recruitment Methods

4.1 Identification of subjects

4.1.1 Cancer patients
Research staff members will pre-screen electronic medical records weekly for: new patients scheduled to receive radiation therapy at the Penn State Cancer Institute, and are diagnosed with cancer. Following identification of these patients, research staff will email the patient’s radiation oncologist via secure email for approval to approach the patient for the study and for medical clearance.

4.2 Recruitment process

4.2.1 Cancer Patients
If the radiation oncologist gives clearance, research staff will approach the patient either by phone following oncologist clearance (see script), or at their first fraction for presentation of the study. Meeting and consenting the patient earlier in their treatment would allow them to digest the information being discussed and start the study earlier in their treatment.

4.3 Recruitment materials

4.3.1 Cancer Patients
See attached script for staff member presentation of study.

4.4 Eligibility/screening of subjects

4.4.1 Cancer Patients
After initial presentation of the study to the patient, research staff will confirm eligibility utilizing the eligibility checklist. If the patient is deemed ineligible during this time, we will inform the patient that deidentified information/data will be kept and the purpose of keeping this information.

5.0 Consent Process and Documentation

5.1 Consent Process

5.1.1 Obtaining Informed Consent

5.1.1.1 Timing and Location of Consent
5.1.1.1.1 Cancer Patients
If the patient remains interested in the study at the end of the study presentation we will confirm eligibility via the eligibility checklist. We will then walk through the consent form and answer any remaining questions. We will then obtain written informed consent.

5.1.2 Coercion or Undue Influence during Consent

5.1.2.1 Cancer patients
While exercise is recommended during cancer treatment, patients will be reminded that self-directed physical activity is also an available alternative for them. Further, because faculty, staff, and students of Penn State University will not be excluded, we will include specific language to clarify that the patient relationship with their clinicians at Penn State will not be altered if they choose not to consent or choose to withdraw later.
5.1.2 Waiver or alteration of the informed consent requirement
Requested for screening of medical records for recruitment purposes only. We also request that we are able to keep de-identified pre-screening data for those ineligible or not interested in the study.

5.2 Consent Documentation
5.2.1 Written Documentation of Consent
Written informed consent document will be obtained from all patient participants prior to participation in any study activities.

5.2.2 Waiver of Documentation of Consent (Implied consent, Verbal consent, etc.)
N/A

5.3 Consent – Other Considerations
5.3.1 Non-English Speaking Subjects
Study staff are not fluent in languages other than English.

5.3.2 Cognitively Impaired Adults
N/A

5.3.2.1 Capability of Providing Consent
This will be determined by the radiation oncologist in cancer patient clearance for the study and is assumed for the radiation oncology clinician participants.

5.3.2.2 Adults Unable To Consent
A contraindication to exercise training/counseling, and thus an ineligibility criteria is mental impairment leading to inability to cooperate. It is assumed that this will not be an issue for the radiation oncology clinicians.

5.3.2.3 Assent of Adults Unable to Consent
N/A

5.3.3 Subjects who are not yet adults (infants, children, teenagers)

5.3.3.1 Parental Permission
N/A

5.3.3.2 Assent of subjects who are not yet adults
N/A

6.0 HIPAA Research Authorization and/or Waiver or Alteration of Authorization

6.1 Authorization and/or Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

Check all that apply:

- [ ] Not applicable, no identifiable protected health information (PHI) is accessed, used or disclosed in this study. [Mark all parts of sections 6.2 and 6.3 as not applicable]

- [x] Authorization will be obtained and documented as part of the consent process. [If this is the only box checked, mark sections 6.2 and 6.3 as not applicable]
Partial waiver is requested for recruitment purposes only (Check this box if patients’ medical records will be accessed to determine eligibility before consent/authorization has been obtained). [Complete all parts of sections 6.2 and 6.3]

☐ Full waiver is requested for entire research study (e.g., medical record review studies). [Complete all parts of sections 6.2 and 6.3]

☐ Alteration is requested to waive requirement for written documentation of authorization (verbal authorization will be obtained). [Complete all parts of sections 6.2 and 6.3]

6.2 Waiver or Alteration of Authorization for the Uses and Disclosures of PHI

6.2.1 Access, use or disclosure of PHI representing no more than a minimal risk to the privacy of the individual

6.2.1.1 Plan to protect PHI from improper use or disclosure
Information is included in the “Confidentiality, Privacy and Data Management” section of this protocol.

