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Implement exercise in the oncological setting

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Implement exercise in the oncological setting – Alice Avancini

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Abstract

Over the past 20 years, the understanding of the role of physical activity in cancer has been increased. Traditionally, patients were advised to rest, recovery, and save energy during and after anticancer treatments. Nevertheless, it is now clear that physical activity may help alleviate some side effects caused by therapies and a sedentary lifestyle; consequently, cancer patients should be encouraged to perform exercise.

Epidemiological evidence shows that post-diagnosis physical activity is associated with enhancing patients 'survival, especially in breast, colon, and prostate cancer. In cancer patients, exercise acts by improving health-related skills, particularly cardiorespiratory fitness, strength, and body composition. Moreover, several trials demonstrated that a regular exercise program effectively relieves some cancer and treatments 'side effects, such as fatigue, nausea, and vomiting, thereby improving patients' quality of life. The last update of the American College of Sports Medicine' guidelines recommends that patients perform 90 minutes per week of aerobic exercise at moderate intensity, with strength activities twice a week.

Despite these important benefits, in Italy, the spread of exercise-oncology programs and the research in the exercise oncology field are still poor, negatively impacting patients and producing a gap in the literature.

The purpose of this thesis is trying to fill this gap, increasing the available literature, and proposing an exercise program based on patients' needs and the current guidelines. Chapter one is dedicated to a brief introduction about physical activity in cancer. In chapters two, three, four, and five, the experimental studies that led to the development of patient-centred exercise program are presented. Chapters six and seven report two other studies investigating exercise as part of the multimodal approach in counteracting cancer cachexia. The last chapter is dedicated to a summary of the main thesis results.

Sommario

La comprensione del ruolo svolto dall'attività fisica dopo la diagnosi di cancro si è ampliata negli ultimi 20 anni. Tradizionalmente, durante e dopo il trattamento antitumorale ai pazienti veniva consigliato il risposo ed il risparmio di energie, tuttavia ora si è capito che l'attività fisica può aiutare ad alleviare alcuni effetti collaterali causati dalle terapie e dalla sedentarietà, e per questo motivo anche le persone con diagnosi di cancro dovrebbero essere incoraggiate a svolgere un programma regolare di esercizio fisico.

Evidenze epidemiologiche mostrano come l'attività fisica svolta dopo la diagnosi sia associata ad una diminuzione del rischio di mortalità, specialmente nei tumori della mammella, del colon e della prostata. L'esercizio fisico agisce migliorando le capacità salute-correlate nei pazienti, in particolare la fitness cardiorespiratoria, la forza muscolare e la composizione corporea. Numerosi trials hanno mostrato inoltre come un programma regolare di esercizio risulti efficace nell'alleviare alcuni effetti collaterali del cancro e delle sue terapie, come ad esempio la fatica cancro-correlata i sintomi di nausea e vomito, migliorando di conseguenza la qualità della vita dei pazienti. Le ultime linee guida dell'American College of Sports Medicine raccomandano ai pazienti di svolgere circa 90 minuti settimanali di esercizio aerobico ad intensità moderata inserendo almeno due volte settimanali attività di forza.

Nonostante i numerosi benefici derivanti dall'attività fisica, in Italia sia la diffusione, ma anche la ricerca riguardante l'esercizio fisico in oncologia risultano ancora scarsi, generando da un lato un impatto negativo per i pazienti e dall'altra un *gap* all'interno della letteratura internazionale.

Lo scopo di questa tesi è di cercare di colmare queste lacune, aumentando la letteratura disponibile, arrivando a proporre un programma di esercizio fisico basato sulle evidenze e sulle necessità dei pazienti. Il capitolo uno è dedicato ad una breve introduzione e panoramica dell'attività fisica nelle patologie oncologiche. Nel capitolo due, tre, quattro e cinque vengo presentati gli studi sperimentali che hanno portato allo sviluppo di un programma di esercizio fisico basato sulle esigenze dei pazienti e sulle attuali linee guida. I capitoli sei e sette riportano altri due studi

riguardanti l'esercizio fisico, come parte dell'approccio multidisciplinare nel contrastare la cachessia neoplastica, mentre l'ultimo capitolo è dedicato ad un riassunto dei principali risultati emersi dalla tesi.

CHAPTER 1
GENERAL INTRODUCTION

OVERVIEW OF CANCER DISEASE

The term cancer derives from Greek *"karkinos",* i.e. crab, and refers to a group about 200 different diseases characterized by abnormal cell growth, and released from the body's normal control mechanisms (1).

Noncommunicable diseases represent the leading cause of death globally, and cancer is expected to become the major responsible cause of mortality in the 21st century. In 2018, 18.1 million new cancer cases and 9.6 million deaths from cancer had been estimated worldwide (2). For both sexes combined, lung cancer (11,6%) is the most diagnosed cancer, followed by female breast cancer (11,6%) and colorectal cancer (10,2%). Regarding the mortality, lung cancer (18,4%) still remains the deadliest malignancy, followed by colorectum (9,2%) and stomach (8,2%) (2).

In Italy, it is estimated that 377.000 newly cancer cases will be diagnosed in 2020. Breast cancer is the most frequently diagnosed cancer (14,6% of all cancer), followed by colorectum (11,6%) and lung (10,9%). Similarly to worldwide data, lung cancer (18,8%) is the highest cause of cancer-specific mortality, followed by colorectum (10,8%) and breast (7,2%) (1). However, the improvement in the screening programs and cancer treatments led to an increase in the number of people living with cancer. Indeed, in 2020, about 3.609.135 of Italian people live with a cancer diagnosis, representing the 5,7% of the Italian population (1).

As previously mentioned, cancer is characterized by uncontrolled cellular growth, resulting in cells' genetic information changes. Cancer cells, often originated by a single cell, are affected by a sequential series of genome alterations, transmitted to cell progeny. The cause of genomic damage can be endogenous and/or exogenous (environmental), as the lack of physical activity.

However, physical activity is emerging as a preventive factor against cancer and as an adjunct "therapy" during and after cancer treatments, being associated with

several benefits (e.g., reduction in cancer-related fatigue or improvement in the quality of life).

PHYSICAL ACTIVITY AND CANCER PREVENTION

Convincing epidemiological evidence shows that physical activity diminishes the risk of developing several cancer types, and for this reason, American Cancer Society (3) includes it among the preventive strategies. Indeed, the exposure to "physiological" lifestyle behavior might prevent the cancer risk, making physical activity a potential approach to delay the carcinogenesis.

Recently, Moore and colleagues have performed a pooled analysis to evaluate the association between leisure-time physical activity and risk of 26 different cancer types (4). To date, this investigation results the largest, including a total of 1.44 million participants and 186,932 cancer cases. After a categorization of participants 'self-reported physical activity into higher level (90^{th} percentile) and lower level of activity (10^{th} percentile), Moore found a strong inverse association for seven cancers (esophageal adenocarcinoma, liver, lung kidney, gastric cardia, endometrium and myeloid leukemia). Moderate correlation was observed for myeloma, colon cancer, head and neck cancer, bladder cancer, rectal cancer, and breast cancer, while an increase in risk was found for prostate cancer and melanoma. The adjustment for body mass index modestly modified the association, making the relationship for endometrial, liver, and gastric cardias not significant (4). These findings were also supported by the recent International consensus guideline panel (Table 1.). Indeed, the last update of the American College of Sports Medicine reports that physical activity lowers risk of colon, breast, kidney, endometrial, bladder, esophageal and stomach cancer, with strong level of evidence and a magnitude of association ranging between 10% and 24% (5). Moderate level of evidence exists for lung cancer prevention, while as suggest by Moore at al., an increase in melanoma risk was found (5).

Cancer	Physical activity and lower risk
Colon	Strong
Breast	Strong
Kidney	Strong
Endometrial	Strong
Bladder	Strong
Esophageal (adenocarcinoma)	Strong
Stomach (cardia)	Strong
Lung	Moderate
Hematologic	Limited
Head and neck	Limited
Pancreas	Limited
Prostate	Limited
Ovary	Limited
Brain	Not assignable
Thyroid	No effect (Limited)
Rectal	No effect (Limited)

Table 1. The level of evidence linking physical activity with lower of cancer in 2018 according to the Physical Activity Guidelines for Americans Advisory Committee (adapted from Patel et al. (5))

From these observational studies, it is clear that physical activity may play an important role in preventing cancer. Nevertheless, an important question is begged: what kind and amount of physical activity is necessary to reduce cancer risk? The World Health Organization recommends that all adults should engage in a regular physical activity (6), including at least 150-300 minutes of moderate aerobic physical activity, or 75-150 minutes of vigorous activities or an equivalent combination of both. In addition, muscle-strengthening activities at moderate intensity should be also performed two times per week (6). Actually, it remains difficult to determine the precise type, amount and intensity needed to reduce cancer risk, due to the lack of studies investigating different type of activity (e.g., resistance training), the different methods utilized for physical activity assessment and

classification (5). However, the current amount of aerobic physical activity is considered protective against cancer (5).

PHYSICAL ACTIVITY AND CANCER SURVIVORSHIP

Physical activity and exercise may be an attractive strategy to adopt in the cancer setting. Over the past two decades, several studies have investigated physical activity and exercise as an adjunct therapy in cancer patients. Observational studies have examined the relationship between pre-diagnosis, post-diagnosis of physical activity and mortality among cancer patients (5). Considering the physical activity at pre-diagnosis, highest levels was linked to an 18% lower breast cancer and 23% lower colorectal cancer mortality risk, while the reduction of overall mortality ranged between 13%-25% for breast, colorectal and prostate cancer patients (5). After a cancer diagnosis, physical activity is confirmed a potential approach able to decrease the risk of overall-mortality (ranging from 21% to 45%) and cancer specific mortality (ranging from 26% to 69%), especially in breast, colorectal and prostate cancer.

Exercise is a safe and feasible approach in cancer patients, connected with significant enhancements in symptoms-related outcomes (e.g. cardiorespiratory fitness, muscle strength) as well as those patient-reported (e.g. fatigue, quality of life) (7). Indeed, exercise acts on health-related skills improving cardiorespiratory fitness (8), muscular strength and mass (9), which are prognostic factors in cancer (10). Randomized controlled trials, as well as reviews and meta-analysis, confirm that exercise training is safe and tolerable by the patients, able to prevent and/or mitigate the adverse physiological and psychosocial effects of cancer and its treatments (11, 12). Specifically, exercise can alleviate some treatment-related adverse events, such as fatigue, anxiety and depression levels, lymphoedema, as well as preserving bone health, sleep quality, cognitive function, diminishing the cardiotoxic risk and the chemotherapy-induced peripheral neuropathy (7).

Preclinical *in vivo* studies report that exercise can inhibit tumor growth across a wide range of cancer type, although not all the investigation confirm it (13). Several

factors have been proposed to modulate cellular processes and tumor growth. On one side, host-related factors, such as adiposity, sex-steroid, metabolic and sex hormones and immune-inflammatory axis, oxidative stress, have been proposed as potential mechanisms susceptible to be regulate by exercise (13). Moreover, exercise may impact the tumor microenvironment, through managing tumor hypoxia, controlling angiogenesis, tumor cell metabolism and antitumor immune phenotype (14). Hence, being physically active may be considered one of the most important steps for cancer treatment and control.

On the basis of the available evidence, different national societies have proposed cancer-specific exercise guidelines for use of exercise during and following the completion of the therapies (7, 15, 16). In 2019, the last update of the American College of Sports Medicine has defined the exercise prescription, conformed to the FITT (frequency, intensity, time, type), for each outcomes showing sufficiently evidence of improving by exercise (Table 2.) (7). Collectively, an effective exercise prescription should comprise 30 minutes of aerobic moderate-intensity at least three times per week and resistance training, two times per week, using at least two sets of 8-15 repetitions at least 60% of one repetition maximum, for at least 12 weeks (7).

Outcome	Type	Intensity	Duration (Min) or Sets (Reps)	Frequency (Sessions per Week)	Length (Weeks)	Setting (supervised, Home-based or Combination)	Dose Response	Special Considerations	Evidence Primarily from These Cancer Types
Anxiety	Aerobic	60%-80% HRmax 60%-80% VO2max RPE 13-15	30-60	3	12	Supervised more effective	Moderate to vigorous may be more effective than light to moderate	Not known	Breast (majority), prostate, colorectal, gynecological (ovarian, endometrial, cervical), head and neck, lung hematological cancer
	Resistance	Efficacy not demonstrated	NA	NA	NA	NA	NA	NA	
	Aerobic + Resistance	60%-80% HRmax 60%-80% VO2max RPE 13-15 65%-85% 1-RM	20-40 2 sets of 8-12 reps	2-3	6-12	Supervised or combination of supervised & home-based	None observed	Not known	
Depressive Symptoms	Aerobic	60%-80% HRmax 60%-80% VO2max RPE 13-15	30-60	3	12	Supervised more effective	Benefit up to 180 min/wk	Not known	Breast (majority), prostate, colorectal, hematological
	Resistance	Efficacy not demonstrated	NA	NA	NA	NA	NA	NA	
	Aerobic + Resistance	60%-80% HRmax 60%-80% VO2max	20-40 2 sets of 8-12 reps	3 2-3	6-12	Supervised or combination of supervised & home-based	None Observed	Not known	

		RPE 13-15 65%-85% 1-RM							
Fatigue	Aerobic	65% HRmax 45% VO2max RPE 12	30	3	12	Supervised and unsupervised appear similarly effective	No dose response by intensity; possible > benefits with ↑ duration & length of program	No evidence of benefits from light intensity	Breast (majority), prostate, mixed
	Resistance	60% 1-RM RPE 12	2 sets of 12-15 reps	2	12	Supervised and unsupervised appear similarly effective	None observed	Not known	
	Aerobic + Resistance	65% HRmax 45%VO2max RPE 12 60% 1-RM RPE 12	30 2 sets of 12-15 reps	3 2	12	Supervised and unsupervised appear similarly effective	None observed	Not known	
Health-related quality of life	Aerobic	60%-80% HRmax RPE 11-13	30	2-3	12	Supervised more effective	None observed	NA	Breast (majority), prostate, colorectal, lung, head and neck, bladder, gynecological, mixed, hematological cancer, hematopoietic stem cell transplant
	Resistance	60%-75% 1-RM RPE 13-15	2-3 sets of 8-15 reps	2-3	12	Supervised or combination of	None observed	NA	

						supervised & home-based			
	Aerobic + Resistance	60%-80% HRmax RPE 11-13 60%-80% 1-RM RPE 12-14	20-30 2 sets of 8-15 reps	2-3	12	Supervised more effective	None observed	aerobic and resistance combined most effective	
Lymphedema	Aerobic	NA	NA	NA	NA	NA	NA	Generally safe, as no increase in number of lymphedema-related adverse events reported in RCT of aerobic exercise	
	Resistance	60%-70% 1-RM RPE 15	1-3 sets of 8-15 reps	2-3	52	All the interventions reviewed started with supervision to teach the exercises	NA	Start resistance a low weight and progress slowly	
	Aerobic + Resistance	NA	NA	NA	NA	NA	NA	NA	
Physical function	Aerobic	60%-85% HRmax 60%-85% Vo2max RPE 12-13	30-60	3	8-12	Supervised more effective	If supervised requires higher weekly exercise expenditure (unclear what the threshold is)	NA	Breast (majority), prostate, colorectal, lung, bladder, head and neck, hematological cancer, hematopoietic stem cell transplant

	Resistance	60%-75% 1-Rm RPE 13-15	2 sets of 8-12 reps	2-3	8-12	Limited evidence to determine benefits of unsupervised	NA	NA	
	Aerobic + Resistance	60%-85% HRmax 60%-85%VO2max RPE 12-13 60%-75% 1-RM RPE 13-15	20-40 2 sets of 8-12 reps	2-3	8-12	Both supervised and home-base suitable in older adults	NA	Community-based interventions that met in group % used behavior change strategies may produce larger effects in older adults	

Abbreviations: NA, not applicable.

Table 2. Cancer-related health outcome with sufficient evidence for development of FITT prescription (adapted from Campbell et al. (7)).

Nevertheless, not all patients meet the exercise guidelines. Wong and colleagues, in a systematic review including a total of 10,530 participants, found a large heterogeneity in the percentage of patients resulting sufficiently active, ranging from 16% to 88% (17).

Making exercise a standard in cancer care requires a series of considerations to translate the research in *"exercise oncology*" into real world practice. Tailor exercise on cancer patients is crucial to increase adherence and maintenance over time of an active lifestyle (10). Cancer patients may encounter a series of obstacles, potentially interfering with exercise. Some of them could be related to cancer and its treatments, such as pain, neuropathy and joint stiffness, other could be more general like lack of time or interest (10). Contrarywise, understand patients preferences about different issues of exercise programs, as well as apply models (e.g., social cognitive theory, theory of planned behavior, and self-determination theory) is important to increase patients motivation and to answer to their needs (10). However, exercise program should be evidence-based, thus based on the aforementioned guidelines for example. It necessary consider that the minimum levels of exercise proposed by the guidelines, could be difficult to achieve, especially for physically deconditioned patients. Reasonably, an exercise program should be flexible, start easily and progressively increasing, according to patient's rhythm and body response. Besides, an heterogeneity in physical, psychological status, and treatment-related side effects needs to be considered (10). According to available evidence, an accurate baseline assessment, including clinical, physical, and psychosocial conditions, is fundamental to schedule a tailored exercise program. Recognizing the presence of relevant comorbidities to adapt activity and avoid potential exercise-induced risks is fundamental (10). The presence of extreme fatigue or high physical limitation could be a contraindication to start an exercise program, or a low cardiorespiratory fitness may suggest performing exercise with low intensity and for short time. Considering all these factors, in clinical practice close collaboration among oncologists and kinesiologists (or cancer exercise specialists or physiotherapists) may allow developing specific exercise programs based on patient's needs, preferences, and physical and psychological status (Figure 1.) (10).

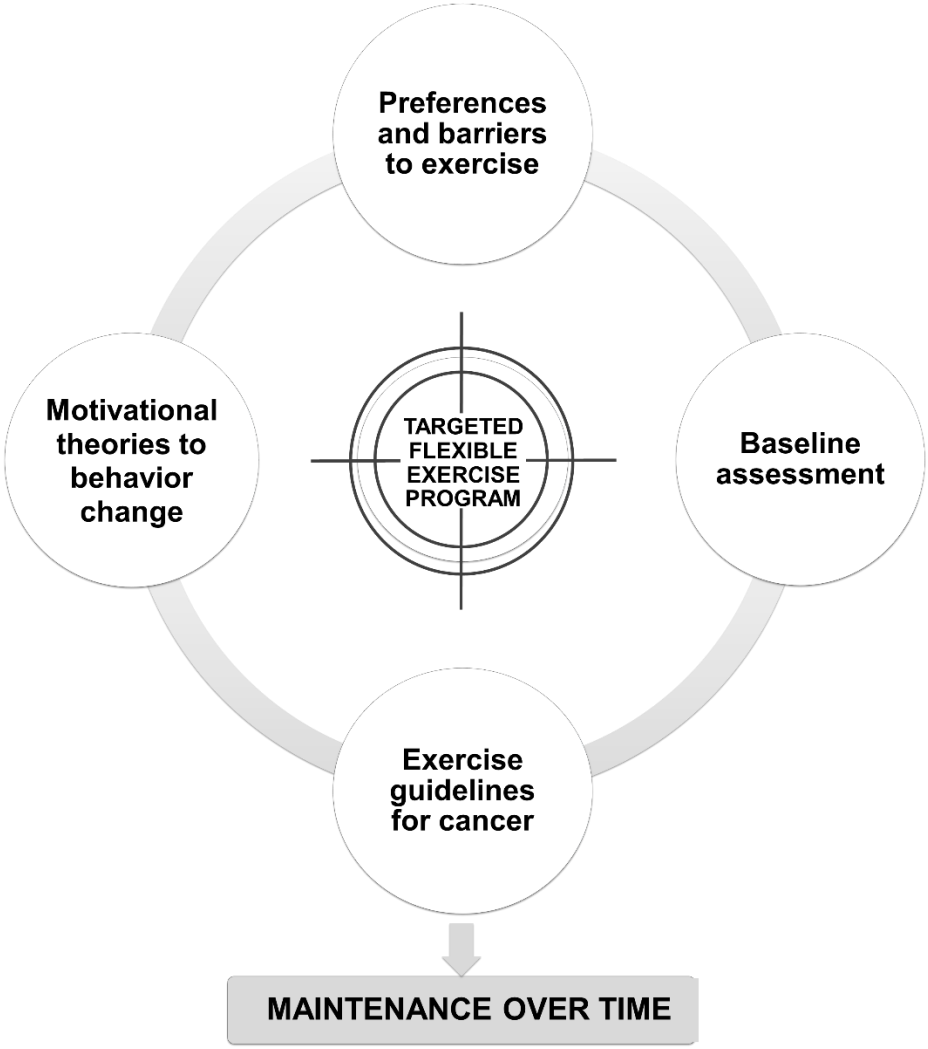

Figure 1. Tailored exercise program: a proposed model (adapted from Avancini et al. (10))

However, addressing this issue broadly, a series of stakeholders should be involved to enhance the development of exercise oncology, including oncology clinicians, healthcare providers, policy makers, researchers, educators, non-profit associations and fitness industry, with the aim to create a network to refer patients (18).

MULTIDISCIPLINARITY OF SUPPORTIVE CARE IN CANCER

A multidisciplinary approach is largely utilized in cancer care, in which different specialists (e.g., medical oncologists, surgeons, radiotherapists, pathologists)

collaborate closely to achieve the best possible results for the patient. A similar parallelism may be formulated for the supportive care in cancer. Indeed, exercise may be a piece of a larger intervention, including a series of experts, e.g., dietitians, psychologists, social workers, to offer the best possible therapeutic approach to cancer. On one hand, these non-pharmacological interventions may help improve quality of life, physical functions, psychological aspects, and treatment-related adverse events and reduce symptoms and complications occurring during cancer care. Over the years the literature is moving towards the use of multidisciplinary and multimodal approach in the cancer setting. For instance, the Enhanced Recovery After Surgery (ERAS®) Society, has developed a series of consensus statements and guidelines to improve the quality of surgical care (19). These guidelines are becoming targeted for specific surgical procedures, identifying the most appropriate interventions for preoperative, intraoperative and postoperative care (19).

A common topic emerging from available experiences explores the potential synergistic impact of strongly integrated interdisciplinary approaches, encompassing coordinated exercise, nutritional, and psychological and behavioral interventions. From a theoretical standpoint, it is reasonable to speculate that behavioral and psychological intervention or counseling may reinforce motivation and compliance, thus potentially favoring adherence to tailored exercise programs. On the other hand, nutritional counseling may help to counteract sarcopenia and muscle wasting, thereby rendering exercise more effective in maintaining muscle mass and improving strength. Indeed, a meta-analysis showed that combined exercise and psychological intervention is more effective than a pharmacological approach to counteract fatigue (20). Similarly, an integrated approach encompassing exercise, dietary guidance, social counseling, and a smoking cessation program clearly improved quality of life, emotional well-being, and mental health, while reducing anxiety, depression, and distress (21).

Overall, exercise may be administered as part of a multidimensional, comprehensive approach in cancer care, contributing to patients' well-being.

OVERVIEW AND AIMS OF THE DISSERTATION

In Italy, the literature about physical activity and exercise in cancer patients is still scarce, with only few available investigations.

Some case reports have been reported, especially on breast cancer (22, 23). De Luca et al. conducted a randomized controlled trial in 20 breast cancer patients who concluded all cancer treatments at least six months before. After 24 weeks of combined aerobic and strength training program, significant improvements in cardiorespiratory fitness, strength, quality of life, and body composition were found (24). Rispoli and colleagues have investigated the prehabilitative role of exercise in lung cancer patients candidate for lobectomy. Four weeks of aerobic and strength exercises were efficacious in increasing forced expiratory volume in one second, functional capacity, and diminishing the postoperative complications, only in patients who performed at least three sessions per week (25).

However, the scarcity of research in the exercise oncology field reflects another problem, i.e., the lack of awareness and dissemination of exercise programs specifically dedicated to cancer patients. In Italy, sporadic initiatives to support exercise in cancer patients exist often addressed to breast cancer. There is the need to implement the study of exercise oncology, on the one hand, to expand the knowledge in a country as Italy still lacking, and on the other to begin supporting the diffusion of exercise oncology culture on the principal stakeholders (patients, clinicians, nurse, etc.).

The purpose of this dissertation is to increase the research about exercise in oncology in Italy.

The first part of the dissertation comprises four papers and is concerned about the implementation of exercise in the cancer context. Paper 1 examines the exercise level and preferences in Italian cancer patients. Paper 2 qualitatively investigates the barriers and cues to action to exercise in cancer patients. Paper 3 is based on the results of Paper 1 and 2 and consisted of the protocol of an interventional study, currently ongoing and tailored to cancer patients. Unfortunately, the outbreak of COVID-19 has disrupted and slowed down our trial. Nevertheless, this emergency, composed of social distancing, closure of several services (gym included), brought out the necessity to adapt the exercise programs. In this sense, Paper 4, a

commentary about physical activity in cancer patients during the COVID-19 pandemic, attempts to suggest a series of proposals to develop and perform remote exercise programs.

The second part of the dissertation is composed of two papers. It is about the possibility to utilize a multidisciplinary intervention, including pharmacologic agents, exercise, nutrition, and psychological support, to improve and/or manage cancer-related cachexia. Paper 5 is a special report examining the current state of the art in cancer cachexia. Paper 6 is a case report investigating the effect of multidisciplinary intervention in a pancreatic cancer patient affected by cachexia.

