HRP-591 - Protocol for
Human Subject Research

Protocol Title:
Exercise in Radiation Therapy (EXERT)

Principal Investigator:
Nicholas G Zaorsky, MD
Department of Radiation Oncology
Penn State Cancer Institute
500 University Drive
Hershey, PA 17033
USA. Tel: +1-717-531-8024
Fax: +1-717-531-0446
E-mail: nzaorsky@pennstatehealth.psu.edu

Version Date:
1/3/2018

Clinicaltrials.gov Registration #:
N/A

If you need help…	
University Park and other campuses: Office for Research Protections Human Research Protection Program The 330 Building, Suite 205 University Park, PA 16802-7014 Phone: 814-865-1775 Fax: 814-863-8699 Email: irb-orp@psu.edu	**College of Medicine and Hershey Medical Center:** Human Subjects Protection Office 90 Hope Drive, Mail Code A115, P.O. Box 855 Hershey, PA 17033 (Physical Office Location: Academic Support Building Room 1140) Phone: 717-531-5687 Fax number: 717-531-3937 Email: irb-hspo@psu.edu

Table of Contents

1.0 Objectives

2.0 Background

3.0 Inclusion and Exclusion Criteria

4.0 Recruitment Methods

5.0 Consent Process and Documentation

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

7.0 Study Design and Procedures

8.0 Subject Numbers and Statistical Plan

9.0 Confidentiality, Privacy and Data Management

10.0 Data and Safety Monitoring Plan

11.0 Risks

12.0 Potential Benefits to Subjects and Others

13.0 Sharing Results with Subjects

14.0 Subject Stipend (Compensation) and/or Travel Reimbursements

15.0 Economic Burden to Subjects

16.0 Resources Available

17.0 Other Approvals

18.0 Multi-Site Research

19.0 Adverse Event Reporting

20.0 Study Monitoring, Auditing and Inspecting

21.0 Future Undetermined Research: Data and Specimen Banking

22.0 References

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**).

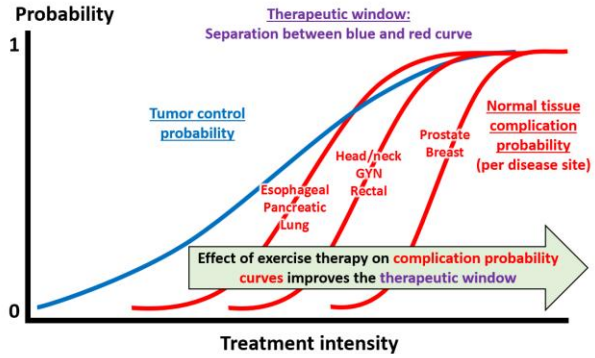


Figure 1. Summary of central hypothesis. As treatment intensity increases (with RT), so do the tumor control probability and normal tissue complication probability. Complications vary per disease site. ET may increase the therapeutic window by shifting the complication

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,[1,2] using granulocyte colony stimulating factor support, [3] introducing religion and spirituality,[4] and using cognitive behavioral therapy.[5] 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.[6-9] 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.[10-13]

Guidelines for exercise therapy among *cancer survivors*

However, despite guidance on implementing ET recommendations for cancer patients,[14] 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.[15,16]

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**).

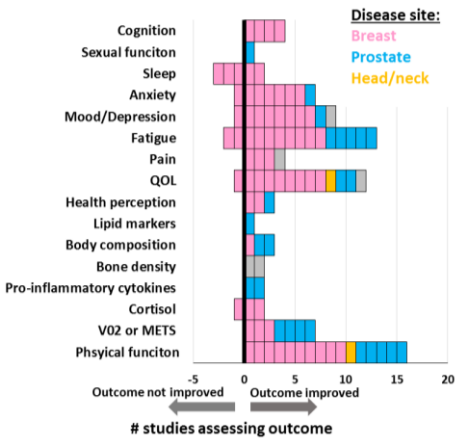


Figure 2. Outcomes statistically significantly improved vs not improved among RT+ET studies (Zaorsky et al, unpublished systematic review). The colors correspond to the disease sites where RT+ET have been tested concurrently.

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[15] performed a systematic review and meta-analysis of trials concurrent RT+ET. Among 9 studies,[17-25] 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[16] 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.[26] Similarly, ET stimulates epinephrine-dependent Hippo YAP signaling, decreasing cancer cell seeding and formation of metastases.[27,28] 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),[29-32] 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;[33] 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).[34] Further, over weeks, ET increases systemic muscle mass.[35,36] 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][37] and myostatin[38]), as seen in **colon and lung cancer**; and (3) **patients receiving systemic treatments** that cause sarcopenia, including androgen deprivation and chemotherapy.[39-42] Prevention of sarcopenia decreases the risk of perioperative complications with neoadjuvant RT.[43] 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.[44-47] 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.[44,48-51] DNA damage caused by RT is contingent on oxygenation, and an improvement in tumoral oxygenation would be expected to increase cancer killing.[52] 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.[53-57] These myokines cause NK and T-cell proliferation, differentiation, maturation, infiltration of tumor.[26,53,58-63] ET and RT also independently increase peritumoral release of TNF-α,[64 65] 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,[66-69 70] 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.[71,72] Additionally, ET decreases immunosuppressive factors, including lactate[73] and lactate dehydrogenase.[74] 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 1. Interaction between exercise therapy and radiation therapy on various body systems and cancers