6.2.1.2 Plan to destroy identifiers or a justification for retaining identifiers
We will identify eligible patients through electronic medical records prior to their consent in the study (pre-screen eligibility criteria). Information from the pre-screening will be collected and retained (not to include PHI) in order to track trends of those being screened, deemed ineligible, etc.

6.2.2 Explanation for why the research could not practicably be conducted without access to and use of PHI
As we will be conducting the exercise intervention in the Exercise Medicine Unit located in the Penn State Cancer Institute we will be reviewing electronic patient records for this location. Further, this location also conducts infusions for MS patients, transplant patients, and rheumatoid arthritis patients. Therefore, screening patients at this location is necessary for identification of eligible patients.

6.2.3 Explanation for why the research could not practicably be conducted without the waiver or alteration of authorization
Pre-screening individuals through electronic medical records allows for the timing of physician approval and approach of the patient. This study flow is being utilized to minimize clinician burden for clearing patients for eligibility, and to maximize our ability to determine the denominator of patients who could have participated in the study, which is required for the primary outcomes of safety, feasibility, and acceptability. In order to lessen the burden on the patient by extending a current visit or asking for additional visits to the institution, we will seek verbal consent authorization over the phone.

6.3 Waiver or alteration of authorization statements of agreement

Protected health information obtained as part of this research will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other permitted uses and disclosures according to federal regulations.
The research team will collect only information essential to the study and in accord with the ‘Minimum Necessary’ standard (information reasonably necessary to accomplish the objectives of the research) per federal regulations.

Access to the information will be limited, to the greatest extent possible, within the research team. All disclosures or releases of identifiable information granted under this waiver will be accounted for and documented.

7.0 Study Design and Procedures

7.1 Study Design
Pre/post single group (non-controlled) feasibility intervention trial. The study schema is outlined in Figure 3.

Figure 3. Study schema. In Part I, a patient is seen in consultation, consented, and simulated for radiation therapy. Prior to initiation. In Part II, radiation therapy is delivered, once per day, five days per week, for 1-8 weeks. A weekly exercise therapy session is performed, and the patient is counseled on home exercise. Part III is the first follow up of the patient.

7.2 Study Procedures

7.2.1.1 Clinical covariates:
Detailed clinical covariates will be obtained from a Health Behaviors Questionnaire (HBQ Exert) and medical record review including demographics (age, gender, race), cardiovascular history and risk factors (hypertension, arrhythmia, hyperlipidemia, tobacco use, family history of cardiac disease), clinical variables (blood pressure, weight), cancer factors (stage, histology, location), cancer treatment regimen (radiation dose, chemo use), and medication use. These factors will be assessed in examining the patient acceptability of the study.

7.2.1.2 Safety assessment
Our team has developed a standardized survey (Injury History Questionnaire) for assessing injuries as well as discomfort from exercise. This survey will be administered at the end of radiation therapy. We will evaluate the number of injuries over the length of each patient’s chemo regimen and adjust the number by the number of weeks of radiation therapy. In addition, the exercise professional delivering the intervention will ask about any new injuries or discomfort at each encounter (radiation fraction) and record any issues that require a modification to exercises.