CHAPTER 2
STUDY 1

Exercise Levels and Preferences in Cancer Patients: A Cross-Sectional Study

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Abstract

Background: Despite the benefits related to physical exercise, large numbers of cancer patients are not sufficiently active. **Methods:** To investigate exercise levels and preferences in cancer patients, a cross-sectional study was conducted on a random sample of 392 cancer outpatients who anonymously completed a questionnaire investigating general and medical characteristics and expressed willingness to participate in exercise programs. Current exercise levels were estimated with the Leisure Score Index (LSI). **Results:** Most patients (93%) were insufficiently active but 80% declared an interest in exercise programs. Patients preferred oncologist-instructed programs and specified particular exercise needs. Multivariate logistic regression showed that willingness to exercise was associated with education (OR: 1.87; 95% CI: 1.15-3.04 beyond age 14 years vs. up to 14 years) and current physical activity (OR: 1.92; 95% CI: 1.92-3.63 for sweat-inducing activity >2 times/week vs. <1 time/week). Patients given chemotherapy were less inclined to exercise (OR: 0.45; 95% CI: 0.23-0.86) than those who did not. LSI was lower if cancer stage was advanced (β: -0.36; 95% CI: -0.75 to -0.02) than if it was in remission. High LSI was also associated with longer education, lower BMI, and longer time after diagnosis. **Conclusion:** Cancer patients are insufficiently active but are willing to participate in personalized exercise programs. Information from this survey may help in designing personalized interventions so these patients will achieve sufficient exercise.

Introduction

In 2019 it was estimated that about 3.5 million Italians (5.3% of the entire population) are living after a cancer diagnosis (26). Improvements in medical treatments have led to a substantial increase in the proportion of cancer patients with death rates similar to those of the general Italian population (27).

Cancer and its treatments are associated with various side effects that negatively affect the patient's quality of life for a long time after the conclusion of therapies (28, 29). There is growing evidence that in cancer patients (especially breast, colon and prostate) (30-32) an active lifestyle is associated with a lower risk of recurrence and mortality. Physical activity (PA) refers to any bodily movement produced by skeletal muscles that requires energy expenditure (33). Exercise is defined as a subcategory of PA, consisting of structured, planned and repetitive movement (33). Exercise was shown to be safe and feasible in oncological settings (11) and several studies found that exercise improved patients' quality of life during (34, 35) and after treatment (35). Positive effects of exercise include increasing cardiorespiratory fitness (8) and muscular strength (36), and improvement in body composition (36). Additionally, exercise helped regulate several side effects of cancer treatment, such as fatigue (37), and nausea (38), and improved the psychological status, for instance, reducing levels of anxiety and depression (39).

Despite the benefits related to PA and exercise a large percentage of cancer patients from 25% to 84% - are not sufficiently active (17, 40, 41) and the level of exercise has been seen to decrease after cancer diagnosis (42). A multitude of factors influence the participation of the general population in exercise programs (e.g. lack of time, cost, logistic difficulties, etc.) (43). Cancer patients face further obstacles on account of their condition (e.g. cancer-related fatigue, muscle weakness, nausea, sleep disorders) (44, 45). To develop a successful exercise intervention, cancer patients' barriers and preferences must be considered, allowing them to pick the activities they perceive as beneficial and enjoyable (45-48). International studies investigated the preferences and determinants of exercise levels in cancer patients and survivors (40, 49-55), but data on the Italian population are lacking. Furthermore, cultural differences in this area might be significant. In order to overcome this information gap the STIP-ON (Sustainable training in pazienti

oncologici) survey was designed with the following aims: i) To understand the size of the problem, i.e.: to calculate the prevalence of insufficient exercise among cancer patients; ii) to analyze the patients' characteristics associated with insufficient exercise; iii) to analyze the patients' characteristics associated with their motivation/willingness to take part in a future intervention program on exercise; iiii) to describe patients' preferences about exercise.

The rationale of the study is that understanding patients' preferences and barriers to physical activity will make it easier for them to participate successfully in a future intervention study to improve their physical fitness.

Materials and Methods

Study design and participants

This STIP-ON study is a cross-sectional survey. Data was collected and recorded anonymously from patients visiting the cancer outpatients' facilities at the Oncology Unit of "Azienda Ospedaliera Universitaria Integrata", University of Verona, Verona, Italy between July 2018 and April 2019. Cancer patients' eligibility criteria were: age ≥18 years, a cancer diagnosis and adequate Italian language proficiency to answer the survey questionnaire (QEX). Invited participants included all kinds of cancer survivors (including those whose diagnosis had just been made or was being defined). The STIP-ON sample was thought to be representative of patients visiting the cancer outpatients' facilities: on randomly selected days they were approached face to face, informed about the study and asked whether they would be willing to complete the questionnaire anonymously to investigate their characteristics and preferences regarding exercise. Invited participants were systematically asked by the staff if they had already completed the survey another time/day before this QEX was administered. A duplicate check was done, looking for duplicates by date of birth, province of residence, sex, education, and marital status. If interested in participating, patients were asked to give signed informed consent, and received a leaflet (Supplementary Material 1) describing the purpose of the study and a copy of QEX. QEX was completed on the spot or could be taken home and returned within a week. In both cases participants were asked to leave the completed QEX anonymously in a special 'ballot box'.

The project was reviewed and approved by the Ethics Committee for Clinical Trials (Prot. No. 49018), University of Verona. All study procedures were conducted following the last revision of the declaration of Helsinki as well as the declaration of Oviedo. The study protocol was designed to adhere to Good Clinical Practice principles and procedures and had to comply with Italian legislation.

The survey questionnaire (QEX)

The QEX is a self-administered survey to collect cancer patients' preferences and characteristics associated with exercise. The questionnaire is the result of a co-design process that involved patients (via patients' associations) and experts, including oncologists, kinesiologists, epidemiologists and psycho-oncologists. The pilot version of QEX was developed based on a literature review (49-53) made available to these 'reviewers' to give feedbacks and make an unofficial peer review to develop the current version. While QEX is a self-reported, anonymous survey, staff support (including dedicated personnel in the room) was available during the survey to address any questions. The QEX comprises 31 items (Q1 - Q31), divided into four sections: a) General characteristics (from Q1 to Q9); b) Physical exercise level (from Q10 to Q11); c) Physical exercise preferences (from Q12 to Q26); d) Cancer diagnosis and treatment (from Q27 to Q31). A copy of QEX is available online as Supplementary Material 2.

Questions 1-9: General characteristics

The following demographic, anthropometric and socio-economic characteristics of patients are collected in the QEX: birth date (day, month, year), sex, province of residence, education level (elementary (up to age 10-11 years)/ secondary-up to 14 years/ secondary-up to 18-19 years/college-university /postgraduate), marital status (single/married/divorced/widowed, occupational status (retired/homemaker/part-time employed/full-time employed/ other), perceived economic adequacy (inadequate/barely adequate/adequate/more than adequate), body weight (kg) and height (cm) (both continuous). Age was calculated by subtracting the date of birth from the date of QEX compilation and classified in two categories (<65; ≥65y). Body mass index (BMI) was calculated from the weight in kilograms divided by

the height in meters squared (kg/m^2). BMI categories were defined as follows: underweight (BMI <18.5 kg/m^2), normal weight (BMI 18.5-24.9 kg/m^2); overweight (BMI 25-29.9 kg/m^2); obese (>29.9 kg/m^2) (56).

Questions 10-11: Level of physical exercise

The QEX inquiry about current exercise level was based on questions from the Godin Leisure-Time Exercise Questionnaire (GLTEQ) (57, 58) which is widely used for cancer patients (58). A detailed description of the computation of LSI from GLTEQ is found elsewhere (57, 58). In brief: i) The GLTEQ enquires about the previous week's leisure time frequency (times/week) of vigorous, moderate and mild intensity exercise; ii) Each exercise intensity is associated with the metabolic equivalent of the task (MET): MET = 9 for vigorous, MET = 5 for moderate, MET = 3 for mild intensity exercise (57); iii) The LSI is then calculated as the sum of (vigorous * 9) + (moderate * 5) per-week exercise frequency according to Godin and Shepard (57). Based on their LSI, patients are classified as active (if LSI ≥24) or insufficiently active (if LSI <24) according to the 2010 release of American College of Sports Medicine (ACSM) Exercise Guidelines for cancer patients (59). The ACSM guidelines suggest cancer patients engage in at least 150 minutes/week of moderate or 75 minutes/week of vigorous exercise (59). The QEX includes an additional self-rated question about the frequency (times/week) of sweat-inducing activity. There are three categories of frequency (often/sometime /never-rarely) These questions and categorization are also taken from GLTEQ (57).

Questions 12-26: Physical exercise preferences

Exercise preferences were investigated by questions from previous studies (49-53). The first question concerns the patient's willingness to participate in an exercise program (yes/no/maybe). Respondents were asked about their preference regarding: who would give them exercise instructions (oncologist/nurse/ kinesiologist/nutritionist/physiotherapist/another cancer patient/no preference/ other); how to receive exercise instructions (face to face/by telephone/videotape/ television/brochure-pamphlet/over the internet/no preference/other); with whom they would prefer to exercise (nobody/other cancer patients/family members/

friends/a group/no preference/other); where (at home/at a community fitness center/at an adapted exercise fitness center/outside/no preference/other); what time of day (morning/afternoon/evening/no preference); what part of the week (weekday/weekend/no preference) and how often (from never to seven times/week). Further information was collected on preferred intensity (mild/moderate/ strenuous/no preference), session content variability (same each time/different each time/no preference), "helper" during the program (nobody/exercise specialist/ neighbor/colleague/friend/son-daughter/spouse/other relative), supervision (unsupervised/ supervised/no preference) and kind of exercise program (individual with a program to follow at home/individual with personal trainer/in a group with a kinesiologist/physiotherapist/exercise specialist). There were also two open-ended questions in which respondents were encouraged to list the top three preferred exercise activities in winter and summer.

Questions 27-31: Cancer diagnosis and treatment

Medical variables were self-reported by patients and included: tumor site (lung/ colorectal/breast/head-neck/upper gastrointestinal/ gynecological/ urogenital/ melanoma/ hematological/ other), disease status (unknown/in remission-cured/ early/advanced/metastatic), date of diagnosis (month/year), type of treatment (surgery/chemotherapy/ radiotherapy/hormone therapy/ other) and current treatment status (about to start/ ongoing/ completed/not known).

Time from diagnosis was calculated by subtracting the date of diagnosis from the date of QEX compilation and was classified in two categories using the median (≤30 months; >30 months).

Statistical analysis

Descriptive analyses are presented as mean, medians and IQR for continuous variables and frequencies and percentages for categorical variables. Categorical non-ordinal variables were incorporated as dummy variables (Xd) in regression models so that Xd=1 if the condition is true and Xd=0 if not. Minimally adjusted models to investigate patients' characteristics associated with willingness to participate and current exercise level included age and sex as explanatory variables.

Multivariable regression models to investigate patients' characteristics associated with their willingness to participate and current exercise level included explanatory variables, selected in advance, in the fiducial model that subsequently maximized the goodness of fit, according to the Akaike information criterion (AIC) (60).These variables included: sex, age, education, residence, perceived income adequacy, marital status, occupational status, frequency of sweat-inducing activity, tumor site, disease, chemotherapy, surgery, radiotherapy, hormone therapy, other treatments, treatment status, time from diagnosis, “lack of preference” (score 0 for no no-preference reply, score 1 for 1 no-preference reply, score 2 for 2 or more no-preference replies to exercise preference questions), “independence” (score 0 if “on my own” never chosen in exercise preference questions, score 1 otherwise.

The sample size of 200 cancer patients was based on the feasibility criteria of the study. The expected sample allowed estimates of binary variables [e.g. percentages of active (p) vs. percentages of insufficiently active (P=1-p) or percentages of patients expressing interest vs. percentages expressing no strong interest] with a standard error of 0.035 and a confidence interval between 0.43 and 0.57, assuming the most unfavorable proportion equal to 0.5 (P=0.5) and alpha 5%.

Statistical tests were two-sided and p values <0.05 were considered significant. The Stata statistical package, version 14 (Stata Corp, Texas, USA) was used.

Results

The flow diagram of participants is shown in Figure 1. Among the 694 patients approached, 249 (36%) declined to participate in the survey. The most frequent reason for declining was lack of interest. Among the 445 who agreed to participate, 53 did not return the QEX, leaving the final study sample of 392 subjects (55% of the patients approached).

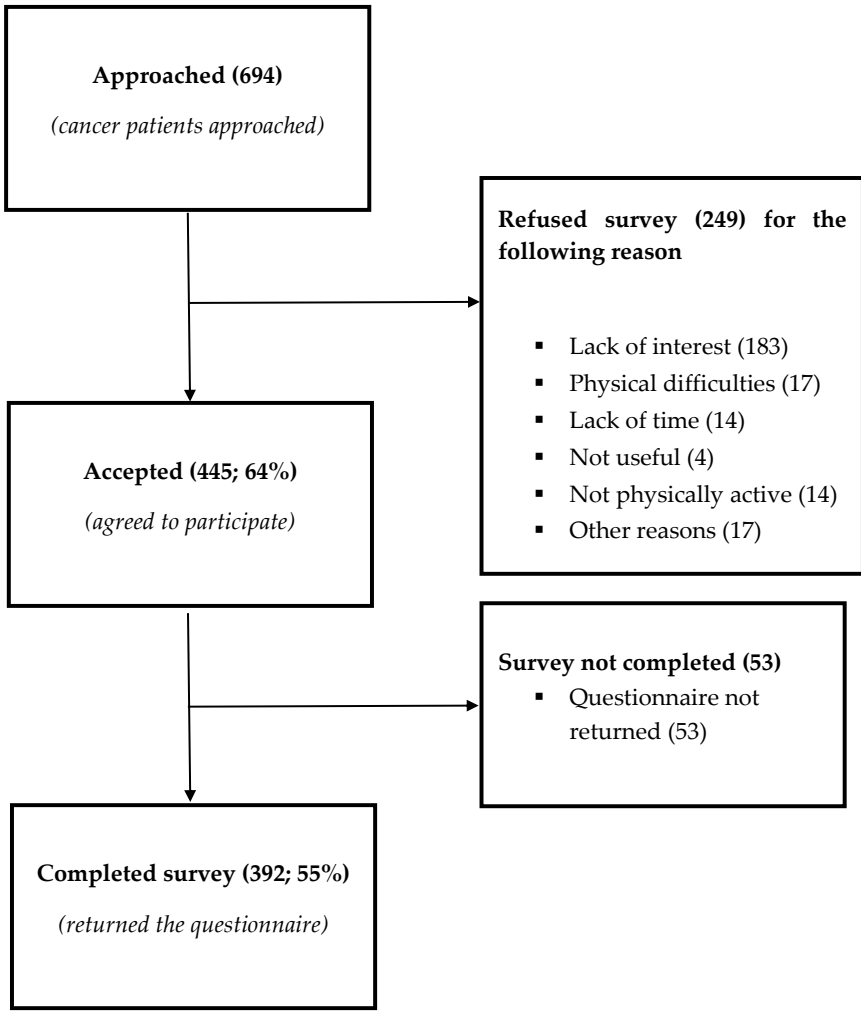

Figure 1. Flow of participants through the study.

General and tumor characteristics

Demographic and medical variables stratified by the willingness to participate in the exercise program are set out in Table 1. The participants' mean age was 59.6±12.2 y, 61% were female, 69% were married and 61% had at least higher education, up to age 18-19 years. Overall, 83% of participants were still on active treatment; the most frequent tumor sites were upper gastro-intestine (42%) and breast (26%), with a mean time from diagnosis of 2.4 years.

Table 1. General and tumor characteristics of 392 cancer patients† according to willingness to participate in a specifically designed exercise program.

		Willingness to participate‡						
	All	**Yes**		**Maybe**		**No**		**P-value§**
	(392)	(179)		(134)		(79)		
	No.	%	No.	%	No.	%	No.	
Age (years)								
< 65	239	48	115	38	91	14	33	0.023
≥ 65	149	42	63	28	41	30	45	
Sex								
Female	238	51	121	32	77	17	40	0.023
Male	154	38	58	37	57	25	39	
Province of residence								
Verona	244	43	105	34	82	23	57	0.114
Other	148	50	74	35	52	15	22	
Education								
Elementary (up to 10-11 years)	32	28	9	28	9	44	14	0.002
Secondary (up to 14 years)	119	41	49	37	44	22	26	0.451
Secondary (up to 18-19 years)	162	50	80	36	59	14	22	0.031
College/University	52	54	28	25	13	21	11	0.308

Postgraduate	18	50	9	33	6	17	3	0.920
Body Mass Index								
Underweight	19	58	11	32	6	11	2	0.455
Normal weight	228	46	104	34	78	20	46	0.994
Overweight	107	41	44	36	39	22	24	0.503
Obese	30	57	17	27	8	17	5	0.461
Marital status								
Single	51	43	22	35	18	22	11	0.903
Married	269	45	122	35	94	20	53	0.819
Divorced	35	46	16	34	12	20	7	0.999
Widowed	34	56	19	24	8	21	7	0.371
Occupational status								
Retired	161	46	74	30	48	24	39	0.151
Homemaker	43	44	19	30	13	26	11	0.622
Part-time employed	45	49	22	42	19	9	4	0.118
Full-time employed	123	46	57	38	47	15	19	0.242
Other	20	35	7	35	7	30	6	0.462
Perceived income adequacy[††]								
Inadequate	28	50	14	36	10	14	4	0.746
Barely adequate	120	45	54	40	48	15	18	0.152
Adequate	180	44	80	34	61	22	39	0.676
More than adequate	61	51	31	23	14	26	16	0.103
Exercise level[‡‡]								
Insufficiently active	363	45	162	35	127	20	75	0.338
Active	27	59	16	26	7	15	4	
Tumor site								
Breast	101	54	55	31	31	15	15	0.096
Lung	22	41	9	36	8	23	5	0.894

Colorectum	39	31	12	49	19	21	8	0.091
Head/neck	9	44	4	22	2	33	3	0.554
Upper gastro-intestine	166	46	77	35	58	19	31	0.821
Gynecological	8	50	4	38	3	13	1	0.862
Urogenital	19	53	10	21	4	26	5	0.450
Melanoma	14	21	3	29	4	50	7	0.015
Other	14	36	5	36	5	29	4	0.659
Disease status								
Unknown	53	40	21	32	17	28	15	0.274
In remission/cured	62	56	35	27	17	16	10	0.178
Early	86	48	41	37	32	15	13	0.411
Advanced	85	38	32	40	34	22	19	0.239
Metastatic	106	47	50	32	34	21	22	0.866
Treatments [§§]								
Surgery	215	44	95	32	69	24	51	0.167
Chemotherapy	329	44	144	36	119	20	66	0.102
Radiation therapy	113	44	50	29	33	27	30	0.119
Hormone therapy	50	56	28	30	15	14	7	0.249
Other	27	59	16	19	5	22	6	0.190
Treatment status								
About to start	11	55	6	27	3	18	2	0.829
Ongoing	325	44	144	35	115	20	66	0.452
Completed	35	51	18	29	10	20	7	0.728
Unknown	21	52	11	29	6	19	4	0.804
Time from diagnosis	21	52	11	29	6	19	4	0.804
≤30 months	178	48	86	37	65	15	27	0.080
≥30 months	214	43	93	32	69	24	52	

[†] Participants of STIP-ON study conducted in Verona, Italy, from July 2018 to April 2019. [‡] Willingness to participate in exercise program assessed by the question: Would you be interested in participating in an exercise program designed for cancer patients? [§] Pearson's chi-squared used the null hypotheses of no association between physical exercise level and other patient/disease characteristics. [¶] Body Mass Index categories are those of the World Health Organization (56).

[††]Perceived income adequacy assessed by the question: Does your monthly income cover your monthly expenditure? [‡‡] Exercise level according to Leisure Score Index (LSI). Patients are active if LSI ≥24 and insufficiently active if LSI <24 (58). [§§] Treatments, which may be completed or in course, and are not mutually exclusive.

Exercise behavior

Details on participants' exercise behavior by sex and age are shown in Table 2. Patients reported mean frequencies of strenuous, moderate and mild exercise of 0.2 ± 0.84; 0.71 ± 1.43 and 1.56 ± 2.15 times/week respectively. The LSI found 93% of patients insufficiently active, and only 7% met physical activity recommendations [33]. Men and women reported similar exercise behavior through age. Older patients (≥65 years) reported a decline in strenuous and moderate exercise frequencies and an increase in mild exercise compared to <65 years.

Table 2. Characteristics of preceding week's exercise in cancer patients† by age and sex.

	All patients		**Age <65years**				**Age ≥65years**			
	(392)		**Men** (81)		**Women** (158)		**Men** (71)		**Women** (78)	
Exercise frequency (times/week) by intensity ‡	Mean (SD) §	Median (IQR) ¶	Mean (SD) §	Median (IQR) ¶	Mean (SD) §	Median (IQR) ¶	Mean (SD) §	Median (IQR) ¶	Mean (SD) §	Median (IQR) ¶
Strenuous	0.20 (0.84)	0 (0)	0.21 (0.85)	0 (0)	0.29 (1.03)	0 (0)	0.13 (0.70)	0 (0)	0.08 (0.42)	0 (0)
Moderate	0.71 (1.43)	0 (1)	0.64 (1.30)	0 (1)	0.77 (1.40)	0 (1)	0.61 (1.53)	0 (0)	0.75 (1.53)	0 (1)
Mild	1.56 (2.15)	0 (2)	1.20 (1.68)	0 (2)	1.31 (1.99)	0 (2)	2.24 (2.49)	2 (4)	1.68 (2.38)	0 (3)
Exercise level††	N	%	N	%	N	%	N	%	N	%
Insufficiently active	363	93	76	94	144	92	66	94	74	95
Sufficiently active	27	7	5	6	13	8	4	6	4	5
Sweat-inducing activity‡	N	%	N	%	N	%	N	%	N	%
Often	60	16	9	11	23	15	15	21	13	17
Sometimes	121	32	28	35	54	35	16	23	21	27
Rarely/never	204	53	43	54	77	50	39	56	43	56

† Participants of STIP-ON study conducted in Verona, Italy, from July 2018 to April 2019. ‡ Exercise intensity according to (57). § SD, standard deviation. ¶ IQR, interquartile range. †† Exercise level according to Leisure Score Index (LSI): active ≥24; insufficiently active <24 (58).

Exercise preferences

Participants exercise preferences are listed in Table 3. Overall, 80% of the respondents were willing (i.e. yes or maybe) to participate in an exercise program designed for cancer patients. Over half (57%) preferred to receive exercise instructions from an oncologist, about 30% from a physiotherapist and 20% from a kinesiologist. The preferred way to receive exercise instructions was with a face-to-face approach (72%), followed by no preferences (12%). The people they preferred to exercise with were other cancer patients (27%). The favorite place for exercise was outside (27%), followed by an adapted exercise fitness center (22%) or at home (21%). Almost half (48%) indicated they preferred exercising in the morning and 70% preferred exercising during a weekday. Just over a third (37%) opted to exercise twice a week and another 30% three times a week. Walking, swimming and biking were the favored activities in summer, while in winter participants opted for walking, gym-training and swimming. Participants also specified that they preferred training at mild (48%) or moderate (39%) intensity. About 34% of patients preferred exercise sessions to vary. Most of them (62%) preferred supervised exercise. The preferred helpers were spouses (28%), exercise specialists (22%) or friends (19%). The preferred exercise program was in a group with an expert (40%).

Table 3. Exercise preferences in cancer patients [†].

Preference as expressed by answers to questions	%	No.
Are you interested in participating in an exercise program designed for cancer patients? (392)		
Yes	46	179
No	20	79
Maybe	34	134
Who would you prefer to receive exercise instructions from? (392) [‡]		
Oncologist	57	224
Nurse	7	26
Kinesiologist	20	80
Nutritionist	20	80
Physiotherapist	30	118

Another cancer patient	3	11
No preference	20	79
Other	2	8
How would you prefer to receive exercise instructions? (376)		
Face to face	72	270
By telephone	3	13
Videotape	2	9
Television	1	3
Leaflet/pamphlet	5	20
Over the internet	3	13
No preference	12	46
Other	1	2
Where would you prefer to exercise? (378)		
At home	21	78
At a community fitness center	12	44
At an adapted exercise fitness center	22	83
Outside	27	103
No preference	18	70
Other	1	2
What time of day would you prefer to exercise? (376)		
Morning	48	179
Afternoon	31	118
Evening	9	32
No preference	13	48
In what part of the week would you prefer to exercise? (367)		
Weekday	70	256
Weekend	9	32
No preference	22	79
How would you prefer to exercise? (363)		
Unsupervised	15	56
Supervised	62	224
No preference	23	83
What kind of exercise program would you prefer? (360)		
Individual with a program to follow at home	27	96
Individual with personal trainer	25	90

In a group with a kinesiologist/physiotherapist/exercise specialist	40	144
Other	8	30
Would you like session content to vary? (363)		
Same each time	29	105
Different each time	34	123
No preference	37	135
Who would you prefer to exercise with? (373)		
Nobody	16	61
Other cancer patients	27	104
Family members	8	29
Friends	8	30
A group	13	47
No preference	27	101
Other	1.3	5
Who would you want as "helper" during the program? (369)		
Nobody	13	48
Exercise specialist	22	83
Neighbor	1	5
Colleague	1	3
Friend	19	71
Son/daughter	13	47
Spouse	28	102
Other relative	3	10
How often would you prefer to exercise? (365)		
Never	1	5
Once a week	15	54
Twice a week	37	136
Three times a week	30	111
Four times a week	5	19
Five times a week	5	19
Six times a week	1	5
Seven times a week	4	16
What exercise intensity would you prefer? (376)		
Mild	48	175
Moderate	39	141

Strenuous	7	24
No preference	6	23

† Participants of STIP-ON study conducted in Verona, Italy, from July 2018 to April 2019 ‡ Replies add up to more than 694 as participants could choose more than one instructor.