Effect	Physiologic effects of exercise therapy (approximate time after event)	Physiologic effects of RT		Biologic effects of combined therapy	Cancers or normal tissue most affected
		Long-course, low dose RT (1.8-2 Gy/ fraction)	Short-course, high dose RT (>6-8 Gy/ fraction)		
Systemic endocrine					
Acute systemic epinephrine production, IL-6 secretion, mobilization of cytotoxic immune cells	Increased in minutes [26]	Negligible / unknown	Negligible / unknown	NK and T-cell proliferation, differentiation, maturation, infiltration of tumor	Multiple cancers
Epinephrine-dependent Hippo YAP signaling, decreased cancer cell seeding and formation of metastases	Decreasing in minutes[27,28]	Negligible / unknown	Negligible / unknown	Possible interaction through abscopal response	Metastatic cancers, particularly those where local RT may be effective in metastatic disease[82]
Long-term changes in pro-inflammatory markers (e.g. CRP, TNF-α, IL-6)	Decreased in weeks [29-32]	Typically negligible	Typically negligible	Decreased toxicities in normal tissues. Decreased formation of second caner.	Multiple cancers. Metastatic cancers.
Comorbid conditions (e.g. diabetes)	Improved in weeks	Negligible; however, worse RT toxicity with comorbidities [33]	Negligible; however, worse RT toxicity with comorbidities [33]	Decreased toxicities in normal tissues.	Normal tissue
Estrogen	Decreased from lower adiposity [34]	Negligible / unknown	Negligible / unknown	Decreased growth stimulus for cancer cells, synergistic with tumoral RT effects	Breast cancer
Testosterone	Decreased with fitness [83]	Negligible / unknown	Negligible / unknown	Decreased growth stimulus for cancer cells, synergistic with tumoral RT effects	Prostate cancer
Fat mass	Decreased in weeks [84]	Negligible direct. However, weight gain after therapy in certain cancers (prostate, breast) [85]	Negligible direct. However, weight gain after therapy in certain cancers (prostate, breast) [85]	Decreased growth stimulus for cancer cells. Decreased ability of cancer cells to repair DNA. Effects synergistic with tumoral RT effects.[84] Decreased systemic low-grade inflammation, insulin production	Multiple cancers (especially prostate, breast); normal tissue
Insulin, IGF1 production	Increased in body within minutes; concurrent reductions in circulating levels [34,36,86,87]	Negligible / unknown	Negligible / unknown	Decreased growth stimulus for cancer cells. Decreased ability of cancer cells to repair DNA. Effects synergistic with tumoral RT effects	Multiple cancers
Leptin	Decreased in weeks[36,84]	Negligible / unknown. Increased in patients who gain weight.	Negligible / unknown. Increased in patients who gain weight.	Decreased growth stimulus for cancer cells. Decreased ability of cancer cells to repair DNA. Effects synergistic with tumoral RT effects	Multiple cancers (especially prostate, breast); normal tissue
Muscle / myokines					
Muscle mass	Increased in weeks [35,36]	Negligible / unknown direct effect. However, decreased with certain treatments (e.g. chemo-RT, ADT)	Negligible / unknown direct effect. However, decreased with certain treatments (e.g. chemo-RT, ADT)	Prevention of sarcopenia/cachexia, which has high incidence in certain cancers. Decreased risk of perioperative complications[43] Important in (1) patients with swallowing dysfunction: pancreatic cancer, esophageal cancer, stomach cancer, head and neck cancer; (2) cancers creating muscle-wasting hormone (PTHrP[37], myostatin[38]): colon, lung; (3) treatment causing sarcopenia: ADT, chemo[39-42]	Muscle tissue.
IL-6, IL-7, IL-15	Increased in minutes [53-56]	Increased [57]	Increased [57]	NK and T-cell proliferation, differentiation, maturation, infiltration of tumor.[53,58,59] Increase immune response Antagonize TGF-β and Wnt signaling	Multiple cancers (especially melanoma).
Oncostatin M	Increased[88]			Decreases cancer cell viability	
SPARC	Increased[89]			Decreases tumorigenesis	
Bone					
Bone mineral density	Increased in weeks	Negligible / unknown; loss of density in irradiated area	Negligible / unknown; loss of density in irradiated area	Possible prevention of loss of function	Multiple cancers (especially prostate, breast); normal tissue (prevention of fracture)

Neuro-cognitive					
Depression, worse cognition	Improved cognition [75-77]	Decreased with brain RT. [78 79] Increased risk of suicide among all. [80]	Decreased with brain RT. [78 79] Increased risk of suicide among all. [80]	Prevention of cognitive decline, depression, suicide	Multiple cancers (especially those of brain)
Extracellular tumoral microenvironment					
TNF release	Increased in minutes; concurrent reductions in circulating levels [64]	Increased in minutes [65]		Induce macrophage activation towards a pro-inflammatory (M1) phenotype and enhance myeloid cell recruitment. Increased anti-tumoral response; decreased chronic tissue injury	Multiple cancers
IL-1β release	Increased in minutes [66] [67,68]	Increased in minutes [69 70]		CD8+ T-cell accumulation; accumulation of monocytes and macrophages with M1 phenotype (classically activated)	Multiple cancers
CCL2	Increased in minutes[66]			CD8+ T-cell accumulation; accumulation of monocytes and macrophages with M1 phenotype (classically activated)	Multiple cancers
M1 macrophage conversion to M2 macrophages	Increased in minutes[71 72]			Intratumoral	Multiple cancers
Parasympathetic stimulation, elevation in pulse and blood pressure, mild hyperthermia	Increased [44-47]			Increased perfusion of tumor, synergy between RT and hyperthermia. Hyperthermia increases NK cell infiltration, cytotoxic T-cell trafficking.	Multiple cancers
Blood vessel diameter size, improved tumor perfusion, reduction in hypoxia	Increased [44,48-51]			Improved efficacy of RT via OER	Multiple cancers
Vascular normalization	Increased [44,48-51]	Minutes [52]		Increased oxygenation, infiltration of tumor by immune cells	Multiple cancers
T-cell infiltration	Increased in minutes [26,63,90] [61,62,91]	Increased in minutes - days	Increased in minutes - days [52,92]	Immune recognition of cancer cells	Multiple cancers
Overall secretion of immunosuppressive factors	Decreased in minutes [93]			Decreased immunosuppressive metabolites, increased immunogenicity in tumors	Multiple cancers (esp. melanoma)
Lactate	Decreased [73]			Decreased immunosuppressive metabolites, increased immunogenicity in tumors	Multiple cancers (esp. melanoma)
LDH	Decreased[74]			Decreased immunosuppressive metabolites, increased immunogenicity in tumors	Multiple cancers (esp. melanoma)
NK cell infiltration	Increased in minutes[26,60-62] [63]			NK cells mobilized within minutes; max levels can be maintained up to 3h by continues training. Immune recognition	Multiple cancers
Intracellular tumoral microenvironment					
Tumor growth kinetics	Decreased melanoma, lung, colon, breast, HCC, head and neck [94-96]	Decreased, short/long-term	Decreased, short/long-term		Multiple cancers
Cellular energy stress	Induces stress, higher susceptibility to fasting, caloric restriction, RT in minutes [87,97,98] [84]	Increased	Increased	Higher susceptibility to damage	Multiple cancers
Peptide pools and mTOR activation	Decreased in minutes [54,98]	Decreased in seconds-minutes [52]		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 [99]	Activated in seconds [100]	Activated in seconds [100]	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 [52]	Increased in minutes, lasting weeks [52 92]	Promotion of tumor death pathways	Multiple cancers
MHC-1		Up-regulation in	Up-regulation in	Increased immune recognition	Multiple cancers