7.2.1.3. Quality of life surveys:
Godin Physical Activity Questionnaire, Barriers to Exercise RM 5-FM, Work Productivity and Activity Impairment Questionnaire, Scored Patient-Generated Subjective Global Assessment (PG-SGA), EORTC Quality of life questionnaire, ECHO EXERT and Health Belief Scale and adverse effects of treatment (CTCAE-PRO), as per Table 3. These will be administered during the first and last scheduled counseling session through REDCap.

The CTCAE-PRO will be analyzed descriptively for future studies.

### Table 3. CTCAE-PRO questions to be used, depending on cancer disease site.

<table>
<thead>
<tr>
<th>Question number</th>
<th>Statistical plan</th>
<th>Head/Neck</th>
<th>Pelvis male (prostate, rectal, anal)</th>
<th>Pelvis female (endometrial, cervix, rectal, anal)</th>
<th>Breast</th>
<th>Thorax (lung, esophagus, select lymphomas)</th>
<th>Brain (glioma, meningioma)</th>
<th>Upper abdomen (pancreas, liver, stomach, retroperitoneal sarcoma)</th>
<th>Extremity (sarcoma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Anxious</td>
<td>Anxious</td>
<td>Anxious</td>
<td>Anxious</td>
<td>Anxious</td>
<td>Anxious</td>
<td>Anxious</td>
<td>Anxious</td>
<td>Anxious</td>
</tr>
<tr>
<td>2</td>
<td>Evaluate</td>
<td>Discouraged</td>
<td>Discouraged</td>
<td>Discouraged</td>
<td>Discouraged</td>
<td>Discouraged</td>
<td>Discouraged</td>
<td>Discouraged</td>
<td>Discouraged</td>
</tr>
<tr>
<td>3</td>
<td>Individual core questions</td>
<td>Sad</td>
<td>Sad</td>
<td>Sad</td>
<td>Sad</td>
<td>Sad</td>
<td>Sad</td>
<td>Sad</td>
<td>Sad</td>
</tr>
<tr>
<td>4</td>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Insomnia</td>
<td>Insomnia</td>
</tr>
<tr>
<td>5</td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>Fatigue</td>
<td>Fatigue</td>
</tr>
<tr>
<td>6</td>
<td>General Pain</td>
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<td>General Pain</td>
<td>General Pain</td>
<td>General Pain</td>
<td>General Pain</td>
<td>General Pain</td>
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</tr>
<tr>
<td>7</td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
<td>Headache</td>
</tr>
<tr>
<td>8</td>
<td>Concentration</td>
<td>Concentration</td>
<td>Concentration</td>
<td>Concentration</td>
<td>Concentration</td>
<td>Concentration</td>
<td>Concentration</td>
<td>Concentration</td>
<td>Concentration</td>
</tr>
<tr>
<td>9</td>
<td>Memory</td>
<td>Memory</td>
<td>Memory</td>
<td>Memory</td>
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<td>Memory</td>
<td>Memory</td>
<td>Memory</td>
<td>Memory</td>
</tr>
<tr>
<td>10</td>
<td>Dry mouth</td>
<td>Diarrhea</td>
<td>Diarrhea</td>
<td>Rash</td>
<td>Difficulty swelling</td>
<td>Difficulty swelling</td>
<td>Dry mouth</td>
<td>Diarrhea</td>
<td>Rash</td>
</tr>
<tr>
<td>11</td>
<td>Difficulty swelling</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>Abdominal pain</td>
<td>Skin dryness</td>
<td>Hoarseness</td>
<td>Difficulty swelling</td>
</tr>
<tr>
<td>12</td>
<td>Mouth/throat sores</td>
<td>Fecal incontinence</td>
<td>Fecal incontinence</td>
<td>Fecal incontinence</td>
<td>Fecal incontinence</td>
<td>Itching</td>
<td>Decreased appetite</td>
<td>Skin dryness</td>
<td>Vomiting</td>
</tr>
<tr>
<td>13</td>
<td>Cheilosis</td>
<td>Painful urination</td>
<td>Radiation skin reaction</td>
<td>Nausea</td>
<td>Mouth/throat sores</td>
<td>Headburn</td>
<td>Numbness/tingling</td>
<td>Abdominal pain</td>
<td>Radiation skin reaction</td>
</tr>
<tr>
<td>14</td>
<td>Voice changes</td>
<td>Urinary urgency</td>
<td>Urinary urgency</td>
<td>Breast swelling and tenderness</td>
<td>Vomiting</td>
<td>Numbness/tingling</td>
<td>Abdominal pain</td>
<td>Radiation skin reaction</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Hoarseness</td>
<td>Urinary frequency</td>
<td>Urinary frequency</td>
<td>Hot flashes</td>
<td>Heartburn</td>
<td>Dizziness</td>
<td>Gas</td>
<td>Numbness and tingling</td>
<td>Abdominal pain</td>
</tr>
<tr>
<td>16</td>
<td>Taste changes</td>
<td>Urinary incontinence</td>
<td>Urinary incontinence</td>
<td>Skin darkening</td>
<td>Abdominal pain</td>
<td>Radiation skin reaction</td>
<td>Taste changes</td>
<td>Bruising</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Nausea</td>
<td>Achieve/ maintain erection</td>
<td>Vaginal discharge</td>
<td>Bruising</td>
<td>Shortness of breath</td>
<td>Blurred vision</td>
<td>Hiccups</td>
<td>Swelling</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Vomiting</td>
<td>Ejaculation</td>
<td>Vaginal dryness</td>
<td>Decreased appetite</td>
<td>Cough</td>
<td>Flashing lights</td>
<td>Shortness of breath</td>
<td>Skin darkening</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>Rash</td>
<td>Decreased libido</td>
<td>Decreased libido</td>
<td>Chills</td>
<td>Heart palpitations</td>
<td>Ringing in ears</td>
<td>Fecal incontinence</td>
<td>Stretch marks</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>Radiation skin reaction</td>
<td>Pain w intercourse</td>
<td>Pain w intercourse</td>
<td>Increased sweating</td>
<td>Chills</td>
<td>Hair loss</td>
<td>Decreased appetite</td>
<td>Bed/pressure sores</td>
<td></td>
</tr>
</tbody>
</table>