Relations between demographic/medical variables within exercise behavior and willingness to participate in exercise program

Table 4 shows the relations between characteristics of cancer patients willing to participate the exercise program. Multivariable logistic regression models showed that these patients most likely attended at least secondary school beyond age 14 years (OR=1.87, 95% CI = 1.15 to 3.04) and had more than double the sweat-inducing activity per week (OR=1.92, 95% CI = 1.92 to 3.63). Among medical treatments, patients who received chemotherapy were less willing to participate (OR=0.45, 95% CI=0.23 to 0.86) than those who did not.

Table 5 shows how patients' characteristics were related to current exercise levels. Levels was lower in patients with BMI ≥25 (β=-0.33, 95% CI -0.57 to -0.10) than those with BMI <25. Exercise levels were higher in patients who had attended at least secondary school beyond age 14 years (β=0.32, 95% CI 0.09 to 0.55) compared with those with less than secondary school. Patients who self-defined their disease stage as "advanced" had lower exercise levels (β -0.36, 95% CI -0.75 to -0.02) than those in remission/cured.

Table 4. Multivariable logistic modeling of associations of characteristics of cancer patients † with willingness ‡ to participate in an exercise program.

		All (No.)	Willing to participate (No.)	Minimally-adjusted model§			Fully-adjusted model¶		
				OR ††	95% CI ††	P-value††	OR††	95% CI ††	P-value††
Age	≤ 65 y (reference)	239	115	1			1		
	≥ 65y	149	63	0.84	0.55; 1.28	0.424	0.63	0.34; 1.15	0.085
Sex	Women (reference)	238	121	1			1		
	Men	154	58	0.61	0.40; 0.93	0.021	0.55	0.32; 0.94	0.029
Education	Up to age 14 years (reference)	151	58	1			1		
	Beyond age 14 years	241	121	1.60	1.04; 2.46	0.031	1.87	1.15; 3.04	0.011
Residence	Outside city (Reference)	148	74	1			1		
	In Verona	244	105	0.70	0.46; 1.07	0.100	0.61	0.38; 0.99	0.045
Perceived income adequacy	Inadequate (reference)	148	68	1			1		
	Adequate	244	111	1.06	0.69; 1.61	0.764	0.94	0.58; 1.51	0.785
Marital status	Married (reference)	269	122	1			1		
	Single	51	22	0.77	0.41; 1.44		0.64	0.31; 1.31	
	Divorced	35	16	0.92	0.45; 1.89	0.366	0.94	0.43; 2.01	0.213
	Widowed	34	19	1.88	0.85; 4.16		2.51	1.04; 6.04	
	Retired (reference)	161	74	1			1		

Occupational status	Homemaker	43	19	0.66	0.31; 1.33	0.354	0.73	0.33; 1.61	0.203
	Part-time employed	45	22	0.83	0.37; 1.62		0.67	0.30; 1.50	
	Full-time employed	123	57	0.83	0.46; 1.43		0.68	0.36; 1.29	
	Other	20	7	0.52	0.17; 1.33		0.58	0.18; 1.90	
Frequency of sweat-inducing activity	<1 time/week (reference)	204	84	1		0.037	1		0.035
	1-2 times/week	121	61	1.46	0.92; 2.32		1.50	0.91; 2.25	
	>2 times/week	60	33	1.79	1.00; 3.23		1.92	1.92; 3.63	
Tumor site[§§, ¶¶]	Breast (reference)	101	55	1		0.251	1		0.423
	Lung	22	9	0.60	0.24; 1.58		0.52	0.16; 1.68	
	Colorectal	39	12	0.39	0.18; 0.86		0.46	0.18; 1.16	
	Upper gastro-intestine	166	77	0.73	0.44; 1.20		0.62	0.31; 1.24	
	Urogenital system	19	10	1.00	0.37; 2.75		1.02	0.28; 3.67	
	Melanoma	14	3	0.23	0.06; 0.88		0.13	0.03; 0.64	
	Other sites[6]	31	13	0.66	0.29; 1.51		0.52	0.20; 1.40	
Disease status	Remission (reference)	62	35	1		0.145	1		0.595
	Early	86	41	0.70	0.36; 1.36		0.61	0.27; 1.37	
	Advanced	85	32	0.48	0.25; 0.95		0.65	0.29; 1.44	
	Metastatic	106	50	0.71	0.37; 1.44		0.72	0.30; 1.73	
	Unknown	53	21	0.51	0.24; 1.08		0.83	0.33; 2.06	
Chemotherapy	No (reference)	55	31	1		0.026	1		0.016
	Yes	329	144	0.51	0.28; 0.92		0.45	0.23; 0.86	
Surgery	No (reference)	169	80	1			1		

	Yes	215	95	0.91	0.60; 1.37	0.644	1.07	0.67; 1.71	0.787
Radiotherapy	No (reference)	271	125						
	Yes	113	50	0.90	0.57; 1.41	0.650	0.97	0.58; 1.61	0.900
Hormone therapy	No (reference)	334	147						
	Yes	50	28	1.45	0.78; 2.71	0.239	1.66	0.83; 3.32	0.152
Other treatments	No (reference)	365	163						
	Yes	27	16	2.10	0.92; 4.82	0.077	1.89	0.81; 4.39	0.142
Treatment status	Completed (reference)	36	18	1			1		
	About to start	11	6	1.46	0.36; 5.84		1.80	0.31; 10.5	
	Ongoing	325	144	0.79	0.37; 1.60	0.695	0.75	0.33; 1.71	0.781
	Unknown	21	11	1.27	0.42; 3.83		1.72	0.45; 6.48	
Time from diagnosis	≤ 30 months (reference)	178	86	1			1		
	> 30 months	214	93	0.79	0.53; 1.19	0.265	0.68	0.42; 1.13	0.126

† Participants of STIP-ON study conducted in Verona, Italy, from July 2018 to April 2019 ‡ Willingness classified as yes vs. no/maybe. § Age- and sex- adjusted models, unless otherwise specified. ¶ Each variable adjusted for the following, unless otherwise specified: Sex (man vs. woman); Age (<65 y vs. ≥65 y); Education (more than 14 years of age vs. up to 14 years); Residence (outside city vs. win city of Verona); Perceived income adequacy (adequate vs. inadequate); Marital status (married, single, divorced, widowed); Occupational status (retired, homemaker, part-time employed, full-time employed, other); Frequency of sweat-inducing activity (<1 time/week, 1-2 times/week, >2 times/week); Tumor site (breast, lung, colorectum, upper gastro-intestine, urogenital system, melanoma, other); Disease status (in remission, early, advanced, metastatic, unknown); Chemotherapy (yes vs. no); Surgery (yes vs. no); Radiotherapy (yes vs. no); Hormone therapy (yes vs. no); Other treatments (yes vs. no); Treatment status (Completed, About to start, Ongoing, Unknown); Time from diagnosis (≤30 months, >30 months); "Lack of preference"

variable (score 0 for no no-preference reply, score 1 for 1 no-preference reply, score 2 for 2 or more no-preference replies given to exercise preference questions); “Independence” variable (score 0 if “on my own” never chosen in exercise preference questions, score1 otherwise. [††] OR (odds ratios), CI (confidence intervals), and P-values from multivariable logistic regression model. [§§] Tumor sites with less than 10 patients are classified as “other site.” [¶¶] Models investigating tumor site (both minimally and fully adjusted models) were not adjusted for sex.

Table 5. Multivariable regression modeling of associations of characteristics of 392 cancer patients [†] with exercise level [‡].

			Exercise level[†]		Minimally-adjusted model [§]			Fully-adjusted model [¶]		
		No.	Mean	SD	β[††]	95% CI [††]	P value [††]	β[††]	95% CI [††]	P value [††]
Age	<65 y (reference)	238	0.61	1.14	Ref			Ref		
	≥65y	148	0.42	0.91	-0.17	-0.39; 0.05	0.125	0.03	-0.24; 0.31	0.801
Sex	Female (reference)	237	0.58	1.10	Ref			Ref		
	Male	153	0.46	0.99	- 0.10	-0.32; 0.12	0.378	- 0.08	-0.32; 0.16	0.489
Body Mass Index (kg/m^2)	<25 (reference)	245	0.67	1.21	Ref			Ref		
	≥25	137	0.31	0.71	- 0.34	-0.57; - 0.11	0.003	- 0.33	-0.57; - 0.10	0.005
Education	Up to age 14 years (reference)	149	0.32	0.75	Ref			Ref		
	Beyond age 14 years	241	0.67	1.19	0.32	0.10; 0.55	0.004	0.32	0.09; 0.55	0.005
Perceived income adequacy	Inadequate (reference)	147	0.52	1.14	Ref			Ref		
	Adequate	243	0.55	1.01	0.06	-0.16; 0.28	0.581	0.03	-0.20; 0.25	0.826
Marital status	Married (reference)	275	0.53	1.00	Ref			Ref		
	Single/other	51	0.63	1.15	0.04	-0.28; 0.37		- 0.05	-0.39; 0.28	
	Divorced	35	0.63	1.52	0.08	-0.30; 0.46	0.86	0.01	-0.37; 0.39	0.781
	Widowed	34	0.41	0.90	-0.06	-0.46; 0.34		- 0.07	-0.47; 0.34	
Occupation	Retired (reference)	160	0.38	0.83	Ref			Ref		

	Homemaker	43	0.40	0.87	-0.05	-0.42; 0.33		0.02	-0.37; 0.41	
	Part-time employed	45	0.66	1.14	0.19	-0.14; 0.62	0.048	0.24	-0.16; 0.64	0.073
	Full-time employed	123	0.76	1.34	0.37	0.07; 0.66		0.32	-0.01; 0.62	
	Other	19	0.38	0.74	-0.01	-0.53; 0.51		0.09	-0.48; 0.66	
Tumor site ‡‡	Breast (reference)	101	0.63	1.27	Ref			Ref		
	Lung	22	0.09	0.33	-0.49	-0.97; 0.02		-0.52	-1.05; 0.01	
	Colorectum	39	0.32	0.94	-0.30	-0.67; 0.12		-0.33	-0.76; 0.10	
	Upper gastro-intestine	164	0.59	1.02	-0.02	-0.29; 0.24	0.579	-0.03	-0.36; 0.31	0.926
	Urogenital system	19	0.39	0.94	-0.18	-0.70; 0.35		-0.26	-0.82; 0.31	
	Melanoma	14	0.79	1.10	0.17	-0.43; 0.76		0.04	-0.61; 0.68	
	Other site §§	31	0.53	0.92	-0.15	-0.51; 0.34		-0.18	-0.65; 0.30	
Disease status	Remission (reference)	62	0.85	1.25	Ref			Ref		
	Early	85	0.73	1.31	-0.10	-0.44; 0.25		0.15	-0.24; 0.54	
	Advanced	84	0.30	0.82	-0.51	-0.86; -0.15	0.006	-0.36	-0.75; -0.02	0.010
	Metastatic	106	0.50	0.97	-0.30	-0.63; 0.03		-0.28	-0.59; 0.08	
	Unknown	53	0.31	0.69	-0.49	-0.87; -0.10		-0.43	-0.81; 0.03	
Chemotherapy	No (reference)	55	0.56	1.05	Ref			Ref		
	Yes	327	0.54	1.07	-0.06	0.36; 0.25	0.720	0.04	-0.34; 0.38	0.914
Surgery	No (reference)	167	0.48	0.98	Ref			Ref		
	Yes	215	0.58	1.12	0.10	-0.12; 0.31	0.366	0.07	-0.16; 0.31	0.540
Radiotherapy	No (reference)	269	0.55	1.10	Ref			Ref		
	Yes	113	0.50	0.97	-0.03	-0.26; 0.21	0.833	-0.10	-0.36; 0.16	0.454

Hormone therapy	No (reference)	332	0.53	1.07	Ref			Ref		
	Yes	50	0.58	1.00	-0.01	-0.34; 0.32	0.955	0.10	-0.26; 0.46	0.581
Other treatments	No (reference)	363	0.53	1.05	Ref			Ref		
	Yes	27	0.60	1.10	0.09	-0.33; 0.51	0.682	0.10	-0.37; 0.57	0.684
Treatment status	Completed (reference)	35	0.83	1.31	Ref			Ref		
	About to start	11	0.54	1.62	-0.20	-0.93; 0.53		0.18	-0.67; 1.04	
	Ongoing	323	0.50	1.00	-0.30	-0.67; 0.07	0.184	-0.14	-0.54; 0.26	0.462
	Unknown	21	0.54	1.08	-0.21	-0.79; 0.37		-0.08	-0.72; 0.55	
Time from diagnosis	≤30 months (reference)	177	0.47	0.94	Ref			Ref		
	>30 months	213	0.59	1.15	0.13	-0.08; 0.34	0.225	0.15	-0.08; 0.39	0.207

† Participants of STIP-ON study conducted in Verona, Italy, from July 2018 to April 2019 ‡ Exercise level assessed using Leisure Score Index (58). § Age and sex adjusted models unless otherwise specified. ¶ Each variable was adjusted for the following, unless otherwise specified: Sex (man vs. woman); Age (<65y vs. ≥65y); Education (beyond 14 years of age vs. up to 14 years); Residence (outside city vs. in city of Verona); Perceived income adequacy (adequate vs. inadequate); Marital status (married, single, divorced, widow); Occupational status (retired, homemaker, part-time employed, full-time employed, other); Tumor site (breast, lung, colorectum, upper gastro-intestine, urogenital system, melanoma, other); Disease status (remission, early, advanced, metastatic, unknown); Chemotherapy (yes vs. no); Surgery (yes vs. no); Radiotherapy (yes vs. no); Hormone therapy (yes vs. no); Other treatments (yes vs. no); Treatment status (completed, about to start, ongoing, unknown); Time from diagnosis (≤30 months vs. 30 months). †† Beta coefficients 9(β), confidence intervals (CI), and P values from multivariable regression models. The β coefficient is the amount of change in exercise level (Leisure Score Index) in each category of predictor variable compared to reference. ‡‡ Minimally- and fully- adjusted models for tumor site not adjusted for sex. §§ Tumor sites with <10 patients classified with other site.

Discussion

The STIP-ON survey found that only 7% of cancer patients do enough physical exercise. Previous studies reported the percentage of cancer patients with adequate exercise levels, between 16-85% (17). Considering the impact of physical inactivity on the quantity (30-32) and quality (34, 35) of life in cancer patients this is an alarming result.

Roughly 80% of patients were willing to start an exercise program designed for cancer patients. Previous studies reported similar results, finding that the majority of bladder (61), non-Hodgkin's lymphoma (51), prostate (49), head and neck (53), endometrial (50), ovarian (52) and breast (49) cancer survivors were interested in an exercise program. This is important because it supports the cancer patients' desire for an exercise service.

Several socio-demographic characteristics were associated with the willingness to participate in an exercise program. Willingness decreased with age, also in fully adjusted models, and this was to be expected given the growing difficulties and comorbidities due to aging. Age has been associated with low adherence to exercise in cancer patients in various studies (52, 62). What is interesting is that even among the older patients more than two thirds said they might be interested in taking part in an exercise program. Women were more willing to participate than men. That was found in all models, even after adjustment for medical and socio-demographic variables. That women cancer patients adhere better than men in exercise programs is suggested by an intervention study in rectal cancer patients (62) although a systematic review evaluating the predictors of adherence to exercise interventions during cancer treatment suggested that adherence was best among men (63). Better educated patients were more willing to participate. This was reported in other studies too (52, 64) and a likely explanation is well-educated people's greater awareness and knowledge of the benefits of exercise. It is interesting that economic security was not related to the willingness to participate, and that too was suggested by other studies (62). This lack of association might be the result of two concomitant and opposing phenomena: those who have less financial availability willingly accept a free offer to exercise; the same poorer people, however, may have less desire to exercise because they are less motivated or because they do manual

work. Patients who reported higher frequencies of sweat-inducing activity were more willing to participate in an exercise program that those less frequently reporting it. This can be summed up with the Italian saying: "it rains where it's already wet": in other words, those who are most motivated are those who would need it less. No similar results were found in the literature, but a possible explanation is that those who have already done more physical exercise perceive the benefits better and are therefore more ready to improve or increase their level (65). Chemotherapy was inversely associated with the willingness to participate. There is one study that found no relation between cancer treatment and adherence in high-intensity and low-to-moderate intensity exercises (64); other studies found chemotherapy (63) and its side effects (44) were associated with low adherence to physical exercise programs. One explanation for these contradictory results may be that chemotherapy is a generic term that includes different drugs and various possible side effects. There were no differences in willingness to participate based on other medical variables, and this is consistent with previous work on this topic (52).

Regarding the preferred source of exercise instruction, the oncologist was the preferred person to deliver instructions in the present survey and this is not in line with the current standard of care. Previous investigations reported an exercise expert (kinesiologist) as the favorite (17). Findings from the present survey may be related to the lack of exercise specialists for patients at the Verona Hospital Oncology Unit. The trusting relationship between the patient and the oncologist built up during the cancer journey is another likely explanation. Less than half of oncologists promote exercise with their patients (66). Barriers that interfere with exercise promotion by oncologists were identified as lack of time, limited access to an exercise specialist/program and lack of knowledge about exercise in cancer (67). However, educational sessions about exercise in cancer patients and caregivers, specific education materials (leaflets, brochures, posters ,etc.) and/or a kinesiologist as part of the clinical team are recognized factors to help promote exercise (67).

Social support plays a role in exercise program compliance (68). In the oncological setting, social support enhances emotional well-being (69) and is related to PA engagement (70). The present results are in line with this: 55% of patients preferred

exercise with others (cancer patients, relatives, friends); about 87% expressed interest in having a helper, i.e. a person to help and motivate them with the exercise, identifying various subjects: the spouse or other relatives, or exercise specialists. Social support from different helpers has been seen to be effective for behavior change (71): family, friends, peers, exercise specialists, healthcare providers, and other influential subjects might be the key figures to support compliance and the maintenance of exercise over time (72).

Although in previous studies there was a marked preference for a home-based program (17, 49, 50, 52, 61), in this study similar percentages of patients preferred exercising outside, or in an adapted exercise fitness center, or at home. This suggests that providing different program options would boost compliance for exercise interventions. To reinforce this assumption, subjects were asked what they would choose out of three exercise options (individually with a program to follow at home/individually in a gym with a kinesiologist/in a group class with a kinesiologist/none of these). More than 90% indicated their preference among these options.

The majority of STIP-ON participants preferred a supervised exercise program. This finding contrasts with studies on bladder (61), head and neck (53), prostate and breast (49) cancer, but is in line with other investigations on mixed (73), lung (74) and endometrial (50) cancers. One explanation might be related to the patients' health condition: cancer-related treatments affect normal physical function and influence daily activities, hence the need for supervision from a qualified figure to avoid adverse effects. Moreover, supervised exercise intervention may give additional benefits for cancer patients. A recent metanalysis including a total of 4,519 patients with mixed cancer types evaluated the effect of exercise on quality of life and physical function; it found twice the effect size for supervised compared to unsupervised training (75).

In line with previous studies (49, 50, 52, 53, 61, 73), a substantial proportion of patients indicated walking as their favorite activity, in winter and summer. Walking programs have been effective to manage treatment side effects and improve physical functions in cancer populations (76, 77). Walking is relatively safe, flexible and easy as it does not require special skills (78). Moreover, walking can

be done in different environmental situations, is accessible and appropriate in groups of different age, sex, ethnicity, education or income levels, and does not require expensive equipment. Walking is also known to reduce social barriers among people of different socio-economics status (79).

Contrary to other reports (49, 50, 53, 73, 74), the present study indicated the preferred exercise intensity as mild. Exercise guidelines for cancer patients suggest they should engage in at least moderate exercise (7). Mild intensity could be the choice to start an exercise program, especially with physically 'deconditioned' people, and should be gradually increased to moderate and vigorous intensity. Several reviews show moderate-to-vigorous but not mild exercise intensity is effective in managing cancer side effects, and improves physical function (37, 80). In light of this evidence the present findings highlight the need to inform cancer patients and their caregivers about the safety of moderate and vigorous intensities exercise. Patients' exercise levels were related to their educational level, type of treatment and body fatness. Several studies have investigated the determinants and triggers of exercise behaviors in patients, but with inconsistent findings (81-83).

This appears to be the first study investigating the determinants of exercise preferences in Italian cancer patients before they were involved in exercise intervention programs. The study results provide useful data for planning future exercise programs. The self-reported QEX permitted the collection of a large amount of data and was quickly administered, without much burden on respondents, or costs. Another point of strength is the collection of information about why individuals did not wish to take part in the study.

Limitations of the study need to be noted: the QEX information was self-reported and therefore open to several sources of bias. The QEX was filled and returned anonymously, so social desirability bias (for instance, patients may exaggerate their physical activity so as not to 'disappoint' the researcher) is less likely. The information leaflet given to patients at recruitment provides minimal information presenting the study but does not contain any recommendations/ guidelines. However, just having provided information might have influenced the replies. Another potential source of error is selection bias: cancer patients who agreed to participate in the survey may be individuals more interested in exercise. To ensure

a representative sample of patients, a random sample of outpatients was selected. Finally, the questionnaire does not serve to classify exercise adherence according to the new ACSM (7) guidelines for cancer patients. These guidelines were released in October 2019, after the QEX had been administered to the study sample of patients (7). Nevertheless, the QEX classifies patients according to the previous ACSM guidelines (59). This allows us to compare patients' exercise levels with the studies that have been reported so far. Classification of the LSI according to the ACSM guidelines for cancer patients (59) allows a full comparison of study finding with the majority of other studies in the field. Nevertheless, this classification may have artificially inflated the percentage of participants who reported insufficient physical activity. The QEX does not collect information about participants' pre-diagnosis exercise and physical activity and that limit its ability to explore associations with other possible determinants of current exercise behavior. The patients in STIP-ON were sampled to be representative of those attending the Verona oncology clinic (and not the full total of patients). Therefore, although more severe patients with severe comorbidities are likely to have been excluded, patients' responses may also have been influenced by other comorbidities that were not investigated by the QEX.

Information from this survey is clinically relevant and may help in designing personalized interventions so cancer patients will achieve sufficient exercise/PA. Here are a few examples: i) Since about 90% of participants said they wanted or needed a helper during the program, a targeted intervention program should include specific activities (and support) for helpers patients will nominate; ii) Because about 30% of respondents said they prefer to exercise with other patients, exercise classes specifically for them and "learning from peers" social occasions should be organized; iii) The majority of patients were insufficiently active and preferred mild exercise or slow walking. So as not to leave anyone behind, for those who are not able to engage in moderate exercise, a mild flexible entry program should be offered according the patient's condition and preferences and then progress slowly towards higher-intensity exercise.

In conclusion, an exploratory survey like STIP-ON could serve as a necessary first step in developing lifestyle improvement interventions for patients. This is

particularly important in a country like Italy where there is little knowledge in this field, and factors such as the family environment and social support are not well understood. Only a small proportion of patients were sufficiently active, although the majority were willing to start an exercise program. Exercise preferences in cancer patients tended to vary substantially. These findings underline the urgency of promoting personalized exercise intervention programs among Italian cancer patients.

CHAPTER 3
STUDY 2

Factors influencing physical activity in cancer patients during oncological treatments: a qualitative study

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Abstract

Introduction: Although the literature supports the importance of physical activity in oncological context, in Italy a large number of patients are not sufficiently active. **Methods:** The present study aimed to explore factors influencing an active lifestyle in cancer patients during oncological treatments. Semi-structured focus groups, including 18 patients with different cancer types, were conducted at the Oncology Unit in the University Hospital Trust of Verona (Italy). The interviews were audio-recorded, transcribed verbatim, and analyzed with content analysis. **Results:** According to the Health Belief Model, transcripts were categorized into the following themes: benefits, barriers, and cues to action. Patients reported a series of physical, physiological, and psychological benefits deriving from an active lifestyle. The main barriers hampering the physical activity participation were represented by treatments-related side effects, advanced disease, and some medical procedures, e.g., ileostomy. Several strategies that can trigger patients to exercise were identified. Medical advice, social support from family and friends, features as enjoyment, setting goals, and owning an animal can motivate patients to perform physical activity. At the same time, an individualized program based on patients' characteristics, an available physical activity specialist to consult, more detailed information regarding physical activity in the oncological setting, and have accessible structures, were found important facilitators to implementing an active behavior. **Conclusions:** Overall, patients have a positive view regarding physical activity, and a variety of obstacles and cues to action were recognized. Considering these information may help to improve adherence to a physical activity program over time, consequently increasing the expected benefits.

Introduction

Cancer is the second leading cause of mortality in Italy (26), and it is expected an increase in cases and deaths between 2018 to 2040, by 22% and 35%, respectively (84). Oncological patients usually receive several integrated and multimodal therapies that may damage patients 'integrity, harming their quality of life (7). The cancer treatment-related side effects are usually cumulative and consequently may entail a progressive impairment of both the physical and psychological status in patients (85).