		seconds-minutes [52]	seconds-minutes [52]		
CD4+ and CD8+ cell production	Minutes [56]	Continued increase over days [52,70]	Continued increase over days [52,92,101]	Cancer cell death, production of anti-tumoral immune response	Multiple cancers
Chemokine release from CD8+ cells; Activation and expansion of tumor-specific CD4+, CD8+ T cells	Minutes [56]	Continued increase over days [52 70]	Continued increase over days [52,101]	Cancer cell death, production of anti-tumoral immune response	Multiple cancers
Reactive oxygen species production in tumor	Increased blood circulation, O2 delivery [49 48,51]	Increased in seconds-minutes [52]	Increased in seconds-minutes [52]	Improved killing by RT	Multiple cancers
Cancer cell necrosis, necroptosis			Seconds-minutes [52,101]	Cancer cell death, production of anti-tumoral immune response	Multiple cancers
HMGB1 production	Minutes [102]		Seconds-minutes [101]	Increased tumor sensitivity to therapy, decreased normal tissue inflammation	Multiple cancers
Novel peptide production; TAA expression / release (e.g. gp70 and p53)	Minutes	Seconds-minutes [52]	Days-weeks [52,92,101]	Increased immune recognition	Multiple cancers

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.[103,104] 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.

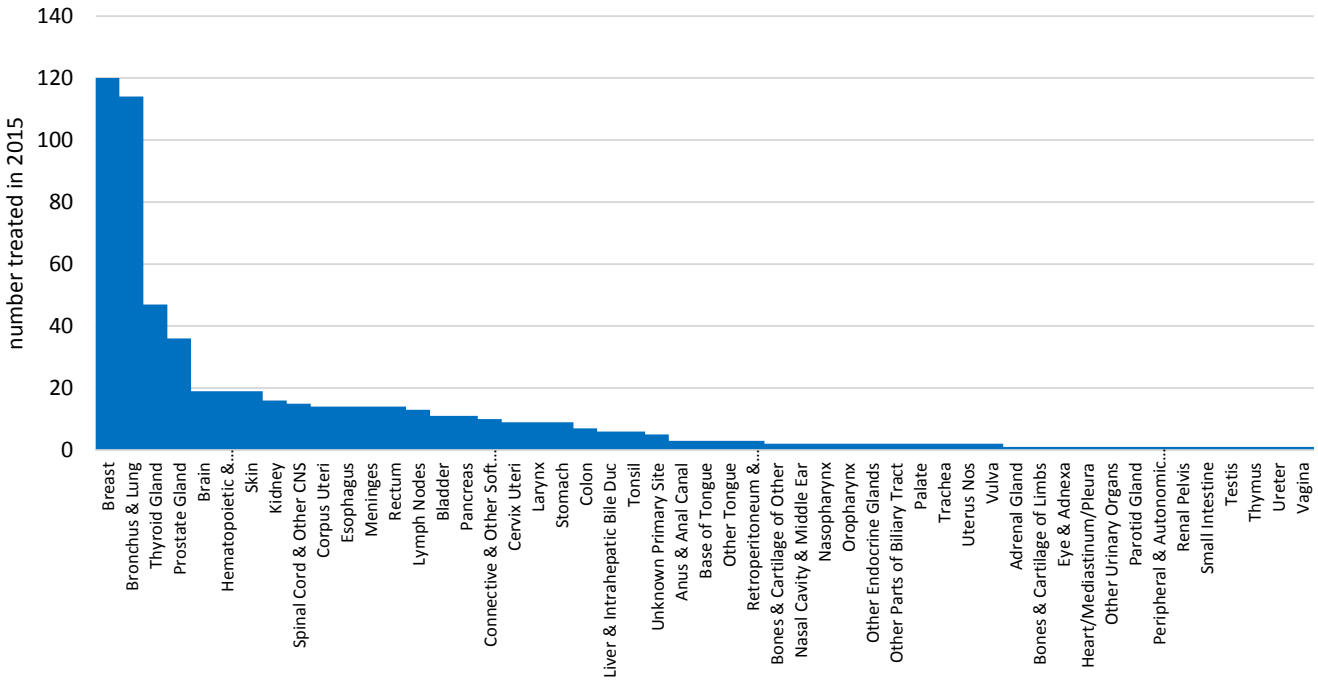
Penn State Cancer Institute

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

Month	High dose rate brachytherapy procedures	LINAC Based Treatment Procedures						Average Daily Patient Load
		New Starts	Total body irradiation	Stereotactic	Intensity modulated	Standard	Total	
July	19	72	8	23	481	616	1120	38
August	0	61	1	13	334	575	922	34
September	0	72	6	23	277	753	1053	42

October	10	70	0	8	294	852	1154	53
November	4	75	0	26	308	759	1093	66
December	11	100	0	20	344	831	1195	68
January	5	53	1	22	374	571	968	58
February	11	79	0	24	313	603	940	48
March	8	68	0	12	402	840	1254	76
April	0	67	1	25	406	621	1052	52
May	0	59	1	19	399	630	1160	53
June	1	66	0	47	307	753	1107	64
	69	842	18	262	4239	8404	13018	54



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.[105] 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:
    - Class II, III or IV heart failure as defined by the New York Heart Association (NYHA) functional classification system
    - 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
    - Uncontrolled arrhythmias; patients with rate controlled atrial fibrillation for >1 month prior to start of radiation therapy may be eligible
    - syncope
    - acute myocarditis, pericarditis, or endocarditis
    - acute pulmonary embolus or pulmonary infarction
    - thrombosis of lower extremities
    - suspected dissecting aneurysm
    - pulmonary edema
    - respiratory failure
    - acute non-cardiopulmonary disorder that may affect exercise performance or be aggravated by exercise
    - 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.