#### 7.2.1.4 Exercise intervention:

The exercise intervention will utilize the “Moving Through Cancer: A Guide to Exercise for Cancer Survivors” framework. A certified cancer exercise physiologist will work through this guide at radiation therapy visits, with at least 1 visit per week, per the study schema. The cancer exercise physiologist will teach participants proper: warm ups, use of equipment, exercise form, modes of activity, intensity of exercise, flexibility exercises, and cool down. The cancer exercise physiologist will tailor the instruction to convey special considerations for exercise based on treatment and cancer type. The patient will perform supervised exercise in the Exercise Medicine Unit under the guidance of the cancer exercise specialist. The exercise done will be educational in nature (i.e. learning about proper walking form, proper intensity for a warm up/cool down, proper techniques for resistance exercises).

In addition, patients will be instructed to exercise on their own, at home, according to the instructions from the cancer exercise specialist. Each patient will be provided a specific exercise prescription to follow at home, in between radiation therapy fractions and will be asked to
record what they do in between daily radiation fraction visits. The exercise intervention is tailored to each patient; exercises as performed between 1 and 7 times per week, depending on the patient’s tolerance to the treatment. The cancer exercise physiologist will review the records at each radiation fraction visit and will provide guidance to revise the program as symptoms change and fitness level shifts. Questions on nutrition will result in a referral to a Registered Dietitian.

7.2.1.5. Physical functioning testing:
Participants will be tested for balance and strength using the following assessments:
- Grip Strength Dynamometer
- 30-second Chair Stand*  
- Timed Up and Go*  
- 4-Stage Balance*

*part of the CDC STEADI program to assess fall risk. Protocols and source docs are provided in attachments.