Physical activity has emerged as an important complementary supportive care for cancer patients (7). Evidence suggests a positive outcome in terms of reduction of recurrence and mortality risks (5) and amelioration of several treatment-related side effects, such as nausea, vomiting, peripheral neuropathy, fatigue, arthralgia, or myalgia (12). From a physical and psychological point of view, physical activity is associated with an increase in cardiorespiratory fitness (8), muscular strength (9), and an improvement in body composition (9), quality of life (75), anxiety (7), and depression levels (7). Despite the benefits, in Italy, only 7% of cancer patients appears to be sufficiently active (86).

Numerous aspects can interfere or contrarywise facilitate patients to adopt an active lifestyle during cancer treatments. Some of these are in common with the general population (e.g., weather, lack of time), whereas others are strictly related to the disease history (45). Also the attitude, i.e., the perception of a behavior as positive or negative, can affect the intention and the maintenance of physical activity performance, also in the oncological context (87). Developing a physical activity program that considers these features may increase the compliance and the maintenance over time of an active lifestyle by the patients. Unfortunately, in Italy, the literature on physical activity and cancer is still limited, with no clear data regarding the adherence to a physical activity program (24). Although several investigations have explored attitude, barriers, motivators, and facilitators, able to influence the adoption of physical activity in oncological settings (46, 47, 88-96), no data on Italian patients are available. In order to fill this gap and to successfully design a future interventional study, we have qualitatively explored those factors

influencing the adoption of an active lifestyle in cancer patients visiting the outpatients' facilities at the Oncology Unit in Verona Hospital.

Methods

Design

This study applied a qualitative approach, through a series of focus groups, to assess the factors influencing physical activity behavior in the cancer setting. This study applied a qualitative approach, through a series of focus groups, to assess the factors influencing physical activity behavior in the cancer setting. The theoretical framework driving the investigation was the Health Belief Model, postulating that health-related practice, especially related to disease conditions, is influenced by several factors, including susceptibility and seriousness of the disease, perceived benefits, and barriers towards a behavior, cues to action, and self-efficacy (97). Because this study was related to health promoting factors, rather than to perceptions of severity or vulnerability to peculiar conditions, it focused on patients' perceptions of the benefits of physical activity, barriers to engagement, and cues to action that would promote physical activity.

All the study procedures were conducted in compliance with Helsinki and Oviedo declaration, and the protocol adhered to Good Clinical Practice principles and Italian legislation. The project was reviewed and approved by the local Ethics Committee for Clinical Trials (Prot. N. 67002), University of Verona. It was carried out following the Standards for Reporting Qualitative Research (SRQR) guidelines for qualitative research (98).

Participants and recruitment

We recruited participants that met the following criteria: (i) were ≥ 18 years of age, (ii) had a confirmed cancer diagnosis, (iii) were currently patients at the outpatient Department of Oncology in the University Hospital Trust of Verona (Italy), (iv) spoke fluently Italian and (v) signed the informed consent. No exclusion criteria were applied. A purposive sample strategy was used to recruit patients. The participants were identified by the dedicated psycho-oncologist, DT, working at the Oncology Department of University Hospital Trust of Verona. With a face to face

approach, the psycho-oncologist introduced the study to the patients, and if they agreed to participate, the interviews were organized. Written informed consent was obtained from included patients the day of the interviews before starting the focus group. Pseudonyms were used to report the data to protect the participants' identities.

Data collection

To explore the factors that influence the physical activity behavior in cancer setting, a flexible semi-structured interview guide, based on the Health Belief Model (97), was developed by AA, DT, and ML. Between September 2019 and February 2020, five focus groups (n=4, 4, 4, 3, and 3) were held in a meeting room at the Oncology Department in University Hospital Trust of Verona. Each discussion lasted up approximately 70 minutes, was audio-recorded and transcribed verbatim. The last author (ML) moderated the discussions; meanwhile, AA and LR observed and assisted. ML is an Associate Professor in Sports Science and Methodology at Verona University with expertise in physical activity and health promotion. AA is a Ph.D. student involved in exercise in oncological patients, with previous interview experiences, and LR is a master's degree student in preventive and adapted physical activity. The sample size was established using the data saturation principle, i.e., data collection continued until no new information seemed to emerge from the discussions. At the end of each focus group, participants completed a questionnaire to provide information about their socioeconomic and demographic data (e.g., birth date, education level, perceived economic insecurity, marital status, and occupational status). Patients' medical history was obtained by medical charts.

Analysis

The data were analyzed with the Atlas.ti^{TM} software, using the content analysis (99). This process comprised some essential steps and involved AA, LR, and ML, that independently examined the transcripts. The investigators read and re-read the entire text several times to get a general idea of the discussion and identify the salient concepts. Subsequently, the analysis process consisted of inductively coding

the features relevant to the research questions. Then, the codes were grouped into categories and organized in themes (99).

Finally, all three authors reviewed the analysis in a process called *triangulation*, which consisted in comparing the codes, the categories, arriving to a consensus on final themes (99).

Results

Participants and demographics

A total of 36 patients were screened for eligibility. During the recruitment 18 patients have declined to participate, due to: unavailability in the proposed days (n=11), worsening in health conditions (n=5), and lack of interest (n=2). Five focus groups with a total of 18 participants, after the discussion among researchers, have permitted to achieve the data saturation.

Demographic and medical variables were reported in **Table 1**.

Table 1. Participants' characteristics.

Variable	
Age[a], mean (SD)	55,2 (10,3)
Body mass index[b], mean (SD)	23,7 (3,0)
Education, N	
Secondary (up to 14 years)	5
Secondary (up to 18-19 years)	8
College/University	4
Postgraduate	1
Marital status, N	
Single	1
Married	16
Divorced	1
Employment, N	
Part-time employed	4
Full time employed	9

Retired	4
Unemployed	1
Family income[c], N	
Barely adequate	8
Adequate	9
More than adequate	1
Met physical activity guidelines (90+ min/week), N	
Yes	10
No	8
Tumor site, N	
Colorectal	1
Pancreas	6
Ovary	1
Lung	1
Breast	6
Head and neck	1
Melanoma	1
Thymus	1
Stage, N	
I	1
II	3
III	4
IV	10
Months from diagnosis, mean (SD)	25,7 (16,5)
Treatment, N	
Surgery	10
Chemotherapy	17
Radiation therapy	8
Hormone therapy	5
Immunotherapy	3
Target therapy	3
Current treatment status, N	
Incoming	0
Ongoing	18

Ended	0
Comorbidity, N	
Yes	10
No	8

Legend: SD, standard deviation, N, number;

[a] Expressed in years; [b] Expressed in units of kg/m^2; [c] Perceived economic insecurity assessed by the question: *Does your monthly income cover your monthly expenditure?*

The mean age of the participants was 55.2 ± 10.3 y, 16 were married, 13 had at least higher education, up to age 18-19. All participants were on active treatment; the most frequent cancer sites were upper gastro-intestinal (n=6) and breast (n=6), with a mean time from diagnosis of 25.7 months. The data were analyzed according to the Health Belief Model (**Figure 1),** and the following common themes were categorized: 1) benefits, 2) barriers, and 3) cues to action.

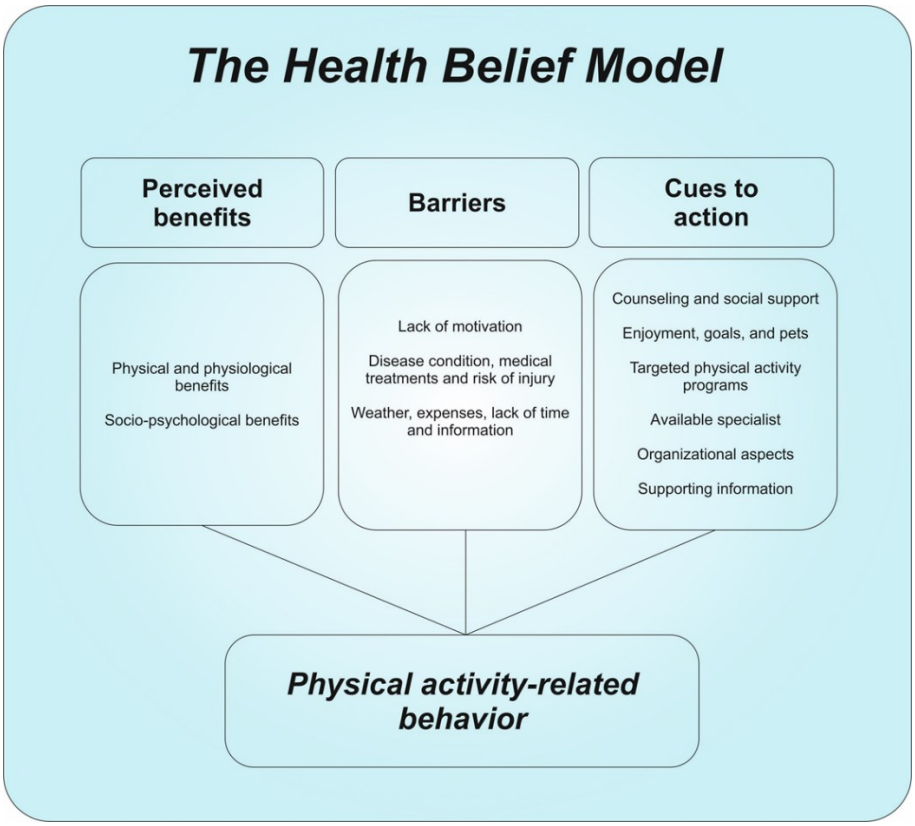

Figure 1. Health Belief Model theoretical framework applied to physical activity in cancer patients

According to these findings, a series of recommendations to promote a successful physical activity program in this population were proposed **(Figure 2).**

Figure 2. Strategies to implement a physical activity program in the oncological clinical setting

Theme 1: Benefits

This theme reflected the belief of the patients regarding physical activity and was grouped into two main categories: *(a) physical and physiological benefits, and (b) socio-psychological benefits.*

a) *Physical and physiological benefits*

All patients strongly expressed that physical activity is beneficial for overall well-being. The positive effects of being physically active were related to physical aspects, as Arianna (breast) told: *"Physical activity has a beneficial impact on my body, also during the chemotherapy treatment: I have more strength, I can maintain my muscle mass and I am in a good mood".* Some subjects also recognized the impact of physical activity to counteract treatments related side-effects: *"I suffered from constipation due to cancer therapies, and walking has been very beneficial for me against this disorder"* (Tiziana, breast) or *"I usually go running before my*

chemotherapy, and I do not experience any treatment-related side effects, while, if I do not, I feel exhausted, I have nausea and vomiting" (Matteo, pancreas). Finally, a patient underlined how to be active can help to fight cancer: *"Physical activity keeps the estrogens at low levels. My cancer eats estrogens, so if I do physical activity, I starve my tumor"* (Tiziana, breast).

b) *Socio-psychological benefits*

Participants identified several advantages related to psychological aspects: *"When you perform physical activity, endorphins are released. This mechanism can help to fight the depression…and consequently to have a different attitude in approaching cancer"* (Maria pancreas). Physical activity was described as a *"natural recharge", "(Physical activity) makes you feel good, especially from the mental point of view…you feel charged and ready to face everything"* (Martina, breast), and, as a *"day organizer", "(Physical activity) can really help you to plan your daytime, and even if something unexpected happens, you are able to manage it"* (Salvatore, pancreas). Moreover, patients expressed that physical activity was a vehicle to increase their perception of control, in the cancer context, as Martina (breast) told, *"when you suffer from cancer, you rely on the oncologists, surgeons, nurses, etc.; physical activity is something that you decide to do! You can take the reins of the situation and control it without being at the mercy of the events".* The subjects also recognized how to be physically active can help them to face the cancer disease also in the family context: *"When I go walking with my husband, we talk about everything, we plan, and we organize our next steps; physical activity has truly reunited us, despite my cancer"* (Maria, pancreas).

Theme 2: Barriers

Many factors were individuated as potential barriers, which can hinder physical activity. Obstacles were grouped into three categories: *(a) lack of motivation, (b) disease condition, medical treatments and risk of injury,* and *(c) weather, expenses, lack of time, and information.*

a) *Lack of motivation*

Lack of motivation, emerged as the self-described *"laziness"*, was the central concept reported about less than half of participants. *"I am the perfect example of laziness. I do not like physical activity even if I recognize its importance"*, said Luca (thymus), or *"Physical activity is secondary for me…my head tells me that it is important, but I am lazy"* (Elisa, breast). However, some of them recognized their predisposition and consequently tried to react positively, as Teresa (colorectal) expressed: *"I am lazy, and I know it. Thus, I put myself in situations that force me to be physically active"*.

b) Disease condition, medical treatments and risk of injury

Health conditions and cancer treatment-related side effects were identified as the major barriers to physical activity. Chemotherapy side-effects can impact on the ability to perform a regular physical activity, as Martina (breast) said "*When you are undergoing cancer treatments, sometimes you are not able to get up from the sofa; neither with your willpower, you can!*", or Debora (pancreas) explained, *"This chemotherapy malaise, expressed especially with fatigue, leads you to do less physical activity"*. The presence of bone metastasis was identified a significant limitation to exercising, as Elisa (breast) expressed, *"I have bone metastasis in the spine, and I know that I must avoid loading in that zone"* or Michele (lung) elucidated, *"I love cycling, but I cannot perform it because I have hip bone metastasis. I am on fracture risk, and I am afraid to get injured"*. Patients indicated some medical procedures that interfere with their physical activity. The presence of ileostomy was emerged as an obstacle, seriously limiting the daily physical activity: *"I have an ileostomy, which has generated a hernia; before I was able to walk for 10 kilometers, but now I can make only one or one and a half. Furthermore, I cannot do some activities, such as swimming, because I have a bag in my belly"* (Maria, pancreas). Also, the central venous catheter (CVC), can impair the perception to be able to perform physical activity: *"I have a psychological block regard the presence of CVC. I know that I could do physical activity without realizing to have the CVC, but this is a huge psychological obstacle for me"* (Luca, thymus). Some concerns were emerged about the risk of injury: *"When I go walking, I experience back pain sometimes"* Elisa (breast), or *"You could get hurt, like injure your knee"* Martina

(breast). During the discussions, also the excess of physical activity, as a potentially harmful factor have been mentioned: *"Exaggeration could potentially be dangerous"* Luca (thymus), or *"One time I overdid, and the day after I was sick, I felt confused,"* expressed Matteo (pancreas).

c) Weather, expenses, lack of time and information

Rain, seasonality, or more, in general, extreme weather, can interfere with physical activity: *"Weather is an obstacle, because if the downpour falls you prefer to stay at home"* (Michele, lung), or "*I am in crisis during the winter season, due to cold and little sunlight"* (Sergio, head and neck). On the contrary, also heat can impede the physical activity predisposition: *"I do not like performing physical activity during the summer, it is too hot; I feel exhausted"* (Alessandro, melanoma). A common factor identified by the patients was the lack of information regarding physical activity in the oncological setting: *"It is hard to find suitable information regarding physical activity"* (Martina, breast) or *"I have an exercise bike at home, but I do not know if it is beneficial for me to load my hips or my knees; I do not have information about this"* (Ennio, pancreas). Lack of time was an obstacle prevalently emerged in patients that were still working: "*Between family and work, it is really difficult to find some time to dedicate in exercising"* (Sergio, head and neck). Finally, one subject expressed some concerns about the cost related to physical activity: *"I would like to try archery, but is too expensive, 500 euros for three lessons. It seems that some sports are only for a small elite group of people"* (Luca, thymus).

Theme 3: Cues to action

Seven categories grouped the stimuli that trigger the decision-making process to perform physical activity: *(a) counseling, social support (b) enjoyment*, *goals, and pets*, *(c) targeted physical activity programs, (d) an available specialist, (e) supporting information, and (f) organizational aspects.*

a) Counseling and social support

Interpersonal factors were important to motive patients to start physical activity. On the one side, the initial advice of oncologists or other relevant figures was a considerable incentive to be physically active, as Alessandro (colorectum) mentioned, *"Talking with doctors can really help you to start exercising,"* or Daniela (breast) said "*When I started my chemotherapy, my physical and psychological status were bad. After the advice of medical staff, I began walking, and I bought a cyclo-ergometer"*. On the other side, another aspect regarded strong support from family and friends. *"My son calls me 100 times per day to remind me to stay active…my strength derives from my sons because they tell me that I am a wonder woman; they give me so much energy"* said Debora (pancreas) or *"I appreciate that my husband come walking with me because I usually do not take many initiatives alone"* specified Marta (ovary). About the friends' support, Alessandro (melanoma) declared: *"My friends stimulate me to restart cycling with them, they are a positive support for me!"*.

b) Enjoyment, goals, and pets

Patients referred to be positively encouraged if they set goals, or a targeted objective, as Gigliola (breast) said, *"During my cancer therapies I gained weight, so I decided to begin physical activity with the aim to improve my body composition. Since January, I have lost 10 kilograms!"*. Some participants reported enjoyment as an incentive to perform physical activity: *"I love walking; it is a positive activity! Maybe I could have started it before!"* (Marta, ovary) or "*Be physically active gives you great satisfaction. I like it"* (Matteo, pancreas). A patient reported that having a pet can help to maintain an active lifestyle: *"Having a dog helps you stay active because you must get it out every day, even when the weather is bad"* (Alessandro, melanoma).

c) Targeted physical activity programs

A targeted, flexible program was identified as a key facilitator by the patients. Almost half of the patients reported that physical activity should be programmed at the beginning of cancer treatments, as Marta (ovary) explained: *"…when you start chemotherapy, you do not think about physical activity. It should be programmed*

at the beginning, after diagnosis, and included in the therapeutic plan". Different preferences have emerged regarding the modality to perform physical activity: *"I want (exercising) alone"* (Michele, lung) or "*Due to work, family and other reason I would prefer training at home, but with monthly counseling with a physical activity specialist"* Sergio (head and neck) or *"I like to do physical activity in-group, with other patients"* Salvatore (pancreas). All the participants agreed that a physical activity program should be targeted on the patient's disease and the comorbidities: *"The activity should be diversified according to the different type of disease; I have had breast surgery with axillary dissection, and some exercises may be better for me but not for those patients that experienced another type of cancer"* Martina (breast) or "*I have a herniated disc so the activity should be adequate also to my comorbidity"* Salvatore (pancreas).

d) An available specialist

Several subjects have expressed the necessity to have a qualified specialist inside the Oncology Unit. Although the initial advice by medical staff can encourage subjects to start physical activity, some patients desired more specific instructions: *"When I received the diagnosis, I asked the oncologists: what do I do? Should I perform physical activity? They usually answered me: do what you feel like doing…but this kind of response is not satisfying!"* Salvatore (pancreas). From their perspectives, an available specialist could strongly help them to be more self-confident in performing physical activity: *"Now the only activity that I perform is walking, because I am afraid of getting injured. I must be cautious due to my bone metastases. In my opinion, having a qualified specialist inside the hospital would give me more confidence"* Arianna (breast) or *"When you are diagnosed with cancer, you do not know whom to ask information. It is helpful to have in the same place oncologist, dietitian, psychologist, surgeon, etc., so even for the physical activity could be the same"* Martina (breast).

e) Supporting information

Promote physical activity, through credible and suitable information, including the benefits and practical consideration to exercising, can facilitate the engagement:

"Promoting the information regarding the benefits of physical activity, specifying the advantages for the body systems and your disease" Ennio (pancreas) and *"I need information about how to perform physical activity because I am 60 years old and I do not think to begin to do an uphill race"* Sergio (head and neck). Participants reported the importance of having specific information: *"Maybe it would be necessary to give patients detailed, and more targeted information, based on the type of disease"* Maria (pancreas) *or " The information should be addressed on the key points that specify the benefits of an active lifestyle related to disease because this can help to consider physical activity as real medicine."*

f) Organizational aspects

Suitable structures can facilitate an active lifestyle. Some patients would perform physical activity outdoor, as Daniela (breast) supported, *"I prefer to do physical activity outside if the weather is good*". Others would desire a gym inside the hospital: *"In each oncological unit there should be a gym, it is necessary, because it is important such as the chemotherapy, and could simplify the approach to physical activity"* Debora (pancreas). Moreover, another important characteristic was the distance from the fitness center: *"Having a gym near home is extremely important because if I have to drive, I will not go"* Gigliola (breast).

Discussion

The present study explored factors that influence physical activity engagement in cancer patients suggests a series of recommendations to promote a successful physical activity program in this population (**Figure 2.**).

Benefits

We found that patients generally have a positive perception of physical activity, reporting a variety of related benefits, from physical factors to those physiological and socio-psychological. These results are consistent with previous studies (65, 89-91, 93, 96). Smith and colleagues reported that patients described physical activity as positive behavior for general health, to manage some treatment-related side effects and other chronic conditions (e.g., cardiovascular disease) (89). Older breast

cancer survivors mentioned that an active lifestyle help to reduce the stress levels and combat depression(90). At the same time, Mazzoni et al. found that patients exercising during oncological treatments reported a feeling of self-control (65).

Barriers

Several barriers inhibiting cancer patients' physical activity participation were identified. Some of them are related to cancer and its treatments. These results are comparable with previous investigations (88, 89, 92, 94, 95, 100). A recent, qualitative meta-synthesis has confirmed that the most relevant obstacles of adopting an active lifestyle were linked to cancer- and treatment-related side effects(94). Fatigue is one of the most reported impediments which hinder the engagement in physical activity in this study, but also other works (89, 93, 100). Nevertheless, a recent meta-analysis, including 113 studies with a total of 11,525 patients, showed that exercise was more effective than pharmaceutical interventions to ameliorate the level of cancer-related fatigue (101). To date, it is well consolidated the role of physical activity to improve fatigue in cancer so much that also the recent ESMO clinical practice guidelines for cancer-related fatigue include exercise as an efficacious tool to manage this symptom (102). Thus, inform patients regarding the beneficial effect of physical activity on fatigue is crucial. Although similar reports reported safety issues, including the risk of injury (93, 94, 100), as features hindering physical activity, this appears the first investigation finding bone metastasis as a factor, seriously limiting the engagement in physical activity. Exercise oncology in advanced cancer is rapidly increasing during recent years. Promising results, such as the safety of fracture risk and the preliminary efficacy of exercise in patients with bone metastasis (103), were showed, also for resistance training, the activity traditionally considered detrimental for fracture risk (104). Patients with bone metastasis expressed their will to be active, but also the impediment of not knowing which exercises are safe and whom to rely on to practice physical activity. In this regard, reassuring patients about safety and adapt the activities to their ability should be considered. In line with prior studies (88, 100), some procedures, as the ileostomy and the CVC were recognized, potential obstacles to exercising. Henriksson and colleagues found a similar concern about

the peripherally inserted central catheter in patients during adjuvant treatments (88). One possible explanation could be, that this type of procedure undermines patients' confidence on their ability, thus doubting of the possibility to perform physical activity. Another related concept is just about the available information on physical activity. Patients referred to the lack of specific material and suggest that having targeted information may facilitate the engagement by the patients. The lack of accessible and evidence-based information about physical activity in cancer is a persistent problem in the current literature. A recent study reviewed the website in the English language that provide information on maintaining or improving physical activity after a cancer diagnosis (105). The results showed that the importance of physical activity is frequently mentioned, while the available information suffer from lack of comprehensive, specific advice as well as detailed mention to practice (105). Thus, in this work authors suggested that written or online health information to be efficacious should be high quality and accessible, evidence-based, should motivate and guide the engagement, outlining the risk and advising the seeking of professional advice (105).

Although not surprising, the presence of obstacles related to external situations (e.g., bad weather, expenses, etc.), consistently mentioned in previous works (95, 106), the lack of motivation, self-described by patients as "laziness", was not so usual. In other investigations[106), (95) patients reported laziness as a feature hindering their willingness to exercising, suggesting that planning a physical activity intervention aimed also to appropriately build patient's motivation could be an effective way to overcome this state of mind.

Cues to action

Regarding the cues to action, social support by family and friends motivated patients to stay active. However, the literature showed mixed results. On the one side, social support was a vehicle to increase the physical activity motivation (89); on the other, an investigation found indifferent the relationship with the family and others (96). Focusing on counseling, patients reported medical advice as an important motivator to support an active lifestyle. A previous work finds that patients preferred to receive initial information by their oncologist (86), and a

randomized trial indicated that a 30-seconds oncologist recommendation was able to significantly increase exercise levels in breast cancer survivors attending a primary adjuvant treatment consultation (107), thus supporting the importance to get the endorsement by the oncologist. However, the advice of medical staff can be the first step to manage behavior; in our study, having the opportunity to consult a physical activity specialist can be encouraging patients to receive a program adapted to their necessity and conditions and can consequently stimulate them to improve their lifestyle. This agrees with prior investigations (89, 94), and, interestingly, also with the oncology care providers' perspectives. Indeed, from the medical staff point of view, having a physical activity specialist as part of the clinical team and educating patients about physical activity are considered the optimal strategies to engage patients in exercising (67).

Moreover, also enjoyment and setting goals are effective strategies to support patients and to increase adherence in a physical activity program and contrast lack of motivation. According to the present research, also in the study of Mikkelsen and colleagues, patients with advanced cancer reported the importance of enjoyment, setting goals, and tracking progress as a strategy to increase motivation (93). Interestingly, our work found that having a pet can act as a motivator to promote physical activity. To our knowledge, no prior research found a similar result. Nevertheless, the use of pet therapy, i.e., offer several activities, using an animal in order to maintain both mental and physical human health, is a broader topic, which can provide numerous benefits. Contact with pets may reduce loneliness, offering security, and giving encouragement. Moreover, a recent systematic review showed that animal-assisted interventions in oncology settings have a positive association with physiological and psychological outcomes, including oxygen saturation, quality of life, perceived satisfaction, and depression, and other negative mood states (108).