5.1.1.2 Coercion or Undue Influence during Consent

5.1.1.1.1. 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]*

☒ **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**.

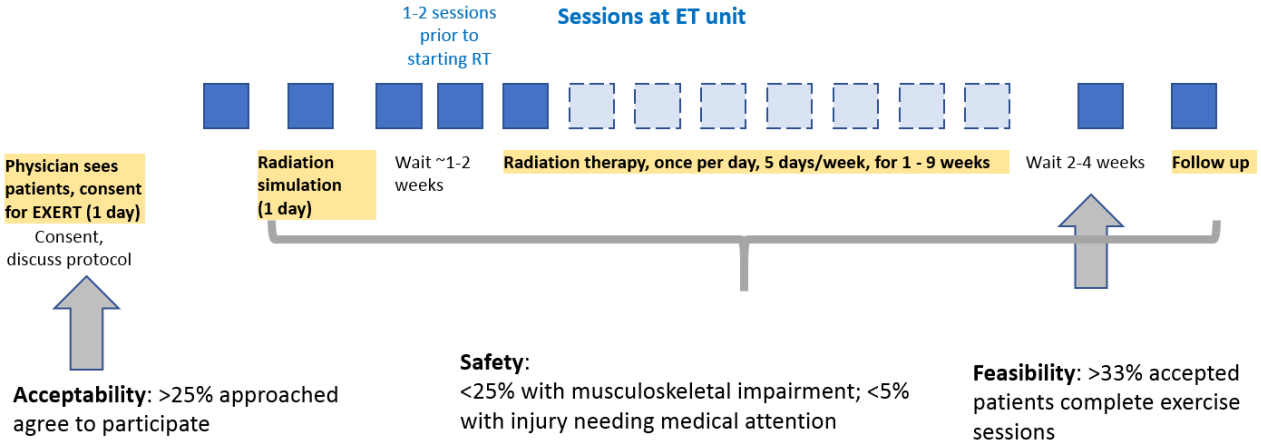


Figure 3. Study schema. In Part I, a patient is seen in consultation, consented, and simulated for radiation therapy. Prior to initiation. In Part II, radiation therapy is delivered, once per day, five days per week, for 1-8 weeks. A weekly exercise therapy session is performed, and the patient is counseled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

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

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 warmup/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.[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%.[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% [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[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)[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.

Points for Mirels score	1	2	3
site	upper extremity	Lower extremity	peritrochanteric
pain	mild	moderate	mechanical
radiograph	blastic	mixed	lytic
% of shaft	<33%	34-67%	>68%

Mirels score	n	fracture rate, %
<7	11	0
7	19	5
8	12	33
9	7	57
10-12	18	100

SINS variable	**0**	**1**	**2**	**3**	**4**
Location	Rigid (S2-S5)	Semirigid (T3-T10)	Mobile (C3-C6, L2-L4)	Junctional (Occiput-C2, C7-T2, T11-L1, L5-	-

				S1)	
Pain	None	Occasional	-	Yes	-
Bone lesion	Blastic	Mixed	Lytic	-	-
Radiographic alignment	Normal	-	De novo kyphosis/ scoliosis	-	Subluxation/ translation
Vertebral body collapse	None, <50% vertebral body involved	None, >50% vertebral body involved	<50%	>50%	-
Posterior involvement	None	Unilateral	-	Bilateral	-

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

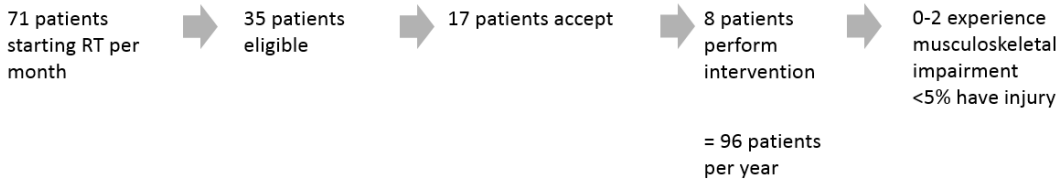
All recruitment and testing will be conducted at the Penn State Hershey Medical Center, in the dedicated Exercise Therapy Unit.