7.3 Duration of Participation

Cancer Patients
Estimated time to enroll all subjects = <12 months
Length of a participant’s participation = 3-8 weeks, depending on the length of their radiation therapy

8.0 Subject Numbers and Statistical Plan

8.1 Number of Subjects
50 total participants planned to accept the study.

8.2 Sample size determination
Cancer Patients
Our primary aim is to establish safety and feasibility. Our sample size is based on review of the volume of patients seen at the cancer institute for radiation therapy. We hope to recruit over 25% of radiation therapy patients into this intervention trial, as described in the section on “Feasibility of recruiting the required number of subjects.”

Patients will have the opportunity to decline enrollment but all attempts to recruit all patients will be done. Records will reflect the number of patients for determining the proportion that agree to exercise counseling and a brief set of measures. Therefore, our sample size is based on expected # of patients, rather than the ability to power a specific statistical test.

8.3 Statistical methods
Our primary outcomes are descriptive. We will compare pre- and post- values for all of our secondary outcomes, within patients. A two-sided significance level of 0.05 will be used for all statistical tests.

Acceptability is defined as: (number of patients agreeing to perform RT+ET)/(number approached); feasibility is defined as: (number of patients who completed RT+ET)/(number agreeing to perform RT+ET); safety is defined as freedom from any Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher event.
These values do not have associated statistical tests of 95% confidence intervals, but are vital to establishing that it is possible to do the intervention in a manner that will support future research and translation into clinical practice. Dr. Schmitz’ laboratory has used this same approach in multiple prior studies.\textsuperscript{108}

Other outcomes in our study include timed up and go, grip strength, and quality of life surveys. Our goal with this pilot and feasibility study is to demonstrate the effect size that might be expected in future studies. As such, statistical tests are not appropriate at this stage of inquiry.

Finally, we will also be abstracting data from the medical record regarding the progress of the patient through radiation therapy (e.g. recording dose alterations and delays and adverse effects of treatment). We will compare the results to published values for these outcomes. This comparison will not include any statistical testing; it will be done for the purpose of determining the effect size that might be expected in future research.

9.0 Confidentiality, Privacy and Data Management
See the Research Data Plan Review Form

10.0 Data and Safety Monitoring Plan
10.1 Periodic evaluation of data
As part of the exercise session the cancer exercise physiologist will review any new health issues. Further, prior to every session, the study staff will review the medical record to identify any changes in status that might influence exercise capacity. It is fully expected that exercise capacity will vary throughout radiation therapy and exercise counseling will reflect personalized response to these fluctuations in functional capacity.

10.2 Data that are reviewed
Laboratory reports and clinician progress notes.

10.3 Method of collection of safety information
The cancer exercise physiologist will document any adverse events in participants.

10.4 Frequency of data collection
At each counselling session.

10.5 Individuals reviewing the data
Kathryn Schmitz (Kinesiology; Physical Medicine and Rehabilitation), Diane Hershock (Medical Oncology), Nicholas Zaorsky (Radiation Oncology), Jessica Moyer (project manager), and a masters trained exercise physiologist.

10.6 Frequency of review of cumulative data
We will review cumulative data quarterly.

10.7 Statistical tests
Fisher’s exact tests and $\chi^2$-tests will be used to examine pre-post differences in all secondary outcomes (e.g.; symptoms, function).

10.8 Suspension of research
There is some level of injury expected from strength training. The injury rate observed in the general population in those who report involvement in strength training over the past 30 days is 3-4%.\textsuperscript{9,103} The
principal investigator will review adverse event rates at 6 months into the intervention. Any training injury rate over 24% in 6 months will be reported to the safety officer and the Penn State IRB.

For patients with breast cancer, we will use the PAL trial results as guide to know whether to stop the intervention. For patients who enter the study with lymphedema, we expect 15% of them to experience at least 1 ‘flare-up’ or exacerbation of lymphedema over 12 months. If the proportion of lymphedema flare-ups exceeds this rate, we will stop the intervention for patients with lymphedema. Similarly, we expect the onset rate of lymphedema to be about 4%. If the proportion of participants who experience lymphedema onset exceeds 4% we will stop the intervention.