Regarding the preferred structures to perform physical activity, the participants ‘opinions were heterogeneous. For some patients, the program should be delivered in the hospital, while for others in a gym near home. This was reported in other studies on preferences too (47, 92), and one possible explanation could be that some patients, especially with advanced disease, may feel more confident in a hospital

setting. Consistent with previous research (106), patients have declared that physical activity programs should be tailored according to their cancer type and the presence of comorbidities. Moreover, different preferences were found regarding the modality to perform the physical activity; some patients preferred to exercise individually, others with a program to follow at home, while some choose a group-based program. This finding supports a survey-research, which found that 40% of cancer patients preferred a group-based physical activity program, 25% an individual program with a personal trainer, and 27% chose an individual program to follow at home (86). Overall, these results suggest that offer different programs, according to patients' preferences and disease status may optimize uptake and adherence.

Limitations

Our study had some limitations, including the low response rate, which may have introduced a selection bias, even if the main reasons to decline the participation in the study did not support this hypothesis. In our investigation, about half of the patients met the current exercise guidelines, while literature usually reports low physical activity levels in this population (17, 86). Nevertheless, differently from previous investigations applying the prior guidelines version, this study has followed the recent American College of Sports Medicine guidelines for cancer patients, released in October 2019 (7). Therefore, although we cannot exclude that our sample was positively biased towards physical activity, we assume that the obtained results may at least partially mirror the current situation in general cancer population. Moreover, in our study, patients had different cancer types, and consequently, the results may not be generalizable. Nevertheless, our research aimed to investigate the features that affect the engagement in physical activity in a *"real world"* context of the Oncology Unit. For this reason, we believe that including in the sample participants with different socioeconomic status, demographic characteristics, and various cancer types was a strength of our investigation.

Finally, in our sample, more than half of the participants were affected by an advanced stage disease. In this light, our findings may be partially biased, being

more applicable to those patients dealing with more burdensome symptoms and treatment issues than those at earlier stages. From the other side, this population is usually understudied regarding physical activity predispositions and practice supporting the relevance of this data in providing a specific intervention potentially able to preserve their quality of life and autonomy.

Conclusion

In conclusion, physical activity has been demonstrated to represent an essential complementary tool in cancer patients. In order to develop a lifestyle intervention, exploring factors influencing physical activity behavior is particularly important, especially in Italy, where the literature on this field is scarce. Overall, we found that patients had positive beliefs, reporting a variety of benefits. The barriers were mainly oriented to the disease conditions and treatment-related side effects. Nevertheless, several strategies were identified to support and motivate cancer patients to start or maintain a physical activity program.

CHAPTER 4
STUDY 3

Choose Health, Oncological patients Centered Exercise – the CHOiCE trial: a study protocol of phase II randomized controlled trial

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Abstract

Introduction: Physical activity is associated with reducing mortality risk and improvement in quality of life and health-related skills in cancer. Nevertheless, a large percentage of Italian cancer patients do not engage in regular exercise. In this sense, we have developed the CHOiCE (Choose Health, Oncological patients Centered Exercise) trial. **Methods:** A prospective randomized study will evaluate the exercise intervention in 80 patients with mixed cancer types at early stages. Exercise will consist of 3-months of bi-weekly training, including aerobic and resistance training activities. The aerobic component will comprise cardiovascular exercises, progressively increasing from 10 to 30 minutes at moderate intensity, i.e., 3-5 of the 10-point Borg Rating of the Perceived Exertion Scale (RPE). Resistance training components will include six body weight or elastic bands exercises performed in 2-3 sets of 8-12 repetitions, at moderate intensity, i.e., 3-5 of the RPE. The primary endpoint will be exercise feasibility, defined as recruitment rate, adherence, withdrawals, and adverse events. Adverse events will be categorized according to the Common Terminology Criteria for Adverse Events. Secondary endpoints will include functional capacity, assessed using "Six minutes walking test", muscular strength, measured with handgrip, and leg press strength. Patients' quality of life (QoL) will be assessed using the European Organization for Research and Treatment of Cancer Quality of Life and Core Questionnaire.

Introduction

Cancer is a significant public health problem worldwide, as well as in Italy, being the second leading cause of mortality (109). The costs associated with cancer care are growing due to the new expensive therapeutic strategies and the combination of increases in cancer cases and survival rates, which has enhanced the prevalence; indeed, it is estimated that it will be about 3.6 million Italian people with a cancer diagnosis in 2020 (110).

Cancer and its specific anti-tumor treatments, like chemotherapy, radiation, hormonotherapy, but also the new therapeutic options (e.g., target therapy or immunotherapy), can profoundly harm the patient's integrity, with significant consequences on the physical and psychological point of views (7).

Cancer patients experience multidimensional side effects, like fatigue, nausea, pain, anxiety and psychological distress, and an accelerated functional decline (7). These patients are at higher risk of developing serious comorbid conditions, such as metabolic disorders, cardiovascular diseases, sarcopenia, and osteoporosis, compared to the general population (111). Collectively, these sequelae can lead to an impairment in quality of life during patient disease trajectory (111).

Physical exercise is emerging as an important adjunct therapy in the cancer context. Epidemiological studies show that post-diagnosis physical activity is associated with increased cancer patients' survival, especially breast, colon, and prostate cancers (5). Exercise is an effective strategy to relieve some symptoms and impairments occurring in cancer patients (111). Specifically, studies report a range of benefits deriving from an active lifestyle, as control fatigue, anxiety, and depression levels, alleviate psychological distress and counteract functional decline by improving health-related skills and quality of life (111).

Although physical exercise is routinely recommended by several important organizations like the American Cancer Society (112), American College of Sports Medicine (7), Clinical Oncology Society of Australia (15), most patients do not reach the appropriate levels of exercise (86).

Exercise is a complex behavior that to have successful results in terms of maintenance over time, and outcomes should take into account motivation, preferences, and barriers experienced by the patients (10).

In this sense, we have developed the CHOiCE (Choose Health, Oncological patients Centered Exercise) trial. The CHOiCE study consists of an exercise intervention aiming to alleviate cancer- and treatment-related side effects and improve patients' physical and psychological outcomes (Figure 1.). To create a patient-centered program, we have been performed two implementation studies exploring patients' exercise preferences (86), on one hand, barriers and facilitators of adopting an active lifestyle (113), on the other. These investigations revealed that cancer patients have a series of favorite issues regarding exercise counseling, programming, and organization as well as specific barriers (e.g., treatments side effects, medications) and facilitators (e.g., setting goals, exercise program targeted on patient' disease and comorbidities, available exercise specialist), that can potentially hinder or trigger patients exercise. Tailor an exercise program, considering preferences, barriers, and cues to action of cancer patients may positively affect exercise adherence maintenance. Simultaneously, to propose an evidence-based program in terms of health-related outcomes, the CHOiCE intervention is implemented according to the current American College of Sports Medicine exercise guidelines for cancer patients (7). These guidelines suggest that an exercise prescription should last 8-12 weeks and include moderate-intensity aerobic exercise at least three times per week, 30 minutes each session, and strength activity, two times, per week, with two sets of 8-15 repetitions at least 60% of one-repetition maximum. Herein, we present the study protocol of the CHOiCE trial, aiming to test its safety and feasibility and explore its preliminary efficacy on physical outcomes and quality of life.

Methods

Study design

The CHOiCE trial is a two-sites, prospective, two-armed, phase II randomized controlled trial, promoted by the University of Verona, Department of Neuroscience, Biomedicine e Movement Sciences, Verona, Italy, and by the Italian cancer patients' organization "LILT (Italian League for Fight Against Cancer), Biella, Italy. The study was approved by the Ethics Committee for Clinical Trials for the University of Verona (Prot. No. 33320), and the Ethics Committee of Novara

for LILT (Prot. No. CE 158/19), Novara, and is registered on ClinicalTrials.gov (ID: NCT04226508). All the procedures, based on the SPIRIT guidelines (114), are represented in Table 1, and the study's flow diagram is shown in Figure 2.

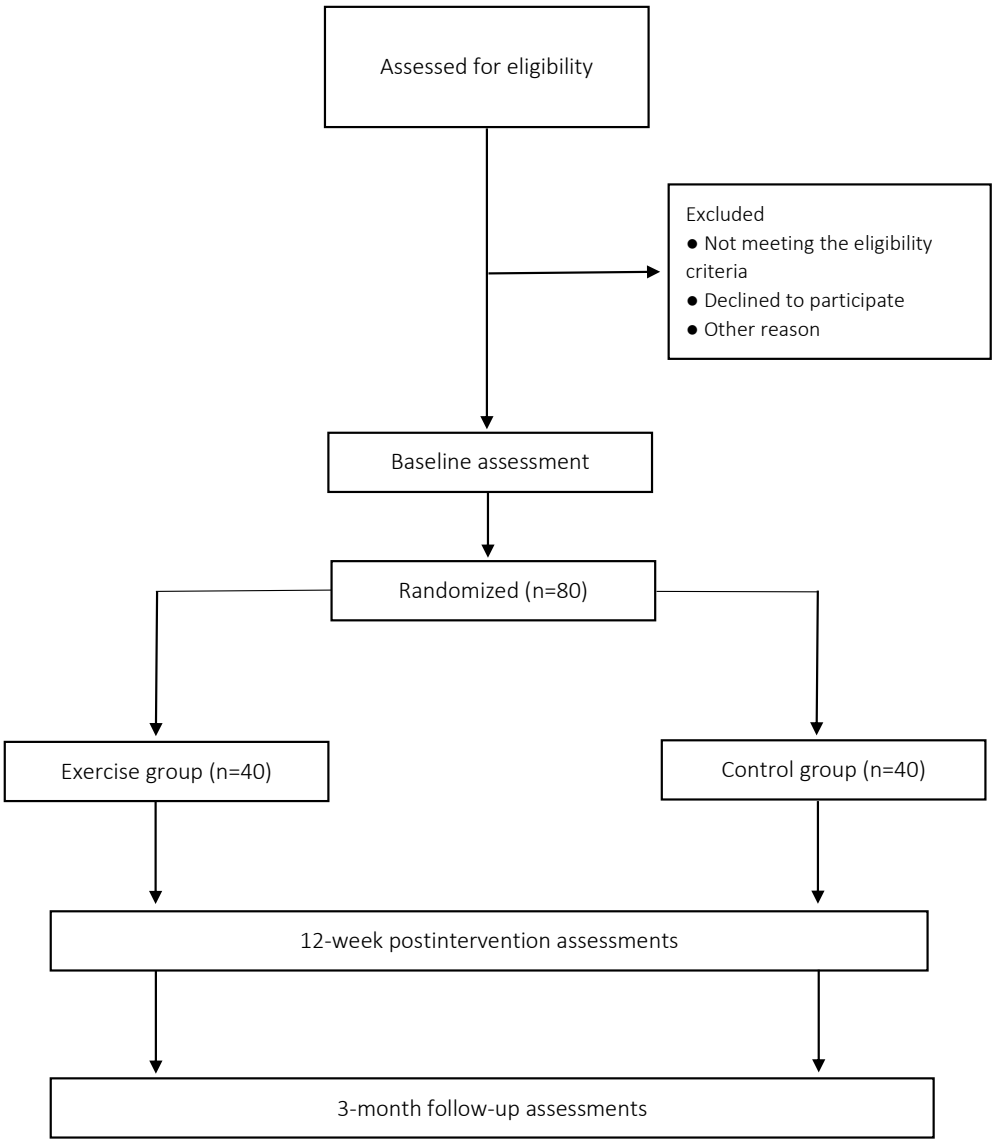

Figure 2. Flow diagram of the CHOiCE trial

Study population

Eligibility criteria are: (i) age ≥18 years, (ii) medical clearance to participate in the study, (iii) a confirmed cancer diagnosis, from 2017 onwards, of one of following

cancer sites: female breast, colorectum, lung, prostate, ovary, uterus, or cervix. Exclusion criteria include: (i) recurrence or metastatic disease, (ii) pregnancy, (iii) Karnofsky index (performance status) <50, (iv) a compromised mental status, (v) < 8 weeks from latest surgery, and (vi) a planned surgery during the intervention.

Recruitment

Patients are recruited through the facilities of Oncology Units of Verona and Biella, Italy. Eligible patients are identified through medical records, and during the checkup visits, a physician introduces the study. If interested, the patients are contacted by the research team to receive a detailed explanation about the study's procedures and conduction. Those patients who agree to participate are asked to sign the written informed consent.

Table 1. Study activity/assessment plan for the CHOiCE trial based on the Standard Protocol Items: Recommendation for Interventional Trials

Activity/ assessment	**Staff member**	**Approximately time to complete**	**T-1 Screening/ consent**	**T0 Baseline assessment/ randomization**	**T1 Start intervention**	**T2 End intervention**	**T3 Postintervention assessment**	**F1 3-month follow-up**
Enrolment								
Eligibility screen	Study coordinator	5 min	X					
Informed consent	Study coordinator	5 min	X					
Randomization	Study coordinator	5min		X				
Interventions								
Exercise training	Kinesiologist	~ 1 hour per session			●	●		
Usual care	N/A				●	●		
Assessments								
Demographic/ behavioural/ medical variables	Study coordinator	10 min		X				
Feasibility of the intervention	Kinesiologist			X	●	●	X	X
Physical function (e.g. functional capacity strength)	Kinesiologist	25 min		X			X	X
Patient-reported outcomes	Kinesiologist	10 min		X			X	X

Randomization and blinding

All study participants are randomly assigned to the intervention or control arm. For the two sites (Verona and Biella), block randomization of four is performed to facilitate an equal distribution matching per center between the two study groups. The computer generation of numbers is produced by the coordinating center and concealed from study staff involved in the recruitment and baseline assessment. Due to the nature of the exercise intervention, it is not possible to blind participants or interventionists to group allocations. Assignments to controls or intervention are made in the order in which participants complete the baseline assessment.

Interventions

Exercise intervention arm

Patients randomized to the intervention group are asked to complete a 12-week supervised training. The participants can choose between the following three exercise modality:

- Autonomous supervised program, which consists of a personalized written exercise program to perform at home. In this program, all the activities to perform, the frequency, the duration, and the intensity are specifically described. Periodical meetings, at 2, 4, and 6 weeks, are scheduled to hand the new program and try the exercises with a kinesiologist. A detailed training diary is proposed for monitoring the intervention.
- Personal training program, which consists of an intervention with a kinesiologist-patient ratio of 1:1. The intervention takes place in the gym.
- Group training program, which consists of an intervention to perform in small groups at the facilities of the two centers. The kinesiologist-patients ratio is 1:4-1:8, basing on the functional conditions of the participants.

The training progression and prescription of aerobic and strength exercises are the same for all three modalities, depending on the patient's baseline conditions (Table 2.), and are planned according to the current exercise guidelines for cancer patients.

Exercise sessions consist of bi-weekly training, including warm-up, aerobic and resistance training, and cool-down (Table 2.). Warm-up lasts 5-10 minutes, and it is composed of 10 dynamic stretching exercises to prepare the body for exercise and reduce the risk of injury. The aerobic component comprises cardiovascular exercises, such as walking, jogging, cycling, lasting from 10 to 30 minutes at moderate intensity, i.e., 3-5 of the 10-point Borg Rating of the Perceived Exertion Scale. The amount of aerobic activity starts according to the patients' baseline conditions, progressively increases over the weeks until it reaches 30 minutes each session at moderate intensity. Resistance training components include six body weight or elastic bands exercises involving the major upper and lower body muscle groups. The selection of exercises is individually prescribed, and each of these is performed in 2-3 sets of 8-12 repetitions, at moderate intensity, i.e., 3-5 of the 10-point Borg Rating of the Perceived Exertion Scale. Resistance training prescription progressively increases, basing patient response. Cool-down is composed of 5 stretching exercises of the major muscle groups for 30 seconds duration each.

Additionally, all patients are encouraged to perform a walking activity autonomously. Steps goals are proposed, through a personalized pamphlet, to be achieved at least one day in a week, with a gradual increase over the week, with the aim to reach at least 10,000 steps, approximately corresponding to 30 minutes. A walking diary is proposed for monitoring the number of steps achieved.

Each patient is provided with a Borg Scale copy, a pedometer (OnWalk 500, Geonaute® France), and an elastic band (Thera-bands, Hygenic Corp. Akron OH).

Table 2. CHOiCE intervention exercise prescription

Intervention week	**Aerobic exercise**			**Strength exercise**			**Walking**	
	Frequency per week	*Duration in minutes (range allowed)*	*Intensity: rating of perceived exertion (scale of 0 to 10)*	*Frequency per week*	*Set x reps*	*Intensity: rating of perceived exertion (scale of 0 to 10)*	*Frequency per week*	*Number of steps*
1	2	15 (10 to 20)	3-5	2	2x8	3-5	1	6000 (5000 to 7000)
2	2	15 (10 to 20)	3-5	2	2x8	3-5	1	6500 (5500 to 7500)
3	2	20 (15 to 25)	3-5	2	2x10	3-5	1	7000 (6000 to 8000)
4	2	20 (15 to 25)	3-5	2	2x10	3-5	1	7500 (6500 to 8500)
5	2	25 (20 to 30)	3-5	2	2x12	3-5	1	8000 (7000 to 9000)
6	2	25 (20 to 30)	3-5	2	2x12	3-5	1	8500 (7500 to 9500)
7	2	30 (25 to >30)	3-5	2	3x8	3-5	1	9000 (8000 to 10000)
8	2	30 (25 to >30)	3-5	2	3x8	3-5	1	9500 (8500 to >10000)
9	2	30 (30 to >30)	3-5	2	3x10	3-5	1	10000 (9000 to >10000)
10	2	30 (30 to >30)	3-5	2	3x10	3-5	1	>10000 (9500 to >10000)
11	2	30 (30 to >30)	3-5	2	3x12	3-5	1	>10000 (10000 to >10000)
12	2	30 (30 to >30)	3-5	2	3x12	3-5	1	>10000

Control arm

Patients randomized in the control arm are instructed to manage their lifestyle in a completely autonomous way. They are informed face to face about the benefits of exercise and the guidelines for cancer patients, but no instructions or advice are delivered to improve their exercise. At the end of the intervention study, patients allocated in the control arm will be offered to participate in one of the three programs proposed to the intervention group.

Outcome measurements

All assessments occur at baseline, postintervention at three months, and six months follow-up.

Primary outcome

Safety and feasibility. Safety and feasibility are recorded continuously during the study. Regarding safety, we record the adverse events, defined as any undesirable medical or health-related event that occurred during study participation. They are classified as either non-exercise adverse events (adverse events reported to have occurred during study participation but considered unrelated to exercise) or exercise-related adverse events (events that occurred during or as a direct result of exercise). Adverse events are categorized according to the Common Terminology Criteria for Adverse Events (version 5.0) (115). Feasibility variables include: recruitment rate, adherence, and withdrawals. The recruitment rate will be evaluated by dividing the number of randomized patients by the patients considered eligible. Adherence at assessments will be determined by the total attendance at the evaluation moments. Adherence at the training sessions will be calculated by the total attendance at the training sessions. The withdrawal rate will be registered, including the number of patients that leave the study.

Secondary outcomes

Functional capacity. Functional capacity is measured through the *"Six minutes walking test,"* conducted according to the American Thoracic Society guidelines

(116). This assessment is largely utilized and proven to be safe in subjects with cancer (117). Following a standardized protocol, the patients are instructed to walk at their own pace in a 20-m hallway. The goal is to cover as much distance as possible in 6 minutes. Pulse rate and oxygen saturation are monitored before, during, and after testing. The patient's perceived exertion is recorded after testing using Borg Scale.

Strength. Muscular strength is evaluated through maximal voluntary isometric contraction of upper and lower limbs. Handgrip strength test, using a hydraulic hand dynamometer (Model SH5001, Saehan Corporation, South Korea), is proposed to evaluate the grip strength. The subject is sitting in a straight-backed chair with the feet flat on the floor, the shoulder adducted and neutrally rotated, elbow flexed at 90 degrees, forearm in a neutral position, and the wrist between 0-30 degrees extension and between 0-15 degrees ulnar deviation (118). An isometric leg press test is proposed for lower limb strength, using a load cell (564QDT, S2Tech Srl, Italy) mounted a horizontal leg press. The load cell is positioned in series with the leg press's sliding axis to register the direct line of force. The dynamometer is routinely calibrated using ISO-certified weights. The leg-press back, on which the subjects were lying, was inclined 30° from the horizontal plane. The knee angle is set at about 100° and was controlled using a goniometer (119). For both strength assessments, five tests are performed; each voluntary contraction will be kept for 2-4 seconds. The patient's perceived exertion is recorded after testing using Borg Scale.

Flexibility. The sit and reach test measures the lower body flexibility. The participant sits on the floor and extends the legs straight out in front of the hip with foot flexed and heel resting on the floor. The object is to reach forward as possible or past to toes. For upper limbs, we use the back-scratch test. This test, which involves a combination of shoulder abduction, adduction, internal and external rotation, involves measuring the distance between (or the overlap of) the middle fingers behind the back (120). For both evaluations, two tests are performed.

Anthropometric measures. Anthropometric parameters include body weight and height and the hip and waist circumferences of the subjects. Anthropometric measurements are taken by trained personnel using standard protocols (121).

Weight and height are measured with subjects wearing no shoes to the nearest 0.1 kilograms and to the nearest 1.0 centimeter). Waist circumference (cm) is measured at the narrowest circumference of the torso, while hip circumference (cm) is measured horizontally at the level of the largest lateral extension of the hips.

These data allow the calculation of the body mass index (BMI) - obtained by the weight (in kilograms) of the subjects divided by the square of their height (in meters) - and of the waist-hip ratio - obtained by the ratio of waist and hip circumferences (in centimeters) (121).

Quality of life. Health-related quality of life is measured using the European Organization for Research and Treatment of Cancer Quality of Life and Core Questionnaire (EORTC QLQ C-30), Italian version, a 30-item questionnaire composed of multi-item scales and single items that reflect the multidimensionality of the quality-of-life construct. It incorporates five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and nausea and vomiting), and a global health and quality-of-life scale. The remaining single items assess additional symptoms commonly reported by cancer patients (dyspnea, appetite loss, sleep disturbance, constipation, and diarrhea). For all scales, item scores are summed and linearly transformed into a scale ranging from0 to 100. Higher scores on the functioning scales indicate higher levels of functioning, whereas higher scores on the symptom scales represent more symptom burden (122).

Exercise level. Exercise level is evaluated using the adapted version Godin's Shepard Leisure Time Exercise Questionnaire. The questionnaire enquires about the previous week's leisure time-frequency (times/week) and duration (min/time) of vigorous, moderate-and mild-intensity exercise. Patients are classified as active or insufficiently active based on the leisure score index, using the metabolic equivalent of the task (METs) (58).

Exercise enjoyment. Enjoyment is assessed using the Italian version Physical Activity Enjoyment Scale. The PAES is a 16 items questionnaire to evaluate the person's enjoyment of the physical activity. Enjoyment has shown to be a handy parameter in exercise interventions, both to determining adherence in a program and to be one of the mediators for a lifestyle behavior change (123).

Socio-demographic and medical variables. Socio-demographic information will be collected at baseline with a self-compiled questionnaire investigating: age, gender (male/ female), education (elementary/ secondary/ high school degree/ undergraduate degree/ postgraduate degree), marital status (unmarried/ married/ divorced/ widow), and employment (retired/ in search of employment/ stay-at-home or housewife/ part-time employed/ full time employed). Clinical data will be extracted by medical charts at baseline, including: location of the tumor (organ), stage of the disease, tumor treatment, date of the diagnosis, comorbidity, and drug treatments.

Data Collection and management

The data entry will be executed in parallel with their completion. A sample of questionnaires and functional assessments (10%) will be entered in duplicate by independent operators and compared. If there more than 5% discrepancies, the whole data entry will be duplicated to assure control quality. Computer access and data directory will be protected by username and password, periodically changed. Access to the data entry program for the questionnaires is protected by username and password. Data access will be restricted to the research team and authorized members only.

Staff training

A purposely developed mandatory course, lasting 20 hours, is proposed to the kinesiologist, who conducts the exercise program. The course will cover the following topics: 1) overview of scientific literature concerning exercise in cancer patients; 2) presentation of the CHOiCE study and its protocol; 3) assessment, schedule, and conduct exercise and procedures adopted in the study; 4) emergency and safety procedures in the gym; 5) communication and interaction with cancer patients.

Statistical considerations

Sample size

This study is designed to evaluate the feasibility and to obtain preliminary data for power calculations for a future large randomized controlled trial. Consequently, a priori sample size calculation is not performed. Considering the access rates to the facilities involved in the study, we estimate to include 80 patients.

Analysis

For the primary outcome, absolute frequencies and percentages will be utilized to present the recruitment rate, the adherence to assessments and training sessions, drop-up rate, and adverse events. Descriptive analyses will be generated for demographics, clinic data, and baseline evaluations. Student t-test, for continuous variables and Fisher's exact test, for categorical parameters will be proposed to detect baseline group differences. An intention-to-treat principle will be chosen to include all the study participants in the analysis. To compare the effect of the exercise intervention versus the control, the Student t-test or the equivalent non-parametric U Mann-Whitney test will be proposed if the comparison takes place in a single timepoint. To detect differences at different timepoints, repeated-measure analysis of ANOVA model or the equivalent non-parametric Friedman test, adjusting for baseline characteristics, will be applied. If missing data will be ≥10%, a multiple imputation missing data strategy will be employed. All statistical analyses will be conducted using STATA 14, and interpretation data will be based on the p-value of two-tailed <0.05.