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



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

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

22.0 References

1. Bunn PA, Jr., Kelly K. New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. *Clin. Cancer Res.* May 1998;4(5):1087-1100.
2. Coates A, Gebski V, Bishop JF, et al. Improving the quality of life during chemotherapy for advanced breast cancer. A comparison of intermittent and continuous treatment strategies. *N. Engl. J. Med.* Dec 10 1987;317(24):1490-1495.
3. Thatcher N, Girling DJ, Hopwood P, Sambrook RJ, Qian W, Stephens RJ. Improving survival without reducing quality of life in small-cell lung cancer patients by increasing the dose-intensity of chemotherapy with granulocyte colony-stimulating factor support: results of a British Medical Research Council Multicenter Randomized Trial. Medical Research Council Lung Cancer Working Party. *J. Clin. Oncol.* Jan 2000;18(2):395-404.
4. Balboni TA, Vanderwerker LC, Block SD, et al. Religiousness and spiritual support among advanced cancer patients and associations with end-of-life treatment preferences and quality of life. *J. Clin. Oncol.* Feb 10 2007;25(5):555-560.
5. Osborn RL, Demoncada AC, Feuerstein M. Psychosocial interventions for depression, anxiety, and quality of life in cancer survivors: meta-analyses. *Int. J. Psychiatry Med.* 2006;36(1):13-34.
6. Galvao DA, Newton RU. Review of exercise intervention studies in cancer patients. *J. Clin. Oncol.* Feb 01 2005;23(4):899-909.
7. Courneya KS, Segal RJ, McKenzie DC, et al. Effects of exercise during adjuvant chemotherapy on breast cancer outcomes. *Med. Sci. Sports Exerc.* Sep 2014;46(9):1744-1751.
8. Segal RJ, Reid RD, Courneya KS, et al. Randomized controlled trial of resistance or aerobic exercise in men receiving radiation therapy for prostate cancer. *J. Clin. Oncol.* Jan 20 2009;27(3):344-351.
9. Schmitz KH, Holtzman J, Courneya KS, Masse LC, Duval S, Kane R. Controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Cancer Epidemiol. Biomarkers Prev.* Jul 2005;14(7):1588-1595.
10. Schmitz KH, Courneya KS, Matthews C, et al. American College of Sports Medicine roundtable on exercise guidelines for cancer survivors. *Med Sci Sports Exerc.* Jul 2010;42(7):1409-1426.
11. Hayes SC, Spence RR, Galvao DA, Newton RU. Australian Association for Exercise and Sport Science position stand: optimising cancer outcomes through exercise. *J Sci Med Sport.* Jul 2009;12(4):428-434.
12. van den Berg JP, Velthuis MJ, Gijsen BC, Lindeman E, van der Pol MA, Hillen HF. [Guideline "Cancer rehabilitation"]. *Ned Tijdschr Geneeskd.* 2011;155(51):A4104.
13. Rock CL, Doyle C, Demark-Wahnefried W, et al. Nutrition and physical activity guidelines for cancer survivors. *CA Cancer J Clin.* Jul-Aug 2012;62(4):243-274.
14. Wolin KY, Schwartz AL, Matthews CE, Courneya KS, Schmitz KH. Implementing the exercise guidelines for cancer survivors. *The journal of supportive oncology.* Sep-Oct 2012;10(5):171-177.
15. Lipsett A, Barrett S, Haruna F, Mustian K, O'Donovan A. The impact of exercise during adjuvant radiotherapy for breast cancer on fatigue and quality of life: A systematic review and meta-analysis. *Breast.* Apr 2017;32:144-155.
16. Taaffe DR, Buffart LM, Newton RU, et al. Time on androgen deprivation therapy and adaptations to exercise: secondary analysis from a 12-month randomized controlled trial in men with prostate cancer. *BJU Int.* Sep 05 2017.
17. Chandwani KD, Perkins G, Nagendra HR, et al. Randomized, controlled trial of yoga in women with breast cancer undergoing radiotherapy. *J. Clin. Oncol.* Apr 01 2014;32(10):1058-1065.
18. Chandwani KD, Thornton B, Perkins GH, et al. Yoga improves quality of life and benefit finding in women undergoing radiotherapy for breast cancer. *J. Soc. Integr. Oncol.* Spring 2010;8(2):43-55.
19. Chen Z, Meng Z, Milbury K, et al. Qigong improves quality of life in women undergoing radiotherapy for breast cancer: results of a randomized controlled trial. *Cancer.* May 01 2013;119(9):1690-1698.
20. Campbell A, Mutrie N, White F, McGuire F, Kearney N. A pilot study of a supervised group exercise programme as a rehabilitation treatment for women with breast cancer receiving adjuvant treatment. *European journal of oncology nursing : the official journal of European Oncology Nursing Society.* Mar 2005;9(1):56-63.
21. Mutrie N, Campbell AM, Whyte F, et al. Benefits of supervised group exercise programme for women being treated for early stage breast cancer: pragmatic randomised controlled trial. *BMJ.* Mar 10 2007;334(7592):517.
22. Hwang JH, Chang HJ, Shim YH, et al. Effects of supervised exercise therapy in patients receiving radiotherapy for breast cancer. *Yonsei Med. J.* Jun 30 2008;49(3):443-450.
23. Steindorf K, Schmidt ME, Klassen O, et al. Randomized, controlled trial of resistance training in breast cancer patients receiving adjuvant radiotherapy: results on cancer-related fatigue and quality of life. *Ann. Oncol.* Nov 2014;25(11):2237-2243.
24. Reis D, Walsh ME, Young-McCaughan S, Jones T. Effects of Nia exercise in women receiving radiation therapy for breast cancer. *Oncol. Nurs. Forum.* Sep 2013;40(5):E374-381.
25. Drouin JS, Young TJ, Beeler J, et al. Random control clinical trial on the effects of aerobic exercise training on erythrocyte levels during radiation treatment for breast cancer. *Cancer.* Nov 15 2006;107(10):2490-2495.