11.0 Risks

Cardiovascular

There is some level of injury expected from aerobic exercise training which rises to the level of medical treatment. The injury rate observed in the general population in those who report involvement in aerobic exercise training over the past 30 days was 1.8%, with injuries defined as symptoms that last a week or longer and/or require the attention of a medical professional. Over a 12 month period we might expect 12 times that rate or 21.6%. The principal investigator will review adverse event rates at 6 months into the intervention. Any training injury rate over 10.8% in 6 months will be reported to the safety officer and the Penn State IRB.

The risk of an exercise training induced CV event is 2 nonfatal CV events in 375,000 subject hrs of exercise, or about 1 event per 1.7 million walk/jogging miles, based on a large Dallas, TX physical activity center study. There is some level of injury expected from exercise which rises to the level of medical treatment. The injury rate observed in the general population in those who report involvement in aerobic exercise training over the past 30 days was 1.8%\textsuperscript{109}, with injuries defined as symptoms that last a week or longer and/or require the attention of a medical professional. The injury rate observed in the general population in those who report involvement in strength training over the past 30 days is 3-4%.

In 242 breast cancer patients randomized to an aerobic or resistance training intervention during radiation therapy, the researchers observed an injury rate of 4.4%.

Fracture

There is a risk of fracture in patients with a cancer that involves a long bone or the vertebral column. There are two scoring systems commonly used to estimate the risk of fracture in these scenarios. The Mirels score\textsuperscript{106} is a scoring system used by radiation oncologists to estimate risk of fracture with metastasis in long bones. This study will exclude patients with a score of ≥7. A score of <7 corresponds to a 0% fracture risk. The spinal instability neoplastic score (SINS)\textsuperscript{107} estimates risk of fracture for spine metastases; a SINS score < 5 also corresponds to a 0% fracture risk. All of the patients on EXERT will have scores < 7 or not applicable.

<table>
<thead>
<tr>
<th>Points for Mirels score</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>site</td>
<td>upper extremity</td>
<td>Lower extremity</td>
<td>peritrochanteric</td>
</tr>
<tr>
<td>pain</td>
<td>mild</td>
<td>moderate</td>
<td>mechanical</td>
</tr>
<tr>
<td>radiograph</td>
<td>blastic</td>
<td>mixed</td>
<td>lytic</td>
</tr>
<tr>
<td>% of shaft</td>
<td>&lt;33%</td>
<td>34-67%</td>
<td>&gt;68%</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Mirels score</th>
<th>n</th>
<th>Fracture rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7</td>
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<td>0</td>
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<tr>
<td>7</td>
<td>19</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
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<td>57</td>
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<tr>
<td>10-12</td>
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<table>
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<tr>
<th>SINS variable</th>
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<th>2</th>
<th>3</th>
<th>4</th>
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<tbody>
<tr>
<td>Location</td>
<td>Rigid (S2-S5)</td>
<td>Semirigid (T3-T10)</td>
<td>Mobile (C3-C6, L2-L4)</td>
<td>Junctional (Occiput-C2, C7-T2, T11-L1, L5-</td>
<td></td>
</tr>
</tbody>
</table>

Page 19 of 29
<table>
<thead>
<tr>
<th></th>
<th>None</th>
<th>Occasional</th>
<th>-</th>
<th>Yes</th>
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<tr>
<td>Bone lesion</td>
<td>Blastic</td>
<td>Mixed</td>
<td>Lytic</td>
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<td>Radiographic alignment</td>
<td>Normal</td>
<td>-</td>
<td>De novo kyphosis/ scoliosis</td>
<td>-</td>
<td>Subluxation/ translation</td>
</tr>
<tr>
<td>Vertebral body collapse</td>
<td>None, &lt;50% vertebral body involved</td>
<td>None, &gt;50% vertebral body involved</td>
<td>&lt;50%</td>
<td>&gt;50%</td>
<td>-</td>
</tr>
<tr>
<td>Posterior involvement</td>
<td>None</td>
<td>Unilateral</td>
<td>-</td>
<td>Bilateral</td>
<td>-</td>
</tr>
</tbody>
</table>