Limitations, strengths, conclusion, and future perspectives

The CHOiCE study has important weaknesses that should be noted. The study population is comprised of some cancer type, excluding patients with metastatic or recurrent disease. Thus, the study population may not be representative of all people with cancer, making the results a little generalizable. Evaluation of the CHOiCE program is addressed to explore its feasibility and impact on patient's health-related skills and quality of life, while the impact on cost and cost-effectiveness of the interventions have not been investigated. However, these limitations are offset by strengths to the implementation of the CHOiCE program. This is one of the first

programs in Italy, specifically tailored to patients' preferences, perceived barriers, and needs, and developed from two previous implementation studies. Moreover, this is a feasibility trial to investigate if the program can be done; thus, the current limitations may be fill in a future large trial.

There is a dearth of knowledge about an effective approach to translating exercise oncology evidence into real context, especially in a country like Italy still orphan in exercise oncology. To bridge this gap, the CHOiCE program is specifically designed for cancer patients with the aim to provide the patients an evidence-based exercise approach. If, after this feasibility study, a large randomized controlled trial will demonstrate the efficacy and the sustainability of the CHOiCE, it may be expanded across the country with the aim to reduce the disease burden of cancer and improve the health of cancer patients.

CHAPTER 5
STUDY 4

Physical Activity for Oncological Patients in COVID-19 Era: No Time to Relax

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Abstract

Whereas the coronavirus disease (COVID-19) storm is relentlessly progressing worldwide, a great effort from scientific societies has been made in order to give recommendations for safely continuing oncological care, prioritizing the interventions according to patient's condition, type and stage of tumor. Nevertheless, to date no specific suggestions regarding physical activity and exercise in cancer patients during the COVID-19 era have been released, neglecting the potential deleterious effects of quarantine and sedentary (imposed as containment measures against COVID-19), particularly in these subjects. Moreover, literature is constantly consolidating the crucial impact of regular physical activity in cancer in reducing recurrence and mortality risk. In this Commentary, we discuss possible adaptations of the recently published exercise guidelines to the current pandemic emergency, proposing various modalities to prevent and/or mitigate the physical inactivity risk in cancer patients.

Introduction

Since the new coronavirus (COVID-19), also known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) was announced in Wuhan in late December 2019, it has rapidly spread worldwide, prompting the World Health Organization (WHO) to declare the pandemic on March 11, 2020 (124). Due to the high contagiousness and aggressiveness of this disease, on July 28, more than 16,341,920 cases and 650,805 related deaths have been reported around the world (124). COVID-19 patients can be completely asymptomatic (around 18% of cases) (125) or manifest several symptoms, ranging from mild to severe, mainly including respiratory manifestations (e.g., rhinorrhea, sneezing, sore throat, cough, ground-glass opacities, pneumonia, hypoxemia, dyspnea, acute respiratory syndrome), but also systemic disorders (e.g., fever, fatigue, headache, coagulation disorders, lymphopenia, and other blood alterations, gastrointestinal symptoms as diarrhea and nausea) (126).

Preliminary data suggest that elderly subjects (127) and/or with pre-existing chronic comorbidities (128) may be at higher risk of COVID-19 incidence occurring with a worse outcome (127, 128). In particular, cancer patients seem to represent a high-risk category to experience COVID-19 disease with more severe manifestations, mainly due to compromised immune defenses and *sequelae* of antineoplastic treatments (128). Thus, given the current pandemic emergency, a great effort from scientific societies was performed in order to provide recommendations for safely continuing oncological care, prioritizing the interventions according to patient's condition, type and stage of tumor (129). Nevertheless, the emergency may unequivocally lead to postponing some anticancer treatments (128, 129), further increasing patients' anxiety and distress levels and therefore lowering compliance to therapy.

Because up to now, no vaccine or specific treatments against COVID-19 are available, the only way to keep the spread of the infection under control is the social distancing, i.e., keeping people at home as much as possible, for as long as possible, until pandemic will recede. Indeed, several countries around the world have adopted various containment measures (130). In Italy, for example, the national quarantine, i.e., the prohibition for all people to move except for work, necessity, or medical

needs, began on March 9, 2020, and it lasted until May 18, 2020, when a gradual reopening of commercial, productive and social activities was allowed (131). Although these measures are strictly necessary, social distancing and quarantine may also have negative effects. A recent review has explored the impact of quarantine on psychological status, describing a high risk of post-traumatic stress symptoms, confusion, and anger (132). Moreover, this homestay period may likely lead to reduce physical activity (PA) and thus increase sedentary behaviors. In general population, PA and sedentary time are respectively associated with positive and negative effects on body systems, mainly on muscle mass and cardiorespiratory fitness. Recent evidence highlighted the correlation between lack of PA/sedentary and risk of several chronic conditions as metabolic syndrome, osteoporosis, cardiovascular and respiratory disease, stroke, cognitive function, and type 2 diabetes (133, 134).

Physical activity and exercise in cancer

Despite WHO underlined the importance to be as active as possible during this quarantine period, it is reasonable to speculate that one of the groups significantly decreasing its PA level is the oncological population. In this regard, patients usually reported a reduction in PA level after cancer diagnosis (42), with only approximately one-third of patients satisfying PA recommendations (17). In our experience, such proportion seems to be even smaller (135). Due to the current restrictions, this number could further diminish, amplifying the deleterious effects of sedentary behavior and physical inactivity.

PA is emerging as a key element in the oncological trajectory. A growing body of literature demonstrated the association between PA levels after a cancer diagnosis and survival (5). Collectively, these data reported a consistent, inverse correlation with all-cause mortality (ranging from 21% to 45%) and cancer-specific mortality (ranging from 26% to 69%) risk (5). Furthermore, some physical fitness components harbor a relevant impact in terms of both prognosis and recurrence risk. Cardiorespiratory fitness and muscular strength are prognostic factors in cancer patients(10). In addition, muscle mass wasting has been connected with a worse

treatment tolerance, higher risk of recurrence, overall, and cancer-specific mortality (136, 137).

PA and exercise (EX) interventions are shown to be safe and feasible in oncological patients (7). A recent meta-analysis, including 48 randomized controlled trials with a total of 3,632 patients, found that EX increases the peak of oxygen consumption by +2.80 $mLO_2*kg^{-1}*min^{-1}$ in the interventional group compared with no changes in the control one (8). *Padilha and colleagues* have investigated the role of resistance training or a combined EX program (aerobic + resistance) on muscle mass, strength, and body fat. The results have demonstrated that EX was effective in improving muscular strength, regardless of the type of anticancer treatment, concomitantly increasing lean body mass and decreasing body fat (9). Over the years, the role of PA and EX as a strategy to improve health-related quality of life in cancer patients has been established (7, 17). This could be partially associated with the efficacy of EX in alleviating or preventing cancer- and treatment-related adverse events, such as cancer-related fatigue, lymphedema, anxiety and depression levels, bone health, sleep quality, as well as cardiotoxicity risk, cognitive function, sexual function, chemotherapy-induced peripheral neuropathy, and nausea (7). Finally, limited data also exist concerning treatment tolerance, i.e., the completion of or the adherence to planned therapy. In fact, EX may improve the chemotherapy completion rate in patients physically active during adjuvant treatments comparing to the control group (7).

Efficacy of home EX programs in oncology

The American College of Sports Medicine (ACSM) has released the new EX guidelines for cancer survivors (7). ACSM suggests that an effective EX prescription should include moderate-intensity aerobic training at least three times per week for 8-12 weeks. Moreover, the EX program should add resistance training activities, at least two times per week, using two sets of 8-15 repetitions at least 60% of one maximum repetition (7).

According to the current pandemic emergency, these guidelines should be adapted to a home-based setting since supervised sessions are not possible. A reliable solution can be represented by home-based EX programs. The home-based EX

programs can exploit the telehealth (or telemedicine), i.e., the remote delivery of health care as well as a range of other services, including patient education and wellness promotion through technology (138). Telehealth programs do not have a formal structure to deliver information and can utilize different technologies, therefore allowing the EX prescription and monitoring in several ways (138). For example, in cancer survivors telephone counseling, short message services, digital media (e.g., DVD), tailored and/or mailed materials, and/or computer/web-assisted programs, were applied (139). Moreover, the home-based EX programs are feasible, usually well accepted, and can be facilitated through the social support deriving from the patient's family and the possibility to self-organize the free time, choosing when to perform the activities (140). If well structured, including, for example, an initial phase to educate patients (e.g., to self-monitor the intensity), home-based programs have been demonstrated to be efficacious in improving lifestyle in cancer population. In this regard, *Demark-Wahnefried and colleagues* have proposed a randomized trial, including 519 newly diagnosed breast and prostate cancer survivors, with the aim to improve diet and EX practice using a tailored mail print intervention (141). The intervention included personalized workbooks followed by a series of newsletters (at 6-week intervals) that were tailored to barriers, stage of readiness, and progress towards goal attainment of exercising and nutritional aspects (141). Patients also received a survey on the current health practices and the willingness of starting and maintaining a lifestyle change, which was used to adapt the periodic newsletters (141). The study increased the weekly time spent in EX, improved the overall diet quality, the daily intake of fruits and vegetables, decreasing fat intake and weight (141). In the recent years, thanks to the advent of technology in the PA context, a growing number of studies have tested different internet approaches for PA/EX programs, as web-based system (142), mobile application (143) or social media (e.g., Facebook) interventions (144), finding positive and meaningful results. Along these lines, a recent randomized trial tested a web-based EX program in 68 breast cancer patients undergoing chemotherapy, to determine the effectiveness in preventing the impairment of functional capacity, muscular strength and anthropometric parameters, usually experimented during chemotherapy periods. The intervention

consisted in an 8-week, web-based EX program, with three sessions per week, which were organized in warm-up, aerobic and strength activities. The web system also permitted the communication between patients and research staff and weekly contacts with the aim to assure the correct performance and to tailor the program according to patients' needs (142). The results demonstrated the intervention effectiveness in terms of both cardiorespiratory fitness and muscular strength, ameliorating the detrimental effects of treatments (142).

Nevertheless, the application of telehealth should be also considered outside the pandemic emergency. Due to the constant improvement in prevention, diagnosis and treatments, the number of cancer patients and survivors is fortunately continuously increasing, and the financial resources available for supporting EX program could be limited. The home-based EX program can offer a low-cost and sustainable alternative, especially when the costs are borne by the patients (145). In this regard, *van Waart and colleagues*, in a sample of 230 breast and colon cancer patients, evaluated the cost-utility and cost-effectiveness of two different PA programs compared to usual care. The home-based low-intensity PA program cost €46 (~$53) per participant, whereas the moderate-high intensity, supervised EX program, cost €757 (~$849) (146). Although the high willingness-to-pay may limit the cost-effectiveness of the home-based low-intensity PA program (146), no definitive data are available in this sense.

Apart from the limited cost, telehealth offers the opportunity of easily spreading the access to EX programs for cancer patients. For example, patients living in rural or remote communities are at high risk of being under-served in terms of healthcare and health-related services. Indeed, a recent study has reported that rural cancer survivors are 2.6 times less likely to meet aerobic PA guidelines than urban cancer survivors (147). This population should face the burden and discomfort of travel time to reach the services, thus decreasing the willingness to start a supervised EX program. This statement is also confirmed by interesting research, evaluating the EX preferences in rural breast cancer survivors. Seventy-six percent of patients were interested in participating in an EX program, the majority preferred to perform EX at home (63%), and almost half (47%) of the participants favored an unsupervised program, endorsing the hypothesis that a remote EX program could

be well accepted by a rural cancer population (54). Telehealth can allow overcoming these barriers and indirectly diminish the disparity in survival and disease-related outcomes existing between non-metropolitan and metropolitan patients (148).

Practical considerations to increase EX level in cancer patients during COVID-19 pandemic

According to the aforementioned evidence and with the current containment measures, several modalities are available to support an effective home-based EX intervention (**Figure 1**).

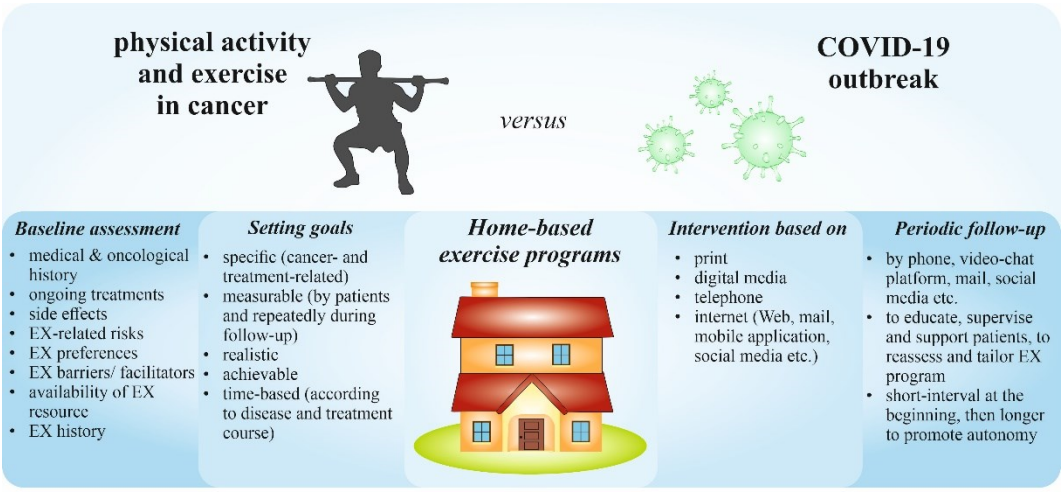

Figure 1. Proposed model of a home-based exercise intervention dedicated to cancer patients.

The COVID-19 outbreak makes necessary to remotely perform all the steps of EX prescription, which are usually carried out face-to-face. The health-related physical fitness can be hard to test in this framework. Nevertheless, an initial evaluation may be proposed at distance through a videoconference for example, especially for those patients starting an EX program (**Figure 1**). Ideally, this phase should include different assessments. From one side, patients' health history (including cancer

type/stage and comorbidities), current treatments, presence and severity of side effects, and screening tools to assess the EX risk are essential to prescribe a safe program (7, 149). On the other hand, understanding EX preferences, barriers, facilitators, availability of resources to support EX engagement, and patients' EX history can be useful to build a tailored and feasible program (7, 149). Several and validate tools are available for the exercise physiologist or kinesiologist to achieve this phase. For example, the Physical Activity Readiness Questionnaire can help defining an initial risk profile of the subject (150), whereas the European Organization for research and Treatment of Cancer QLQ-C30 can measure the quality of life and the severity of some symptoms and treatment-related side effects (122).

Paradoxically, the social distancing period may be a good time to start an EX program, because some barriers that usually interfere with an active lifestyle adoption, e.g., distance from gym, lack of time, traffic and fixed time for lessons are missing. Setting goals and track progresses (**Figure1.**) using different instruments (e.g., wearable technology and/or a personalized diary) can be an ideal strategy to stimulate patients to maintain adherence to the prescribed EX program (149).

Goals should be established with the subjects, according to the following characteristics: specificity, measurability, achievability, realistic goals, and time-availability. Cancer patients have unique needs related to their disease, therefore choosing the most appropriate goals should take all of them into consideration (e.g. symptom control, improving mood and/or bodyweight, increasing EX level), selecting those that are remotely assessable and most important for the subject. Moreover, the kinesiologist or physiotherapist should help the patients to recognize the EX-related goals that are realistic and achievable by themselves. This aspect is particularly crucial because failure in achieving the proposed goals can be extremely demotivating, particularly for oncological patients, with the possible consequence of EX program drop out. Finally, goals should be time-based, remembering that the EX prescription objectives may be influenced by the change in disease and treatment-related toxicities over time.

Another component that should be included into a home-based program, especially during the COVID-19 pandemic period, is the periodic follow-up (**Figure1.**) (149). This is important to maintain high engagement (151) and can be delivered by several modalities, e.g. telephone, video-chat platforms (i.e. Skype), or email. The aims of the follow-up can be various: educate subjects to manage the EX training, supervise the program, support patients to maintain an active lifestyle stimulating their motivation, reassess the situation, and modify the prescription. Follow-up time depends on several factors, e.g., the modality to deliver the program and the patients' needs. These revaluations could be in a short-interval at the beginning of the program to maximize patient's support and longer later to favor the subject' autonomy.

The EX-program components should reflect guidelines, including type, frequency, duration, and intensity of the activities (7). Aerobic and strength exercises should be a key component of the EX prescription, and their balancing should be determined according to the patient's goals and needs. Whereas strength activities require small spaces and limited equipment (e.g., elastic bands, body-weight exercises), the aerobic exercises could be hard to be included into a home-based program. If it is not possible to get outside or if the patient does not hold a specific machine (e.g., treadmill or cycle ergometer), a valid alternative could be represented by adapted exercises as dancing, or walk up and down the stairs, for example. Moreover, the program should also include flexibility and proprioceptive training, especially for patients with specific symptoms or treatment-related side effects. Proprioceptive exercises could improve chemotherapy-induced neuropathy, reducing this tiresome symptom and ameliorating the balance control, whereas regain the joint range of motion through flexibility activities, could be beneficial for patients undergone surgery and presenting a limited range of joint extension.

In the home-based program, patients must be educated to self-monitoring EX-intensity because, even if low-intensity may be appropriated for deconditioned patients, in other cases it may be insufficient to significantly perturb the body homeostasis and increase the functionality, while high intensity may be unsafe. Thus, it is important to educate the patients to understand the intensity level using some practical tools, such as the heart rate or the perceived exertion scale.

Frequency, i.e., the number of sessions per week, and duration, the time or the sets/repetitions per session/activity, are also essential to be defined. Although the ACSM guidelines suggest a frequency of 2-3 times per week of 90 minutes of aerobic activities and two sets of 8-15 repetitions for strength training, it may be necessary to adapt these parameters to the peculiar patient's clinical situation and disease. During the quarantine, patients have more free time to spend in exercising, but they may be sedentary or deconditioned, thus increase the frequency and diminish the duration may be a strategy to adopt. Nevertheless, it is necessary to remember that the *"dosage"* of EX, in terms of type, frequency, duration and intensity, recommended by ACSM, may be not appropriate at the beginning for cancer patients and should be progressively reached, balancing the EX-prescription components with the patient capacity.

Considering all these factors may allow to develop effective tailored EX programs during COVID-19, which can be potentially carried on beyond quarantine period, in order to reduce the negative effect of sedentary, increase benefits related to PA and EX, and ameliorate the psychological impairment due to the isolation and the outbreak emergency.

Conclusion

The COVID-19 outbreak is threat global public health. Until a vaccine and specific therapies against COVID-19 are available, physical distancing and homestay remain effective approaches to slow down the spread of the disease; however, such restrictive measures may decrease PA levels in cancer patients, with consequent deleterious outcomes in the long term. In this light, promoting a remote home-based lifestyle intervention in cancer population is an urgency, because if social distancing is necessary to stay healthy *"today*", the physical inactivity that may be experienced, will have negative and lethal effects *"tomorrow"*, especially in cancer patients.

CHAPTER 6

STUDY 5

A multimodal strategy against cancer-related cachexia: from theory to practice.

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Abstract

Introduction: Cachexia represents a relevant issue in oncological care, still lacking of validate therapies. Although the incidence of cancer cachexia varies across cancer types, it is responsible for approximately a quarter of cancer-related deaths. The pathophysiology of this syndrome is multifactorial, including weight loss, muscle atrophy and impairment of the pro-/anti-inflammatory balance.

Areas covered: Diagnostic criteria and optimal endpoints for cachexia-dedicated trials are still debated, slowing the identification of interventions counteracting cachexia *sequaele*. The multi-faced features of this syndrome support the rationale for a personalized therapy. Multimodal approach is likely to offer the best option to address the key cachexia-related issues. Pharmacologic agents, physical exercise, nutritional and psycho-social interventions may have a synergistic effect, able to improve the quality of life.

Expert opinion: A personalized multimodal intervention could represent the best strategy to effectively manage cancer cachexia. To offer such a comprehensive approach, a specialized staff, including health professionals with different expertise, is necessary. Each specialist plays a specific role inside the multimodal intervention, with the aim to deliver the best cancer care and access to the most effective therapeutic options for each patient.

Introduction

Cachexia, from the Greek terms *kakos*, i.e. "bad", and *hexis*, i.e. "conditions", remains one of the most devastating cancer-related adverse events, typically (but not exclusively) occurring at an advanced disease stage. An international consensus statement defined cachexia as: *"a multifactorial syndrome characterised by ongoing loss of skeletal muscle mass (with or without loss of fat mass) that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment*" (152). Cachexia is prevalent in patients affected by liver (50.1%) pancreatic (45.6%) head and neck (42.3%), thyroid (39.9%), and lung (37.2%) cancers (153). It is an important mortality cause, accounting for almost 20% of cancer patients' deaths (154). Moreover, this condition can interfere with cancer trajectory, reducing treatment tolerance and increasing the length of hospital stay, as well as the overall treatment expenses (155, 156). To date, cachexia represents a major challenge in cancer care because of several gaps existing in its diagnosis, assessment, and treatment.

Symptoms and mechanisms of cachexia

Weight loss is considered one of the major features of cancer cachexia (157). Indeed, cancer patients often present an energy imbalance due to an increased energy expenditure in comparison with the caloric intake (158). In detail, cachectic patients show an alteration in body composition, particularly in terms of muscle depletion with or without body fat loss. Loss of muscle mass, specifically in the fast-twitch muscle fibers, usually accompanied by cardiac muscle wasting (159), is one of the critical manifestations of cachexia in cancer patients, and its consequences include an increase in surgical complications, in chemotherapy-related toxicity, as well as in cancer-related mortality (159, 160). Such muscle atrophy is the result of an impaired control of anabolic and catabolic processes, mainly due to the overexpression of the ATP-dependent ubiquitin-proteasome system and the autophagy/lysosomal proteolytic pathways. Other factors, like myostatin and activin A, can induce muscle proteolysis, whereas reduced m-TOR-dependent protein synthesis and insulin-like growth factor-1 (IGF-1) levels may impair anabolic pathways (161). The inflammatory status represents another

hallmark of cancer cachexia. Pro-inflammatory factors, including interleukin-6 (IL-6), tumour necrosis factor-alpha (TNF-α), and interleukin-1 (IL-1), have been related to cancer-induced cachexia, especially with wasting of both muscle and fat tissue (162, 163). Selective depletion of white adipose tissue is also the result of an unfavourable ratio between lipogenesis and lipolysis, due, for example, to the activation of hormone-sensitive lipases and to the decrease in lipoprotein lipase activity (157). Moreover, emerging evidence suggests that the brain might also play a role in cachexia progression: orexigenic and anorexigenic pathways are impaired, resulting in reduced appetite, early satiation, and altered taste and smell (157). Furthermore, hypothalamic mediators, released in response to persistent inflammatory stimuli, participate in weight loss and muscle atrophy (158).

A large variety of burden symptoms have been associated with cancer cachexia, like pain, fatigue, disturbed sleep, lack of appetite, dry mouth, numbness, and lack of energy (164, 165). Cachectic patients usually experience a progressive impairment of functional abilities and worsening in performance status, which results in a progressive reduction of physical activity, finally leading to losing autonomy and independence (166, 167). In addition, body composition changes can profoundly impair psychological status, enhancing distress, anxiety and depression, social isolation, altered self-perception, negative emotions, and conflicts with family members (154, 164, 168). Thus, cachexia may have emotional and social impact on both patients and their caregivers (169). In conclusion, it is realistic to speculate that cancer-related cachexia might drive patients into a vicious circle of increased treatment toxicities, higher symptoms burden, diminished physical performance, inactivity, malnutrition, and poor psychological status, resulting in an overall compromised quality of life (QoL).

Cachexia-related issues

Pitfalls in diagnosis and assessment

No universally recognized, international diagnostic criteria for cachexia are available, thus making complex to identify this syndrome in clinical practice. *Fearon et al.* proposed weight loss and body mass index (BMI) or sarcopenia as

instruments to recognize cachexia (**Table 1**) (152). This diagnostic criterion was able to distinguish cachectic and non-cachectic subjects in terms of survival, intake, catabolism, and functionality, in a sample of 1,070 patients with advanced cancer (170). Moreover, the prognostic significance of the combination between weight loss and BMI was also demonstrated by a large international data set including 8,675 patients, which allowed to develop (171) and test (172) a grading system able of differentiating groups with distinct median survival. However, the diagnosis based only on anthropometric parameters might not able to comprehensively capture and differentiate the cachectic population, given the complexity of this syndrome. Other authors suggest that, in addition to weight loss history, variable combinations of those key mechanisms driving cachexia, as the estimation of food intake, presence of symptoms, evaluation of systemic inflammation, skeletal muscle mass, should be included for its diagnosis. For instance, the SCRINO working group proposed a simple method to classify patients as cachectic, based on weight loss and presence of anorexia, or fatigue, or early satiation (**Table 1**) (173). Following this line, *Evans and colleagues* defined cachexia as the presence of weight loss plus the presence of three symptoms, including low muscle strength, fatigue, anorexia, low fat-free mass index, and abnormal biochemistry (inflammation, anemia, low albumin) (**Table 1**) (174). Moreover, a classification to categorize the degree of cachexia was proposed to improve treatment selection and early recognize patients at high risk of developing cachexia. In particular, pre-cachexia, cachexia, and refractory cachexia stages were identified according to the percentage of weight loss in combination with the level of depletion of energy stores and body protein mass (152). To simplify the score, some authors proposed to apply only the grades of pre-cachexia and cachexia (175). Nevertheless, the classification intent, especially for the pre-cachexia stage [23], has also been questioned because of inconsistent results, lack of sufficient diagnostic criteria, as well as the very low prevalence (170, 176, 177). This heterogeneity makes difficult to get a definitive concordance between the available different tools (178, 179).