26. Pedersen L, Idorn M, Olofsson GH, et al. Voluntary Running Suppresses Tumor Growth through Epinephrine- and IL-6-Dependent NK Cell Mobilization and Redistribution. *Cell Metab.* Mar 08 2016;23(3):554-562.
27. Gabriel BM, Hamilton DL, Tremblay AM, Wackerhage H. The Hippo signal transduction network for exercise physiologists. *J Appl Physiol (1985).* May 15 2016;120(10):1105-1117.
28. Yu FX, Zhao B, Panupinthu N, et al. Regulation of the Hippo-YAP pathway by G-protein-coupled receptor signaling. *Cell.* Aug 17 2012;150(4):780-791.
29. Friedenreich CM, O'Reilly R, Shaw E, et al. Inflammatory Marker Changes in Postmenopausal Women after a Year-long Exercise Intervention Comparing High Versus Moderate Volumes. *Cancer Prev Res (Phila).* Feb 2016;9(2):196-203.
30. Jones SB, Thomas GA, Hesselsweet SD, Alvarez-Reeves M, Yu H, Irwin ML. Effect of exercise on markers of inflammation in breast cancer survivors: the Yale exercise and survivorship study. *Cancer Prev Res (Phila).* Feb 2013;6(2):109-118.
31. Imayama I, Ulrich CM, Alfano CM, et al. Effects of a caloric restriction weight loss diet and exercise on inflammatory biomarkers in overweight/obese postmenopausal women: a randomized controlled trial. *Cancer Res.* May 01 2012;72(9):2314-2326.
32. Ballard-Barbash R, Friedenreich CM, Courneya KS, Siddiqi SM, McTiernan A, Alfano CM. Physical activity, biomarkers, and disease outcomes in cancer survivors: a systematic review. *J. Natl. Cancer Inst.* Jun 06 2012;104(11):815-840.
33. Zaorsky NG, Shaikh T, Ruth K, et al. Prostate Cancer Patients With Unmanaged Diabetes or Receiving Insulin Experience Inferior Outcomes and Toxicities After Treatment With Radiation Therapy. *Clin. Genitourin. Cancer.* Apr 2017;15(2):326-335 e323.
34. McTiernan A. Mechanisms linking physical activity with cancer. *Nat. Rev. Cancer.* Mar 2008;8(3):205-211.
35. Christensen JF, Jones LW, Andersen JL, Daugaard G, Rorth M, Hojman P. Muscle dysfunction in cancer patients. *Ann. Oncol.* May 2014;25(5):947-958.
36. Pollack MN. Insulin, insulin-like growth factors, insulin resistance, and neoplasia. *Am J Clin Nutr.* Sep 2007;86(3):s820-822.
37. Kir S, Komaba H, Garcia AP, et al. PTH/PTHrP Receptor Mediates Cachexia in Models of Kidney Failure and Cancer. *Cell Metab.* Feb 09 2016;23(2):315-323.
38. Gallot YS, Durieux AC, Castells J, et al. Myostatin gene inactivation prevents skeletal muscle wasting in cancer. *Cancer Res.* Dec 15 2014;74(24):7344-7356.
39. Hojman P, Fjelbye J, Zerahn B, et al. Voluntary exercise prevents cisplatin-induced muscle wasting during chemotherapy in mice. *PLoS ONE.* 2014;9(9):e109030.
40. Casla S, Hojman P, Cubedo R, Calvo I, Sampedro J, Barakat R. Integrative exercise and lifestyle intervention increases leisure-time activity in breast cancer patients. *Integr. Cancer Ther.* Nov 2014;13(6):493-501.
41. Christensen JF, Jones LW, Tolver A, et al. Safety and efficacy of resistance training in germ cell cancer patients undergoing chemotherapy: a randomized controlled trial. *Br. J. Cancer.* Jul 08 2014;111(1):8-16.
42. Nguyen PL, Alibhai SM, Basaria S, et al. Adverse effects of androgen deprivation therapy and strategies to mitigate them. *Eur. Urol.* May 2015;67(5):825-836.
43. Fearon K, Arends J, Baracos V. Understanding the mechanisms and treatment options in cancer cachexia. *Nat. Rev. Clin. Oncol.* Feb 2013;10(2):90-99.
44. Evans SS, Repasky EA, Fisher DT. Fever and the thermal regulation of immunity: the immune system feels the heat. *Nat. Rev. Immunol.* Jun 2015;15(6):335-349.
45. Evans ES, Hackney AC, McMurray RG, et al. Impact of Acute Intermittent Exercise on Natural Killer Cells in Breast Cancer Survivors. *Integr. Cancer Ther.* Sep 2015;14(5):436-445.
46. Chen Q, Fisher DT, Clancy KA, et al. Fever-range thermal stress promotes lymphocyte trafficking across high endothelial venules via an interleukin 6 trans-signaling mechanism. *Nat. Immunol.* Dec 2006;7(12):1299-1308.
47. Fisher DT, Chen Q, Skitzki JJ, et al. IL-6 trans-signaling licenses mouse and human tumor microvascular gateways for trafficking of cytotoxic T cells. *J. Clin. Invest.* Oct 2011;121(10):3846-3859.
48. Garcia E, Becker VG, McCullough DJ, et al. Blood flow responses to mild-intensity exercise in ectopic vs. orthotopic prostate tumors; dependence upon host tissue hemodynamics and vascular reactivity. *J Appl Physiol (1985).* Jul 01 2016;121(1):15-24.
49. Betof AS, Lascola CD, Weitzel D, et al. Modulation of murine breast tumor vascularity, hypoxia and chemotherapeutic response by exercise. *J. Natl. Cancer Inst.* May 2015;107(5).
50. McCullough DJ, Stabley JN, Siemann DW, Behnke BJ. Modulation of blood flow, hypoxia, and vascular function in orthotopic prostate tumors during exercise. *J. Natl. Cancer Inst.* Apr 2014;106(4):dju036.
51. McCullough DJ, Nguyen LM, Siemann DW, Behnke BJ. Effects of exercise training on tumor hypoxia and vascular function in the rodent preclinical orthotopic prostate cancer model. *J Appl Physiol (1985).* Dec 2013;115(12):1846-1854.
52. Kwilas AR, Donahue RN, Bernstein MB, Hodge JW. In the field: exploiting the untapped potential of immunogenic modulation by radiation in combination with immunotherapy for the treatment of cancer. *Frontiers in oncology.* 2012;2:104.