Other risks
There are no medical risks associated with filling out surveys, however a patient may become uncomfortable providing personal information. Any questions that make a patient uncomfortable can be skipped. This will be clarified during the consent process.

There are no reported risks for hand dynamometer testing. Performance of the chair stands, timed up and go, and balance tests can result in muscle injury or falls. This risk will be minimized by having trained staff perform the tests and monitor participants closely. If it becomes apparent that the activity cannot be continued without injury, the staff will stop the evaluation activity.

There is a risk of loss of confidentiality if medical information or identity is obtained by someone other than the investigators, but precautions will be taken to prevent this from happening.

12.0 Potential Benefits to Subjects and Others

12.1 Potential Benefits to Subjects
Cancer Patients: Participants may decrease their risk for chronic diseases and may decrease their cancer related fatigue, dose limiting toxicities, improve quality of life, and complete radiation therapy with better function than if they do not exercise. Participants will also receive exercise training without cost.

12.2 Potential Benefits to Others
The information obtained from this research study may benefit future cancer patients by demonstrating safety and efficacy of exercise counseling in cancer care.

13.0 Sharing Results with Subjects
Patients will be offered a report of the changes in their functional testing from baseline to post-radiation therapy.

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements
None

15.0 Economic Burden to Subjects

15.1 Costs
None
15.2 Compensation for research-related injury
It is the policy of the institution to provide neither financial compensation nor free medical treatment for research-related injury. In the event of injury resulting from this research, medical treatment is available but will be provided at the usual charge. Costs for the treatment of research-related injuries will be charged to subjects or their insurance carriers.

16.0 Resources Available

16.1 Facilities and locations
All recruitment and testing will be conducted at the Penn State Hershey Medical Center, in the dedicated Exercise Therapy Unit.

16.2 Feasibility of recruiting the required number of subjects
Cancer patients: We aim to recruit 50 eligible patients (i.e. 50 people who consent to the study when initially approached) undergoing radiation therapy at the Milton S. Hershey Medical Center.

The Department of Radiation Oncology starts approximately 71 patients on radiation therapy on a LINAC per month (Table 2). There are about 17 GammaKnife Radiosurgery procedures per month; approximately 4 patients receiving SBRT per month; approximately 9 starting definitive intensity modulated radiation therapy per month; and over 30 patients receiving 2D or 3D-conformal radiation therapy per month. The average daily load is about 54 patients receiving some form of radiation therapy. We hope to recruit over 25% of radiation therapy patients into this intervention trial. With a conservative recruitment of only 10% performing the intervention, we would still be able to enroll 96 patients per year.

Anticipated patient accrual per month

71 patients starting RT per month ➔ 35 patients eligible ➔ 17 patients accept ➔ 8 patients perform intervention ➔ 0-2 experience musculoskeletal impairment <5% have injury

= 96 patients per year

16.3 PI Time devoted to conducting the research
The PI (Nicholas G Zaorsky, MD) has assembled a research team composed of clinicians, researchers, and exercise physiologists whom will carry out and oversee the study. While this is an unfunded study, the PI has 40% protected time for this work associated with his recruitment package.

16.4 Availability of medical or psychological resources
All necessary equipment to take part in this study is provided (surveys, testing on site). If medical or psychological needs arise, subjects will be directed to the Emergency Department for follow-up.