Table 1. Main criteria for cachexia diagnosis.

Fearon at al.' criteria (152)	**Bozzetti et al.'s criteria** (173)	**Evans et al.'s criteria** (174)
Weight loss >5% over past 6 months **or** BMI <20.0 kg/m^2 and any degree of weight loss >2% **or** Sarcopenia and any degree of weight loss >2%	Weight loss ≥10% **and** One of the following: anorexia fatigue early satiation	Weight loss >5% over past 12 months or less in presence of underlying disease (or BMI <20.0 kg/m^2) **and** Three out of the following: decreased muscle strength fatigue anorexia low fat-free mass index abnormal biochemistry (C-reactive protein, albumin, anemia)

Legend: BMI, body mass index

The uncertainty in cancer-related cachexia diagnosis led to other crucial issues, as the eligibility criteria for clinical trials, an increase in the attrition rates, and the difficulty in identifying appropriate outcomes, in particular the optimal endpoints for cachexia-dedicated trials. Although a call to enhance the regulatory guidance for cancer cachexia trials from the European Medicines Agency and the US Food and Drug Administration has been advocated (180), up to now, the selection of endpoints in the available trials are heterogeneous, often influenced by the preferences of researchers and/or pharmaceutical companies (181). Several measures have been applied to test the impact of interventions on cancer cachexia. Endpoints reflecting clinical benefits, e.g., survival, treatment tolerance, are appealing outcomes, given the role of cachexia in cancer-related death (182). Due to a series of limitations (e.g., the need for a large sample size to demonstrate survival benefit), other more *targeted* cachexia-related outcomes would be preferable. In this sense, the majority of available studies focused on cachexia mechanisms and symptoms, including anthropometric and body composition measurements, evaluating nutritional status and physical function, as well as the impact of the intervention on patient's QoL and specific biomarkers (e.g., C-reactive protein, cytokines) (181-183). However, variability in terms of endpoints might lead to discordance in studies findings and reduce the comparability among trials, because, although an improvement in cachexia mechanisms and symptoms may be

the optimal goal, these parameters are not always related with each other and with patient's survival (184).

Treatment options in cancer cachexia

Recently, the American Society of Clinical Oncology has released updated cancer cachexia management guidelines, highlighting that to date no validated therapies have been identified (185). In this context, literature proposes supportive care as a suitable approach to manage cancer-related cachexia. In particular, physical exercise, nutritional counseling, and supplementation, as well as psycho-educational and psychological interventions, appropriately integrated with pharmacological agents, may curb weight loss, counteracting some mechanisms and symptoms associated with cachexia. Below, we present available options in each single modality.

Pharmacologic treatments

Pharmacologic options to face cancer-related cachexia are based on three primary mechanisms of action: *i)* stimulation of appetite, *ii)* reduction of inflammation and *iii)* enhancement of the anabolic potential. Among the appetite stimulants, randomized controlled trials investigating cannabis *sativa* (186) and nabilone (187) in patients with advanced cancer and a weight loss >5% in the previous six months did not found improvement in body weight, appetite, and QoL. Similarly, melatonin, tested in cachectic patients with lung or gastrointestinal cancer, was not efficacious in gain weight or in favorably modulating appetite, QoL, fatigue, levels of C-reactive or enhancing overall survival (188). On the contrary, anamorelin, a selective ghrelin receptor agonist, was associated with a significant improvement in weight and lean body mass, but no effect was found for strength and survival in the large randomized, double-blind placebo-controlled trials ROMANA 1 and ROMANA 2 (184). Additionally, another study in cachectic lung cancer patients with anamorelin has confirmed its effect on lean body mass and weight, reporting an improvement in appetite and QoL (189). Several cytokine modulators have been evaluated for their potential impact to counteract cancer cachexia. Etanercept (190) and infliximab (191) reported inconsistent results on appetite (190, 191),

bodyweight (190, 191), QoL (190) and survival (191). However, both studies included patients not selected for weight loss history (190, 191). Also, pentoxifylline failed to increase weight and QoL in a randomized controlled trial including 70 advanced cancer patients with cachexia (192). While thalidomide increased body weight and arm muscle mass, no effects were detected on strength, QoL, and survival (193). Regarding anabolic agents, insulin was evaluated in 138 cachectic patients with advanced gastrointestinal cancer (194). Insulin was found to stimulate carbohydrate intake, to increase body fat and survival, but no positive results were shown for exercise capacity, physical activity level, QoL, appetite, lean body mass, and body weight (194). Enobosarm, given its tissue-selective anabolic and androgenic activity, was also tested in cachexia, showing an increase in lean body mass, exercise capacity, and patients' QoL (195). Nevertheless, the dropout of patients on adherence to treatment is still very high, especially in patients assisted in palliative care. With an appropriate sample size, further studies are needed to clarify the real contribution of pharmacologic agents in cancer cachexia.

Physical exercise treatment

In cancer patients, observational studies suggest that physical activity may increase survival (5), with preclinical data confirming the role of exercise in tumorigenesis inhibition (196). Moreover, in the oncological setting, exercise is a recognized tool to alleviate treatment-related side effects (e.g., fatigue, sleep quality, cardiotoxicity, anxiety, and depression) (7, 10). The American College of Sports Medicine has released the last update for exercise in cancer patients, recommending that the patients should engage in at least 90 minutes per week in aerobic activity at moderate intensity and two days per week in resistance training (7).

However, most of the available studies on exercise in cancer have been performed in patients affected by an early-stage disease. Focusing on patients with advanced disease, in which cachexia may occur more frequently, at first sight, exercise might seem contraindicated due to its requirement for energetic expenditure; instead, it might represent an advantageous strategy to counteract some mechanisms related to cachexia syndrome. Physical exercise in advanced cancer was safe, feasible, and well tolerated by patients (197). Moreover, a recent systematic review, including

25 studies for a total of 1,188 patients with mixed advanced cancers, found that exercise was able to increase aerobic and functional capacity, improve fatigue, QoL, and psychosocial function, as well as increase lean body mass without affecting the fat one (198). In particular, resistance training promotes muscle anabolism and inhibits protein catabolism, resulting in myofibrillar hypertrophy and enhancement of muscle strength through different mechanisms, such as mTOR pathway activation and increased levels of IGF-1 (199-201). Moreover, preliminary studies found that exercise positively modulates chronic low-grade inflammation, decreasing pro-inflammatory cytokines, like TNF-α and IL-6, and increasing those with an anti-inflammatory function (e.g., IL-1a and IL-10) (199, 200, 202, 203). Although a strong rationale supports exercise as a crucial therapeutic option for managing cachexia and its symptoms, future trials should investigate this strategy and determine the best appropriate program.

Nutritional intervention

The nutritional intervention has been advocated as the cornerstone of a multimodal intervention against cancer cachexia (152). A reduction in the supply of energy and protein and/or an increased demand lead to the exhaustion of substrates from the existing body stores (204). It is not plausible to increase or stabilize weight if nutritional needs are not met (205). Most patients with advanced cancer and weight loss have eating habits that are likely to be insufficient to maintain weight, even in healthy individuals. In this light, recent data from a retrospective study have shown that more than 80% of patients referring to the clinic for cancer cachexia were not consuming recommended levels of protein and energy (205). As previously mentioned, several symptoms may hamper the normal food intake in cancer patients, which should be recognized early and specifically treated (206). Optimization of patient's protein and energy intake through an appropriate dietary counseling is the first step, as weight-stable cachectic patients have been shown to have higher intakes of protein and energy than those who were continuing losing weight (207). Dietary recommendations should consider the usual diet, personal eating patterns, manageable food consistency, and medical conditions. If spontaneous food intake remains insufficient after dietary consultation and oral

nutritional supplements have been deployed, escalation to artificial nutritional support is an option (208). Regarding oral supplementation different compounds, as β-hydroxy-β-methylbutyrate and L-carnitine, have been studied, but to date insufficient data exist to largely recommend them (209, 210). Omega-3-fatty acids seem promising in increasing appetite and body weight thus the guidelines on nutrition in cancer support their use (208). Even if several studies found heterogeneous results about nutritional intervention in cachexia, emerging data showed that closing the nutritional gap early during anticancer treatment could prevent further weight and muscle loss, with a possible effect on survival outcomes (211).

Psycho-educational and psychological intervention

Although literature limitedly considers the psychological support in cancer cachexia, cachectic patients are recognized to experience a range of psychological symptoms (212). Moreover, the burden of cachexia also impacts on family members and on patient/family relationships, as recently reported in a survey, which found high levels of eating-related distress in 702 bereaved family members (213). Thus, providing patients and their families with information, delivered by a psycho-oncologist or alternatively by a specifically trained nurse, about their condition and educating them on effective self-management skills may be a good strategy for cancer patients (169). In this sense, psycho-educational and psychological intervention should favor action-oriented, brief interventions, delivering a condensed package of "core" cognitive-behavioral skills (154, 214, 215). Such strategies may include, but are not limited to, cognitive restructuring or cognitive reframing techniques, identification of dysfunctional thinking patterns, stress and relaxation management skills, behavioral activation, social skills improvement, and expressive supportive therapy (216). The shift to the conscious control of eating is often useful, through a reframe of eating as a necessity, rather than a pleasure, for promoting health outcomes such as slowing the disease progression, tolerating the side effects of chemotherapy, and maintaining strength and resistance (217). Teaching cognitive reframing strategies also permits patients to take control of eating habits, supporting self-efficacy, empowering themselves

and improving their QoL(217). Despite some trials have investigated the impact of psychotherapy in advanced cancer patients (218, 219), currently ongoing studies may confirm the positive effect also in cachectic patients (220).

A multimodal strategy for a multifactorial syndrome

Cancer-cachexia may hardly be managed and reversed using a single intervention, given its multifactorial nature. It is reasonable to hypothesize that a multimodal management may offer the best treatment strategy (221, 222). Indeed, integrated exercise-based, and nutritional interventions combined with an appropriate pharmacological therapy could produce a synergistic effect, leading to effectively control or even counteract cachexia (221). For instance, the increase in muscle mass may be synergistically influenced by the four interventions. Exercise can provide an important anabolic stimulus to increase size and number of fast-twitching fibers that may also be improved by specific drugs. However, protein turnover requires adequate protein intake. In that respect, nutritional counseling can offer an optimal strategy to increase the quality of food assumption, while appetite-stimulating drugs could favor hunger and, consequently, lead to a higher caloric assumption (223).
Although a strong rationale reinforces the use of a multidisciplinary approach, limited and preliminary studies have evaluated the combination of different interventions in managing cancer cachexia. A retrospective study has evaluated a multimodal approach in 374 cancer patients, exhibiting weight loss in the previous six months equal to 10% and an impaired QoL (224). The intervention, lasting about 12 weeks and including medications to control symptoms (when appropriate), nutritional and exercise treatments, resulted in a clinically significant improvement in QoL that was greater in those patients who gained weight and increased their functional capacity (224). The NEXACT feasibility trial tested an eight-week multimodal intervention of tailored exercise plus nutrition in advanced lung and pancreatic cancer patients at high risk of cachexia. The exercise intervention consisted of resistance activities and steps program while nutritional support involved a tailored counseling and oral supplementation of branched-chain amino acids, coenzyme Q10, and L-carnitine. Although no relevant improvements in outcomes, such as lean body mass, weight, strength, and functional capacity, were

observed, the approach was safe and feasible, with good patients' compliance (225). The only available randomized phase II trial, called MENAC, investigated a six-week integrated approach in patients with incurable lung or pancreatic cancer undergoing chemotherapy (226). The intervention involved exercise, twice a week of aerobic plus resistance training three times per week, nutrition, counseling plus omega-3-fatty acids supplementation, and pharmacological agent (celecoxib). The MENAC program was considered safe and feasible, though the compliance for oral supplementation resulted suboptimal, stabilizing body weight in the interventional arm, while the controls lost weight (226). However, NEXACT and MENAC were not powered to show program efficacy. Currently, large trials are ongoing and may enhance the understanding of multimodal strategy effect on clinically relevant outcomes in cancer cachexia (NCT04065815; NCT04131426; NCT02330926).

Expert opinion

Cancer cachexia has been considered a terminal cancer-related event, substantially refractory to available treatments and amenable to only palliative support. Mounting evidence consistently suggests that cachexia can be considered an early phenomenon which should be managed as soon as possible during the disease course. Moreover, interventions should start early in order to avoid the worsening of cachexia and prevent the cachexia-related symptoms exacerbation. Thus, it is imperative to regularly assess patients in order to identify those cachectic or potentially at risk earlier before treatments refractoriness occurs.

Although a series of studies improved knowledge about cancer cachexia, several issues are still open. Firstly, refine the diagnostic criteria for cancer cachexia may have an enormous influence to identify/categorize cachectic patients in order to direct them to a prompt intervention and select a homogeneous study population for trials. Secondly, it is necessary to recognize optimal endpoints and appropriate assessment tools to appropriately compare the interventions and establish their real impact counteracting this devastating syndrome. In addition, cancer cachexia remains still an *orphan* condition in terms of effective therapeutic strategies. Evidence suggests that a multimodal therapy, including pharmacologic agents, exercise and nutrition, would likely represent the best strategy to manage cachexia

and its related symptoms and ideally to improve not only the quantity but also the quality of patient's life. From our point of view, the introduction of a psychological intervention, conducted by a psycho-oncologist or alternatively by a specifically trained nurse, in the context of the multimodal approach could crucially contribute to cachexia management (**Figure 1**), favoring the adherence to the other treatments (227, 228).

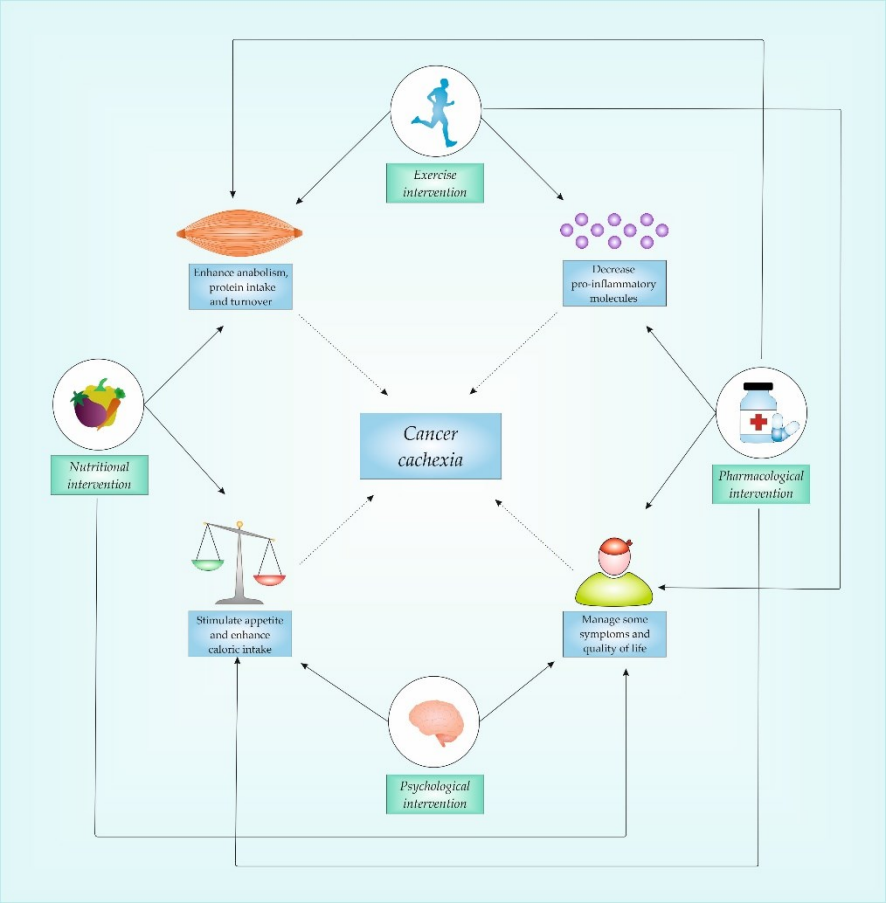

Figure 1. Multidisciplinary approach to manage cancer-related cachexia.

Following this direction, in our Department of Oncology at the University of Verona, an interdisciplinary group, called the *FORCE* team (*Focus On Research and CarE*) was specifically created for cancer patients. Such team is led by a medical oncologist and includes a dietitian with documented skills in evidence-based dietetic practice in cancer patients, a psycho-oncologist, and a kinesiologist,

who work as an integrated team to optimize and personalize each intervention, according to patient's characteristics, needs, and preferences. The multimodal intervention, with appropriate assessments, starts early in the disease journey and continues during treatment in order to support weight and muscle maintenance and, ideally, prevent the progression towards more advanced stages of cachexia. The team tries to deliver comprehensive care and access to the best therapeutic options, according to currently available guidelines, as well as to produce solid scientific evidence in order to increase knowledge in this still relatively unexplored field of research (229).

Overall, the multimodal approach requires greater efforts in terms of staff specialists, facilities, and economic availability. Nevertheless, if this will prove to represent a winning strategy against cancer cachexia and improve patients' QoL, its implementation in clinical practice as a standard of care will be indispensable and mandatory to provide the best comprehensive care to cancer patients.

CHAPTER 7
STUDY 6

Multidisciplinary Lifestyle Intervention to Manage Pancreatic Cancer-Related Cachexia: A Case Report

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Abstract

Introduction: Pancreatic cancer remains an aggressive disease, with a poor prognosis and a high risk of incurring into cachexia. Supportive care, such as exercise, nutritional and psychological support, may be effective in reducing functional loss, psychological distress, and improving nutritional status. **Case presentation:** We report the effect of 12 weeks of multimodal lifestyle intervention in a 55-year-old female, diagnosed with unresectable body/tail pancreatic cancer and metastasis in the liver, bone, lymph node, and lung, to counteract cachexia. **Results:** The multimodal program resulted safe and feasible. Over 12 weeks, considerable improvements were found in body weight, health-related physical fitness, nutritional status, distress scores, anxiety, and depression levels. **Conclusions:** These findings highlight the potential role of integrated supportive interventions to manage metastatic cancer and cancer-induced cachexia.

Introduction

Although relatively uncommon (2.5% of all cancers), pancreatic cancer (PC) remains a lethal malignancy, with a ratio mortality/incidence of 94% and a 5-year survival rate of only 9% (230). To date, effective therapies are available to improve prognosis and relieve patient's symptoms. Surgery with curative intent represents the main opportunity for "cure", even though the vast majority (~85%) of patients presents with unresectable disease (231). Chemotherapy (mostly gemcitabine- and fluorouracil-based polychemotherapy combinations) has a definite impact on survival in both resectable and advanced disease, and radiation therapy is used mainly to treat locally advanced, inoperable disease (231).

PC patients are at high-risk of cachexia, a multifactorial syndrome characterized by an ongoing loss of skeletal muscle mass that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment (152). Currently, no standard treatments are available to contrast the progression of cancer cachexia (232). In light of its dismal prognosis, advanced PC treatment remains palliative in nature, and managing patients' physical function and preserving their quality of life (QoL) is at least as important as extending survival (233). Supportive multimodal care, physical exercise, dietary guidance, and psychological support, have established efficacy to counteract many cancer- and treatment-related side effects (7, 208) and might represent a useful approach to treat or prevent cancer-induced cachexia. Exercise is a potent body modulator, able to increase cardiorespiratory fitness, strength, and muscle mass, which, in turn, represent independent predictors of survival in cancer; moreover, increased physical fitness may counteract some disabling cancer symptoms, such as fatigue, nausea, pain, anxiety, and depression (7). Food intake optimization has been recognized as a crucial approach in the treatment of PC patients, considering that they frequently suffer from malnutrition and experience a reduced food intake due to several reasons (e.g. loss of appetite, anorexia, maldigestion and malabsorption, vomiting, nausea) (234). Therefore, increasing energy intake and protein balance with a personalized nutritional counseling can improve body composition, prevent weight loss, and manage some cancer- and treatment-related side effects (152). Finally, PC patients usually report a high level of distress, which can exacerbate

symptoms burden, impair QoL, and interfere with medical treatments (235). Psychotherapy, including cognitive-behavioral therapy, problem-solving therapy, or mindfulness-based approaches, for example, has demonstrated to reduce anxiety and depression levels in advanced cancer patients (227). Moreover, psychological support can be effective to manage cancer-related fatigue, reduce fear, and improve global well-being (227).

Exercise, nutritional and psychological support complement each other, possibly resulting in synergistic potentiation of the expected clinical benefit by the appropriate combination of these interventions, particularly in a complex and aggressive disease such as PC. Nevertheless, safety and feasibility of an integrated, multimodal approach in advanced cancer with cachexia is still a relatively unexplored area. Here, we report the results of a three-month supervised, integrated supportive intervention, carried out by a dedicated multidisciplinary team (Focus On Research and CarE - FORCE - team), including exercise, nutritional counseling, and psychological support in an advanced, metastatic PC patient with cachexia undergoing II/III-line chemotherapy.

Case presentation

A 55-year-old woman presented in January 2019 with unintentional weight loss and abdominal pain. Computer tomography of the abdomen and subsequent ultrasound-guided fine-needle aspiration biopsy led to the diagnosis of an unresectable body/tail pancreatic cancer (stage III according to TNM classification). She underwent chemotherapy with a combination of fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX), but after three months disease progressed with appearance of liver and bone metastases (**Figure 1**). Second-line chemotherapy was then started with gemcitabine/nab-paclitaxel in June 2019, resulting in disease stabilization and temporary clinical benefit. In November 2019 disease progressed further, involving abdominal lymph nodes, liver, lung and bones, and resulting in a malignant upper left urinary tract obstruction, which required invasive palliation by nephrostomy.

At the time of observation by the FORCE team (November 2019), with a weight loss of 21.4% over the past 6 months without starvation the patient was considered

cachectic (according to EPCRC criteria (170) and the ECOG performance status was 1. Despite the current lack of survival benefit in this setting, therapeutic options, including best supportive care, were discussed with the patient and she was candidate to III-line palliative chemotherapy (FOLFIRI) (**Figure 1**).

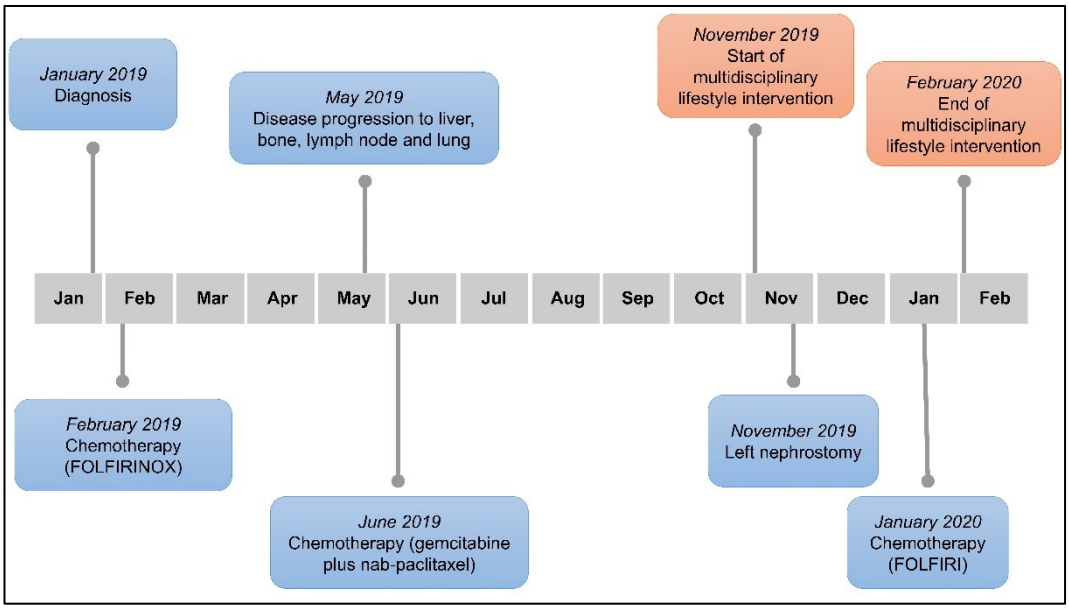

Figure 1. Timeline of disease status and multidisciplinary lifestyle intervention

At the same time, she was offered to participate into an integrated three-month multimodal program, including exercise, nutrition, and psychological intervention. The three-month period was considered an adequate time frame to achieve a meaningful change in weight, also considering the prognostic expectation at this disease stage (236).

The study was conducted according to the Declaration of Helsinki, the Good Clinical Practice and was reported following case report (CARE) guidelines (237). The authors obtained patient's consent for publication of clinical data. The patient's personal details were anonymized.