53. Satoh-Takayama N, Lesjean-Pottier S, Vieira P, et al. IL-7 and IL-15 independently program the differentiation of intestinal CD3-NKp46+ cell subsets from Id2-dependent precursors. *J. Exp. Med.* Feb 15 2010;207(2):273-280.
54. Marcais A, Cherfils-Vicini J, Viant C, et al. The metabolic checkpoint kinase mTOR is essential for IL-15 signaling during the development and activation of NK cells. *Nat. Immunol.* Aug 2014;15(8):749-757.
55. Henningsen J, Rigbolt KT, Blagoev B, Pedersen BK, Kratchmarova I. Dynamics of the skeletal muscle secretome during myoblast differentiation. *Mol. Cell. Proteomics.* Nov 2010;9(11):2482-2496.
56. Conlon KC, Lugli E, Welles HC, et al. Redistribution, hyperproliferation, activation of natural killer cells and CD8 T cells, and cytokine production during first-in-human clinical trial of recombinant human interleukin-15 in patients with cancer. *J. Clin. Oncol.* Jan 01 2015;33(1):74-82.
57. Calveley VL, Khan MA, Yeung IW, Vandyk J, Hill RP. Partial volume rat lung irradiation: temporal fluctuations of in-field and out-of-field DNA damage and inflammatory cytokines following irradiation. *Int. J. Radiat. Biol.* Dec 2005;81(12):887-899.
58. Pedersen BK, Febbraio MA. Muscle as an endocrine organ: focus on muscle-derived interleukin-6. *Physiol. Rev.* Oct 2008;88(4):1379-1406.
59. Pedersen BK, Febbraio MA. Muscles, exercise and obesity: skeletal muscle as a secretory organ. *Nat. Rev. Endocrinol.* Apr 03 2012;8(8):457-465.
60. Timmons BW, Cieslak T. Human natural killer cell subsets and acute exercise: a brief review. *Exerc. Immunol. Rev.* 2008;14:8-23.
61. Ferrone C, Dranoff G. Dual roles for immunity in gastrointestinal cancers. *J. Clin. Oncol.* Sep 10 2010;28(26):4045-4051.
62. Pages F, Galon J, Dieu-Nosjean MC, Tartour E, Sautes-Fridman C, Fridman WH. Immune infiltration in human tumors: a prognostic factor that should not be ignored. *Oncogene.* Feb 25 2010;29(8):1093-1102.
63. Idorn M, Hojman P. Exercise-Dependent Regulation of NK Cells in Cancer Protection. *Trends Mol. Med.* Jul 2016;22(7):565-577.
64. Sloan RP, Shapiro PA, Demeersman RE, et al. Aerobic exercise attenuates inducible TNF production in humans. *J Appl Physiol (1985).* Sep 2007;103(3):1007-1011.
65. Hallahan DE, Spriggs DR, Beckett MA, Kufe DW, Weichselbaum RR. Increased tumor necrosis factor alpha mRNA after cellular exposure to ionizing radiation. *Proc. Natl. Acad. Sci. U. S. A.* Dec 1989;86(24):10104-10107.
66. Fielding RA, Manfredi TJ, Ding W, Fiatarone MA, Evans WJ, Cannon JG. Acute phase response in exercise. III. Neutrophil and IL-1 beta accumulation in skeletal muscle. *Am. J. Physiol.* Jul 1993;265(1 Pt 2):R166-172.
67. Peake JM, Neubauer O, Walsh NP, Simpson RJ. Recovery of the immune system after exercise. *J Appl Physiol (1985).* May 01 2017;122(5):1077-1087.
68. Peake J, Peiffer JJ, Abbiss CR, et al. Body temperature and its effect on leukocyte mobilization, cytokines and markers of neutrophil activation during and after exercise. *Eur. J. Appl. Physiol.* Mar 2008;102(4):391-401.
69. Ishihara H, Tsuneoka K, Dimchev AB, Shikita M. Induction of the expression of the interleukin-1 beta gene in mouse spleen by ionizing radiation. *Radiat. Res.* Mar 1993;133(3):321-326.
70. Hong JH, Chiang CS, Tsao CY, Lin PY, McBride WH, Wu CJ. Rapid induction of cytokine gene expression in the lung after single and fractionated doses of radiation. *Int. J. Radiat. Biol.* Nov 1999;75(11):1421-1427.
71. Kizaki T, Takemasa T, Sakurai T, et al. Adaptation of macrophages to exercise training improves innate immunity. *Biochem. Biophys. Res. Commun.* Jul 18 2008;372(1):152-156.
72. Sugiura H, Nishida H, Sugiura H, Mirbod SM. Immunomodulatory action of chronic exercise on macrophage and lymphocyte cytokine production in mice. *Acta Physiol. Scand.* Mar 2002;174(3):247-256.
73. Aveseh M, Nikooie R, Aminaie M. Exercise-induced changes in tumour LDH-B and MCT1 expression are modulated by oestrogen-related receptor alpha in breast cancer-bearing BALB/c mice. *J. Physiol.* Jun 15 2015;593(12):2635-2648.
74. Hersey P, Watts RN, Zhang XD, Hackett J. Metabolic approaches to treatment of melanoma. *Clin. Cancer Res.* Nov 01 2009;15(21):6490-6494.
75. Cooney GM, Dwan K, Greig CA, et al. Exercise for depression. *Cochrane Database Syst. Rev.* Sep 12 2013(9):CD004366.
76. Mishra SI, Scherer RW, Snyder C, Geigle PM, Berlanstein DR, Topaloglu O. Exercise interventions on health-related quality of life for people with cancer during active treatment. *Cochrane Database Syst. Rev.* Aug 15 2012(8):CD008465.
77. Mishra SI, Scherer RW, Geigle PM, et al. Exercise interventions on health-related quality of life for cancer survivors. *Cochrane Database Syst. Rev.* Aug 15 2012(8):CD007566.
78. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* Nov 2009;10(11):1037-1044.
79. 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.
80. Misono S, Weiss NS, Fann JR, Redman M, Yueh B. Incidence of suicide in persons with cancer. *J. Clin. Oncol.* Oct 10 2008;26(29):4731-4738.
81. Zaorsky NG, Churilla TM, Egleston BL, et al. Causes of death among cancer patients. *Ann. Oncol.* Nov 09 2016.