16.5 Process for informing Study Team
All study team members have been involved in the development of the study and have approved study protocols.
17.0 Other Approvals

17.1 Other Approvals from External Entities
n/a

17.2 Internal PSU Committee Approvals

Check all that apply:

- Anatomic Pathology – Hershey only – Research involves the collection of tissues or use of pathologic specimens. Upload a copy of HRP-902 - Human Tissue For Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

- Animal Care and Use – All campuses – Human research involves animals and humans or the use of human tissues in animals

- Biosafety – All campuses – Research involves biohazardous materials (human biological specimens in a PSU research lab, biological toxins, carcinogens, infectious agents, recombinant viruses or DNA or gene therapy).

- Clinical Laboratories – Hershey only – Collection, processing and/or storage of extra tubes of body fluid specimens for research purposes by the Clinical Laboratories; and/or use of body fluids that had been collected for clinical purposes, but are no longer needed for clinical use. Upload a copy of HRP-901 - Human Body Fluids for Research Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

- Clinical Research Center (CRC) Advisory Committee – All campuses – Research involves the use of CRC services in any way.

- Conflict of Interest Review – All campuses – Research has one or more of study team members indicated as having a financial interest.

- Radiation Safety – Hershey only – Research involves research-related radiation procedures. All research involving radiation procedures (standard of care and/or research-related) must upload a copy of HRP-903 - Radiation Review Form on the “Supporting Documents” page in CATS IRB. This form is available in the CATS IRB Library.

- IND/IDE Audit – All campuses – Research in which the PSU researcher holds the IND or IDE or intends to hold the IND or IDE.

- Scientific Review – Hershey only – All investigator-written research studies requiring review by the convened IRB must provide documentation of scientific review with the IRB submission. The scientific review requirement may be fulfilled by one of the following: (1) external peer-review process; (2) department/institute scientific review committee; or (3) scientific review by the Clinical Research Center Advisory committee. NOTE: Review by the Penn State Hershey Cancer Institute Scientific Review Committee is required if the study involves cancer prevention studies or cancer patients, records and/or tissues. For more information about this requirement see the IRB website at: http://www.pennstatehershey.org/web/irb/home/resources/investigator

18.0 Multi-Site Research

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18.1 Communication Plans
n/a

18.2 Data Submission and Security Plan
n/a

18.3 Subject Enrollment
n/a

18.4 Reporting of Adverse Events and New Information
n/a

18.5 Audit and Monitoring Plans
n/a

19.0 Adverse Event Reporting

19.1 Reporting Adverse Reactions and Unanticipated Problems to the Responsible IRB

In accordance with applicable policies of The Pennsylvania State University Institutional Review Board (IRB), the investigator will report, to the IRB, any observed or reported harm (adverse event) experienced by a subject or other individual, which in the opinion of the investigator is determined to be (1) unexpected; and (2) probably related to the research procedures. Harms (adverse events) will be submitted to the IRB in accordance with the IRB policies and procedures.

20.0 Study Monitoring, Auditing and Inspecting

20.1 Auditing and Inspecting

The investigator will permit study-related monitoring, audits, and inspections by the Penn State quality assurance program office(s), IRB, the sponsor, and government regulatory bodies, of all study related documents (e.g., source documents, regulatory documents, data collection instruments, study data etc.). The investigator will ensure the capability for inspections of applicable study-related facilities (e.g., pharmacy, diagnostic laboratory, etc.).

21.0 Future Undetermined Research: Data and Specimen Banking

21.1 Data and/or specimens being stored
No data or specimens will be stored for research not related to this protocol.

21.2 Location of storage
n/a

21.3 Duration of storage
n/a

21.4 Access to data and/or specimens
n/a
21.5 Procedures to release data or specimens
n/a

21.6 Process for returning results
n/a
References


Tsao M, Xu W, Sahgal A. A meta-analysis evaluating stereotactic radiosurgery, whole-brain radiotherapy, or both for patients presenting with a limited number of brain metastases. Cancer. May 01 2012;118(9):2486-2493.