Multimodal intervention

Exercise. An individual exercise program based on the American College of Sports Medicine guidelines (7) and supervised by an experienced kinesiologist, was

conducted with the aim to improve cardiorespiratory fitness and increase muscle mass and strength. Baseline evaluation included cardiorespiratory fitness, strength, flexibility (Table1), and complete medical history. A twice-weekly program was implemented, with each session lasting 60 min and including in order: warm-up, aerobic exercises, strength activities, and cool-down. Fifteen-min warm-up and cool-down phases comprised dynamic and static flexibility exercises, respectively. The load of aerobic activity, consisting in cycling and walking ergometer, was slowly increased from 10 min at the beginning to 25 min at the end of the program, with an intensity level of 3 to 5 on the CR10 Borg Scale of perceived exertion. Resistance training included six exercises with bodyweight and resistance bands (Thera-Band, Hygenic Corp. Akron OH), covering major functional lower- and upper-body muscle groups. Each strength exercise was performed at 3 to 5 on the CR10 Borg Scale of perceived exertion, in two-three sets of 8-12 repetitions, which were progressively increased during the training program.

Nutritional intervention. Nutritional intervention had the main objective to meet patient's energy and protein requirements and to effectively manage disease- and treatment-related symptoms with a nutritional impact. Nutritional counselling was carried out bi-weekly, in presence, by a registered dietitian with experience in cancer care: intervention consisted in a personalized dietary prescription, including sample meal plans and suggested recipes, tailored to patient's own eating patterns and preferences. Patient was invited to take more time to eat, increase the daily number of meals and snacks, and favor high-protein and -energy food. Total daily energy requirements were calculated at baseline by the Harris-Benedict equation, corrected by a factor of 1.5 (208), whereas daily protein requirement was set at 1.5 g/kg of actual body weight (208). Since spontaneous oral intake was insufficient to cover needs, oral nutritional supplements, with high protein and calories content, were proposed (208). Finally, pancreatic enzyme replacement therapy (PERT) was prescribed for the management of malabsorption symptoms: The initial PERT dose was 40,000 U Ph Eur and 25,000 U Ph Eur of lipase per meal and per snack, respectively. The patient was trained to take PERT during the meal and to adapt the dose based on meal size and fat content; clinical symptoms and the presence of steatorrhea were evaluated bi-weekly.

Psychological support. Weekly psychological support sessions were carried out, with each meeting lasting about 60 minutes. Using cognitive behavioral therapy, the primary focus of psychological treatment was helping the patient to reduce anxiety, depression, and distress levels. After baseline assessment, based on current guidelines (238), intervention started from behavioral reactivation, with the aim to implement patient's daily living activities. Through cognitive restructuring, the existing dysfunctional and irrational thoughts were modified, promoting useful and functional ones. Moreover, a mindfulness-based approach was proposed to implement patient's quality of sleep, reducing the nightly awakening and the ruminations. The sessions also incorporated progressive relaxation techniques and controlled breathing, to decrease muscle tension.

Assessments

Outcome measures were assessed at baseline and at 12 weeks. At baseline, demographic information was self-reported, whereas clinical data were derived from the electronic patient data management system. Resting heart rate and blood pressure were evaluated before health-related fitness assessment, after 10 min of rest in the supine position.

Safety and feasibility. Safety was classified as intervention-related adverse events, occurring as a direct result of exercise or nutritional or psychological support and categorized according to the Common Terminology Criteria for Adverse Events (version 5.0). Feasibility was re-evaluated continuously during intervention, recording the adherence to each intervention, i.e. the number of sessions attended by the subject, compared to the total planned.

Health-related physical fitness. A series of tests were performed to evaluate the physical and functional capacity of the patient. Six minutes walking test was used to assess cardiorespiratory fitness, according to the American Thoracic Society guidelines (116). The test consisted in walking in a 20-m hallway, with the goal to cover as much distance as possible in six minutes. Standardized encouragements were given and the time remaining was called out every minute. Muscular strength was evaluated with the handgrip strength test, using a hydraulic hand dynamometer (Model SH5001, Saehan Corporation, Korea). The subject was sitting in a straight-

backed chair with the feet flat on the floor, the shoulders in adducted and neutral position, and the wrist between 0-30 degrees extension and between 0-15 degrees ulnar deviation. For both arms, five tests were performed, and each voluntary contraction was kept for 2-4 seconds, with one-minute rest between the tests. The highest achieved value in each hand was reported (118). Flexibility was evaluated for upper- and lower-limbs, using back scratch and chair sit and reach test, following the protocol proposed by Rickli and Jones (239). Anthropometric parameters included body mass index (BMI), obtained by the weight of the subjects divided by the square of her height and waist-hip ratio, derived by the ratio of waist and hip circumferences, according to standard procedures (240).

Nutritional assessments. Nutritional risk screening (NRS-2002) was adopted to evaluate nutritional risk through the following variables, referred to the previous week: weight loss, BMI, general conditions, amount of food intake, age, and severity of the disease. According to the scoring protocol the patient is classified at nutritional risk (score equal or more than three) or not (score less than three) (241). The dietitian collected the presence of symptoms potentially affecting patient's feeding, such as early satiety, loss of appetite, dysgeusia, dyspepsia, chemotherapy-induced nausea and vomiting, xerostomia, and symptoms of malabsorption, including increased abdominal bloating or discomfort, excessive gas causing burping or flatulence, increased frequency, light color, floating, frothy, oily, and/or foul-smelling faeces. Energy intake was assessed by a 3-day 24-h dietary recall method (2 *week*days and one *weekend* day). The nutrient contents of foodstuffs and meals were analyzed by the Food Composition Table of National Institute for Research on Food and Nutrition. This energy intake was comparable to the patient's optimal nutritional requirements. Inadequacy of energy intake was considered in the event of a current energy intake <60% of estimated requirements for more than 1–2 weeks, according to the most recent guidelines for nutrition in cancer patients of the European Society for Clinical Nutrition and Metabolism (ESPEN) (208). Body composition was assessed using the NUTRILAB BIVA (Akern s.r.l., Florence, Italy), according to previously described procedures (242).

Psychological and patients reported outcomes. A series of questionnaires were proposed to evaluate psychological status, QoL, and physical activity level.

Psychological status was assessed using validated tools: Hospital Anxiety and Depression Scale (HADS) and the Distress Thermometer (DT) (243). HADS, is a self-reported questionnaire composed by 7-item regarding anxiety (HADS-A) and 7-item concerning depression (HADS-D) and reflects how the patient felt in the previous week. Both scales ranging from 0 to 21, and a score of 8-10 reflect borderline symptoms while scoring ≥ 10 indicates the presence of clinically relevant of anxiety and depression (243). DT is a single-item question, in which on an 11-point numerical analogue scale the subject quantified her distress from 0 (no distress) to 10 (extreme distress). A score equivalent to or greater than 4 suggests a clinically significant level of distress (244). The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ C-30) was used to assess the quality of life. The EORTC QLQ C-30 is a 30 items scale that measures global health status (2 items), symptoms subscale (13 items: fatigue, pain, nausea, vomiting, dyspnea, sleep disturbance, constipation, diarrhea, appetite loss, and difficulties score), and functional scale with social functioning, physical functioning, cognitive functioning, and emotional functioning scores (15 items) (122). Physical activity level was assessed through the modified Godin Leisure-Time Exercise Questionnaire, in which the weekly duration, as well as the frequency of light, moderate and vigorous activity, were reported (58).

Results

No adverse events related to the integrated, multimodal approach were recorded during the 12 weeks of intervention. Compliance to the multimodal program was high: 83% (20/24) for exercise, 100% (6/6) for nutritional counseling, and 75% (9/12) for psychological support sessions, respectively. Reasons for missing sessions were treatment-related side effects (fever) and invasive procedures (nephrostomy positioning). Exercise sessions were well tolerated, the nephrostomy bag did not interfere with the activity, and the planned progression was completed without modifications.

Results of the multimodal intervention are reported in **Tables 1** and **2**.

Table 1. Absolute scores of health-related physical fitness and nutritional parameters

Measure	At baseline	Post-intervention
Resting blood pressure and heart rate		
Resting systolic blood pressure (mmHg)	103	109
Resting diastolic blood pressure (mmHg)	70	61
Resting heart rate (bpm)	68	61
Six minutes walking test (m)	416.0	525.6
Final heart rate	87	86
RPE	3.0	3.0
Handgrip strength (kg)		
Right arm	22	24
Left arm	22	23
RPE	4.0	5.5
Chair sit and reach (cm)		
Right leg	0.0	0.0
Left leg	- 2.0	+ 2.0
Back scratch (cm)		
Right arm (upper)	+ 3.5	+ 5.5
Left arm (upper)	+ 4.0	+ 3.0
Anthropometric parameters		
Usual weight (kg)	63.0	
Usual BMI (kg/m^2)	23.1	
6-months weight loss (%)	21.4	
Body weight (kg)	49.0	53.2
BMI (kg/m^2)	18.0	19.5
Waist (cm)	67.1	70.5
Hip (cm)	89.3	92.0
Waist-hip ratio	0.8	0.8
Body composition		
Phase angle (degrees)	2.9	3.8
Body cell mass (kg)	7.5	10.4
Total body water (l)	20.8	21.0

Fat mass (kg)	6.1	5.2
Fat free mass (kg)	23.9	26.1
NRS-2002 score	3.0	2.0
Dietary assessments		
Estimated energy requirements (kcal/day)	1836	
Estimated protein requirements (g/kg/day)	1.5	
Baseline energy intake (kcal/day)	1271	1874
Baseline protein intake (g/kg/day)	0.8	1.4
Nutritional impact symptoms		
Early satiety	Yes	No
Dysphagia	Yes	No
Loss of appetite	Yes	No
Dysgeusia	No	No
Oral mucositis	Yes	No
Dyspepsia	Yes	No
Xerostomia	Yes	No
Nausea/vomiting	Yes	Yes
Diarrhea	Yes	No
Steatorrhea	Yes	No
Abdominal bloating	Yes	No

Considerable improvements were observed for cardiorespiratory fitness (+ 26.3%), right handgrip strength (+ 9.1%), left handgrip strength (+ 4.5%), some parameters of upper and lower body flexibility and physical activity level (**Table 1**). Resting heart rate and blood pressure remained stable. Despite considerable weight loss in the six months (~21.4%) preceding intervention, anthropometric measures showed an increase in body weight, waist/hip values, and BMI from 18.0 kg/m^2 to 19.5 kg/m^2. Body composition analysis revealed a considerable increment in fat-free mass (+9.2%) and an improvement in phase angle, from 2.9° to 3.8°. Nutritional status improved from a NRS-2002 score of 3 (at risk for malnutrition) at baseline to a NRS-2002 score of 2 (not at risk) at the end of the intervention. Moreover, a substantial increase in energy (+ 47%) and protein (+ 75%) intake above baseline was observed; several nutritional impact symptoms present at baseline, such as

dysphagia, oral mucositis, dyspepsia, xerostomia, diarrhea, steatorrhea and abdominal bloating, disappeared after 12 weeks (**Table 1**). QoL improved in certain domains, such as physical functioning, emotional functioning, social functioning, appetite loss; on the contrary, some symptoms especially fatigue, nausea/vomiting, pain, dyspnea, and insomnia worsened during the intervention period; overall health status remained unchanged (**Table 2**).

Table 2. Absolute scores of patient-reported outcomes

Measure	**At baseline**	**Post-intervention**
Quality of life (score 0-100)		
Physical functioning	73.3	80.0
Role functioning	50.0	50.0
Emotional functioning	75.0	83.3
Cognitive functioning	83.3	83.3
Social functioning	33.3	66.7
Global health status	50.0	50.0
Fatigue	55.6	66.7
Nausea/vomiting	16.6	33.3
Pain	33.3	50.0
Dyspnea	33.3	66.7
Insomnia	33.3	66.7
Appetite loss	33.3	0.0
Constipation	0.0	0.0
Diarrhea	66.7	66.7
Financial problems	33.3	33.3
Physical activity level (min/week)		
Vigorous	0.0	0.0
Moderate	0.0	0.0
Light	210.0	420.0
Psychological status (score 0-21)		
Hospital Anxiety and Depression Scale – anxiety	16	9

Hospital Anxiety and Depression Scale – depression	18	11
Distress Thermometer	8	4

A clinically relevant status of depression and distress remained stable at both baseline and post-intervention time points, while anxiety improved at 12 weeks, resulting in a borderline abnormal level. However, a considerable reduction in HADS-A (from 16 to 9 points), HADS-D (from 18 to 11 points), and DT (from 8 to 4 points) were observed (**Table 2**).

Discussion

This case study highlights the fact that a multimodal intervention including exercise, nutritional, and psychological support carried out by a dedicated multidisciplinary team (FORCE team) is feasible and safe during palliative chemotherapy for a cachectic patient affected by advanced PC. Indeed, no adverse events related to the intervention occurred and the compliance to the three interventions was excellent. Demonstrating the safety of an exercise program, even in the context of an aggressive oncological disease such as PC and in a patient, who recently underwent an invasive palliative procedure, may help to overcome barriers towards physical exercise in this setting (245).

Weight loss is one of the most important factors involved in cancer cachexia (234). Approximately 80% of PC patients present cachexia, which is also a predictor of poor outcomes throughout all disease stages. As evidenced by this case study, structured multidisciplinary assessment, counselling, and intervention, resulted in a substantial (~4.2 kg) increase in body weight (234). It is worth noting that weight gain is an essential component of the so-called clinical benefit response (CBR), a composite endpoint specifically developed to evaluate treatment impact in PC (246, 247) and validated as a surrogate endpoint for survival in this setting (248). Moreover, exercise capacity, muscular strength and mass are prognostic factors in PC (211, 249) and are often impaired due to both cachexia and cancer diagnosis (250, 251). On one side, resistance training is a potent modulator of skeletal

muscles, able to increase strength and muscle mass, whereas aerobic training can control inflammatory and immune response (199). On the other hand, adequate caloric, and especially protein, intake is a key component helping to increase or preserve muscle mass (234). An integrated, synergistic approach can favor protein turnover and increase their skeletal muscle synthesis. Our multimodal intervention resulted in an improvement in cardiorespiratory fitness, muscular strength, and mass; it helped correcting nutritional deficiencies, increasing nutritional intake to meet or exceed optimal requirements, and managing nutritional impact symptoms. Overall, it could be speculated that an increase in functional capacity, adding an adequate caloric, especially protein, intake, and a gain in body weight, can improve muscle mass and consequently prevent or control cachexia (**Figure 2**).

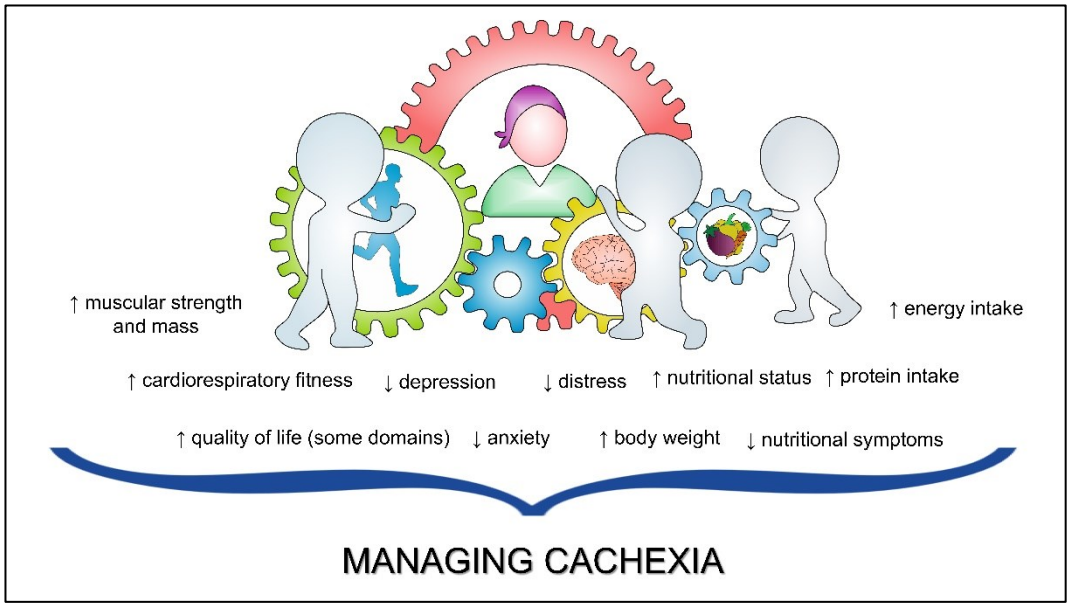

Figure 2. Multidisciplinary intervention as strategy to manage cancer cachexia

In addition, psychological intervention may also indirectly contribute to managing cancer cachexia. We found that distress and depression reduced substantially, and anxiety moved from abnormal levels to borderline. Consistently with a previous study (236), quality of life reported improvement in some domains, while others showed no change or worsening, probably due to disease progression and change in the treatment regimen in the last two weeks of intervention. Patients with advanced cancer or with cachexia may suffer from psychological distress, and

several prior investigations have identified eating-related distress as a significant contributor to these symptoms (252). Moreover, psychological intervention can help patients to feel better, but it can also support the multimodal intervention through better uptake and adherence (**Figure 2**).

To our knowledge, only one trial tested the feasibility of the multimodal approach, including exercise, nutritional supplements, and anti-inflammatory drugs, for the management of cachexia in lung and pancreatic cancer (MENAC trial) (226). This study has the strength to be a randomized controlled trial, and the results showed an improvement in muscle mass and body weight, while no changes were observed for strength and exercise capacity. However, compared to our case-study, the MENAC trial, reported lower levels of intervention adherence, and the program lasted only six weeks (226). Adherence is an important modifiable factor, affecting treatment outcome, and probably represents the most relevant aspect to expect beneficial results from an intervention (253, 254). These may suggest that longer intervention and/or higher adherence are needed to improve the expected results.

The main limitation of this case report is the absence of specific blood tests, which could provide additional information about the patient's inflammatory and immunological status. Nevertheless, this case is unique for both the patient's condition and the multimodal intervention proposed.

Conclusion & future perspectives

We found that intervention, including exercise, nutritional and psychological support, is safe, feasible, and efficacious. Given the clinical importance of the observed results, prospective trials incorporating a multimodal lifestyle approach with a solid design are needed to validate the real benefit and definitely implement this strategy in the therapeutic course of advanced cancer.

CHAPTER 8
SUMMARY OF THE THESIS RESULTS

The purpose of the present dissertation was to enhance the knowledge about exercise in Italian cancer patients. To this aim: 1) exercise preferences, barriers, and cues to action in cancer patients were investigated, 2) a tailored exercise program was developed, 3) the inclusion of exercise as part of multidisciplinary intervention was preliminarily tested.

The study results can be summarized as follows:

Study 1: This study shows that 93% of cancer patients are insufficiently active, with similar exercise behavior in men and women through age. Nevertheless, roughly 80% of the study participants are willing to start and exercise program, specifically designed or cancer patients. The willingness to start an exercise program is associated with some socio-demographics and medical variables, as age, education, and cancer treatment. Exercise preferences in cancer patients tend to vary substantially, suggesting that different exercise proposals may be offered to address patients' needs.

Study 2: This qualitative study reports that several factors can influence the adoption of an active lifestyle in cancer patients. Patients have a positive perception of physical activity, reporting a variety of related benefits. A series of barriers have been identified, especially related to disease, medical treatments, and risk of injury. By the contrary, several strategies, as an available exercise specialist and a targeted physical activity program, may motivate and facilitate patients to start or maintain a physical activity program.

Study 3: Study 1 and 2 provided important information to develop one of the first exercise intervention on cancer patients in Italy. The CHOiCE study is a two-sites, prospective, two-armed, phase II randomized controlled trial, aiming to explore program' safety and feasibility as well as preliminary efficacy on health-related

skills and quality of life. Patients randomized in the interventional arm can choose to perform exercise between three modalities: a written exercise program to perform at home, an individual supervised program, and a group-based program. The 12-week of exercise, consist of aerobic, strength and activities, based on baseline evaluations and progressively increasing over the weeks. There is a dearth of knowledge about exercise oncology in Italy. CHOiCE study tries to bridge this gap seek to propose a program addressing patients' needs.

Study 4: COVID-19 pandemic storm is relentlessly progressing worldwide, disrupting, and slowing down of routine medical care and research and activity related to exercise. Physical inactivity, imposed by the pandemic emergency, may have negative and long-term effects in cancer patients. Adaptations of the current exercise guidelines, through remote approaches, e.g., home-based exercise programs, may help to counteract the sedentary and mitigate the risks deriving from it.

Study 5: Cancer cachexia remains still a critical point in cancer care, without validated therapies. The multifactorial pathophysiology of this syndrome supports the use of multimodal interventions. Theoretically, pharmaceutical agents, exercise nutrition and psychological support may produce a synergistic effect, able to manage and/or improve cancer-related cachexia. However, to offer a personalized program a specialized staff is necessary, requiring efforts also in terms of economic availability.

Study 6: In a case of metastatic pancreatic cancer with cachexia, a multimodal approach, including exercise, nutrition and psychological support was proposed. The intervention consisted in a personalized aerobic and strength activities performed twice a week, tailored nutritional intervention with bi-weekly counseling and psychological support once a week. A 12-week intervention was safe and feasible, showing positive effects to gain weight, enhance strength and functional capacity as well as to improve nutritional and psychological outcomes.

Although, each study has its own limitations, discussed in the respective chapters, this dissertation may provide some important findings about exercise in Italian cancer population. Further studies should continue to study the effect of exercise and its combination with other interventions in the cancer care. On the other hand, in Italy, the dissemination of exercise programs to support cancer patients are necessary.

APPENDIX 1
MANUSCRIPTS AUTHORED AND CO-AUTHORED DURING THE Ph.D. PROGRAM

Avancini A., Belluomini L., Tregnago D., Trestini I., Milella M., Lanza M., Pilotto S., (2021) *Exercise and cancer-related anemia: could make the difference?* [submitted]

Avancini A., Benato G., Tregnago D., Trestini I., Milella M., Lanza M., Pilotto S., (2021) *Development of educational print material for physical activity in cancer: evaluation of readability and suitability* [Journal of Cancer Education]

Avancini A., Cavallo A., Trestini I., Tregnago D., Belluomini L., Micheletto C., Milella M., Pilotto S., Lanza M., Infante M.V., (2021) *Exercise prehabilitation in lung cancer: getting stronger to recover faster.* [European Journal of Surgical Oncology]

Trestini I., Caldart A., Dodi A., **Avancini A.**, Tregnago D., Belluomini L., Milella M., Pilotto S., (2021) *Body composition as modulator of response to immunotherapy in lung cancer: it is time to deal with it* [ESMO Open]

Avancini A., Trestini I., Tregnago D., Lanza M., Milella M., Pilotto S., (2021) *A multimodal strategy against cancer-related cachexia: from theory to practice* [Expert Review of Anticancer Therapy]

Trestini I., Sperduti I., Caldart A., Bonaiuto C., Fiorio E., Parolin V., Zambonin V., Zanelli S., Tregnago D., **Avancini A.,** Pilotto S., Mele M.C., Gasbarrini A., Scambia G., Milella M., Tortora G., Bria E., Carbognin L., (2021) *Evidence-based nutrition educational intervention improves adherence to dietary guidelines, anthropometric measures and serum metabolic biomarkers in early-stage breast cancer patients: a prospective trial.* [The Breast]

Trestini I., Carbognin L., Perretti U., Sperduti I., Caldart A., Tregnago D., **Avancini A.**, Auriemma A., Pilotto S., Bria E., Reni M., Tortora G., Milella M.,

(2021) *Pancreatic enzyme replacement therapy in patients undergoing first-line gemcitabine plus nab-paclitaxel for advanced pancreatic adenocarcinoma: a 'Real-World' study* [Frontiers in Oncology]

Trestini I., Carbognin L., Sperduti I., Bonaiuto C., Tondulli L., **Avancini A.,** Tregnago D., Lanza M., Pilotto S., Tortora G., Milella M., Bria E. (2020) *Tailored nutritional intervention in patients affected by Head and Neck Cancer receiving chemotherapy and/or radiotherapy: a retrospective study.* [submitted]

Belluomini L., Caldart A., **Avancini A.,** Dodi A., Trestini I., Kadrija D., Sposito M., Tregnago D., Casali M., Riva S.T., Sartori G., Menis J., Milella M., Pilotto S. (2021) *Infections and Immunotherapy in Lung Cancer: A Bad Relationship?* [International Journal of Molecular Sciences]

Avancini A., Trestini I., Tregnago D., Cavallo A., Bragato M., Bonaiuto C., Lanza M., Milella M., Pilotto S. (2021) *Multidisciplinary Lifestyle Intervention to Manage Pancreatic Cancer-Related Cachexia: A Case Report* [Future Science OA]

Avancini A., Tregnago D., Rigatti L., Sartori G., Yang L., Trestini I., Bonaiuto C., Milella M., Pilotto S., Lanza M. (2020) *Factors influencing physical activity in cancer patients during oncological treatments: a qualitative study.* [Integrative Cancer Therapies]

Avancini A., Trestini I., Tregnago D., Wiskemann J., Lanza M., Milella M., Pilotto S. (2020) *Physical activity for oncological patients in COVID-19 era: no time to relax* [JNCI Cancer Spectrum]

Avancini A., Pala V., Trestini I., Tregnago D., Mariani L., Sieri S., Krogh V., Boresta M., Milella M., Pilotto S., Lanza M. (2020) *Exercise level and preferences among Italian cancer patients: a cross-sectional study*. [International Journal of Environmental Research and Public Health]

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