82. Rusthoven CG, Jones BL, Flaig TW, et al. Improved Survival With Prostate Radiation in Addition to Androgen Deprivation Therapy for Men With Newly Diagnosed Metastatic Prostate Cancer. *J. Clin. Oncol.* Aug 20 2016;34(24):2835-2842.
83. Hawkins VN, Foster-Schubert K, Chubak J, et al. Effect of exercise on serum sex hormones in men: a 12-month randomized clinical trial. *Med. Sci. Sports Exerc.* Feb 2008;40(2):223-233.
84. Lu YP, Lou YR, Nolan B, et al. Stimulatory effect of voluntary exercise or fat removal (partial lipectomy) on apoptosis in the skin of UVB light-irradiated mice. *Proc. Natl. Acad. Sci. U. S. A.* Oct 31 2006;103(44):16301-16306.
85. Demark-Wahnefried W, Campbell KL, Hayes SC. Weight management and its role in breast cancer rehabilitation. *Cancer.* Apr 15 2012;118(8 Suppl):2277-2287.
86. Thompson HJ, Wolfe P, McTiernan A, Jiang W, Zhu Z. Wheel running-induced changes in plasma biomarkers and carcinogenic response in the 1-methyl-1-nitrosourea-induced rat model for breast cancer. *Cancer Prev Res (Phila).* Nov 2010;3(11):1484-1492.
87. Lee C, Safdie FM, Raffaghello L, et al. Reduced levels of IGF-I mediate differential protection of normal and cancer cells in response to fasting and improve chemotherapeutic index. *Cancer Res.* Feb 15 2010;70(4):1564-1572.
88. Gannon NP, Vaughan RA, Garcia-Smith R, Bisoffi M, Trujillo KA. Effects of the exercise-inducible myokine irisin on malignant and non-malignant breast epithelial cell behavior in vitro. *Int. J. Cancer.* Feb 15 2015;136(4):E197-202.
89. Aoi W, Naito Y, Takagi T, et al. A novel myokine, secreted protein acidic and rich in cysteine (SPARC), suppresses colon tumorigenesis via regular exercise. *Gut.* Jun 2013;62(6):882-889.
90. Idorn M, Thor Straten P. Exercise and cancer: from "healthy" to "therapeutic"? *Cancer Immunol. Immunother.* May 2017;66(5):667-671.
91. Nelson BH. The impact of T-cell immunity on ovarian cancer outcomes. *Immunol. Rev.* Apr 2008;222:101-116.
92. Chakraborty M, Abrams SI, Coleman CN, Camphausen K, Schlom J, Hodge JW. External beam radiation of tumors alters phenotype of tumor cells to render them susceptible to vaccine-mediated T-cell killing. *Cancer Res.* Jun 15 2004;64(12):4328-4337.
93. Hojman P, Gehl J, Christensen JF, Pedersen BK. Molecular Mechanisms Linking Exercise to Cancer Prevention and Treatment. *Cell Metab.* Oct 17 2017.
94. Pedersen BK, Saltin B. Exercise as medicine - evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scand. J. Med. Sci. Sports.* Dec 2015;25 Suppl 3:1-72.
95. Pedersen L, Christensen JF, Hojman P. Effects of exercise on tumor physiology and metabolism. *Cancer J.* Mar-Apr 2015;21(2):111-116.
96. Dethlefsen C, Lillelund C, Midtgaard J, et al. Exercise regulates breast cancer cell viability: systemic training adaptations versus acute exercise responses. *Breast Cancer Res. Treat.* Oct 2016;159(3):469-479.
97. Higgins KA, Park D, Lee GY, Curran WJ, Deng X. Exercise-induced lung cancer regression: mechanistic findings from a mouse model. *Cancer.* Nov 01 2014;120(21):3302-3310.
98. Jiang W, Zhu Z, Thompson HJ. Effects of limiting energy availability via diet and physical activity on mammalian target of rapamycin-related signaling in rat mammary carcinomas. *Carcinogenesis.* Feb 2013;34(2):378-387.
99. Atherton PJ, Babraj J, Smith K, Singh J, Rennie MJ, Wackerhage H. Selective activation of AMPK-PGC-1alpha or PKB-TSC2-mTOR signaling can explain specific adaptive responses to endurance or resistance training-like electrical muscle stimulation. *FASEB J.* May 2005;19(7):786-788.
100. Sanli T, Steinberg GR, Singh G, Tsakiridis T. AMP-activated protein kinase (AMPK) beyond metabolism: a novel genomic stress sensor participating in the DNA damage response pathway. *Cancer Biol Ther.* Feb 2014;15(2):156-169.
101. Meng MB, Wang HH, Cui YL, et al. Necroptosis in tumorigenesis, activation of anti-tumor immunity, and cancer therapy. *Oncotarget.* Aug 30 2016;7(35):57391-57413.
102. Giallauria F, Gentile M, Chiodini P, et al. Exercise training reduces high mobility group box-1 protein levels in women with breast cancer: findings from the DIANA-5 study. *Monaldi Arch. Chest Dis.* Jun 2014;82(2):61-67.
103. Speck RM, Courneya KS, Masse LC, Duval S, Schmitz KH. An update of controlled physical activity trials in cancer survivors: a systematic review and meta-analysis. *Journal of cancer survivorship : research and practice.* Jun 2010;4(2):87-100.
104. Brown JC, Huedo-Medina TB, Pescatello LS, Pescatello SM, Ferrer RA, Johnson BT. Efficacy of exercise interventions in modulating cancer-related fatigue among adult cancer survivors: a meta-analysis. *Cancer Epidemiol Biomarkers Prev.* Jan 2011;20(1):123-133.
105. Santa Mina D, Alibhai SM, Matthew AG, et al. Exercise in clinical cancer care: a call to action and program development description. *Current oncology.* Jun 2012;19(3):e136-144.
106. Mirels H. Metastatic disease in long bones. A proposed scoring system for diagnosing impending pathologic fractures. *Clin. Orthop. Relat. Res.* Dec 1989(249):256-264.
107. Sahgal A, Atenafu EG, Chao S, et al. Vertebral compression fracture after spine stereotactic body radiotherapy: a multi-institutional analysis with a focus on radiation dose and the spinal instability neoplastic score. *J. Clin. Oncol.* Sep 20 2013;31(27):3426-3431.

108. Beidas RS, Paciotti B, Barg F, et al. A hybrid effectiveness-implementation trial of an evidence-based exercise intervention for breast cancer survivors. *Journal of the National Cancer Institute. Monographs.* Nov 2014;2014(50):338-345.
109. Powell KE, Heath GW, Kresnow MJ, Sacks JJ, Branche CM. Injury rates from walking, gardening, weightlifting, outdoor bicycling, and aerobics. *Med Sci Sports Exerc.* Aug 1998;30(8):1246-1249.