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DO COMBINED AEROBIC AND RESISTANCE EXERCISE INTERVENTION IMPROVE THE HRQOL IN EOC PATIENTS UNDERGOING BEVACIZUMAB TREATMENT? STUDY PROTOCOL FOR A MULTICENTER RANDOMIZED CONTROLLED TRIAL

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Abstract

Background: Invasive epithelial ovarian cancer (EOC) is a highly fatal disease when diagnosed at advanced; few improvements in the treatment of EOC were obtained in the last years, till the introduction of bevacizumab therapy. Physical activity has been demonstrated to increase survival with cancer patients, and during chemotherapy is a promising strategy to reduce fatigue and improve health-related quality of life (HRQoL).The main purpose of this study will be to evaluate if a regular and structured exercise, during bevacizumab therapy will be able to improve the HRQoL in ovarian cancer.

Methods/Design: The study is a prospective, randomized, open-label, multicenter phase 2 trial in EOC patients eligible for bevacizumab treatment. Participants will be randomized to an exercise intervention or a control group. The exercise intervention group will participate in a 12-weeks supervised exercise programme and the control group will receive only a general recommendation. The focus of the exercise is resistance training in combination with aerobic training. Participants are measured at baseline, after 12 weeks and after 24 weeks as part of the program. Primary endpoints change the quality of life evaluated by 6MWT test and EORT QLQC-30. Secondary endpoints include CPET, Bio-sample, muscle strength test and IPAQ-SF. Statistical analyses will include descriptive characteristics, t-tests, effect sizes and two-way repeated-measures analysis of variance to examine differences between groups over time.

Discussion: The exercise program is safe, cheap and feasible and the studies have shown protective and treatments effect from cancer but it needs to be further investigated. The study design and the state-of-the-art assessments will help to increase knowledge about EOC in general and exercise as a potential treatment option in these patients under investigation.

Introduction

Epithelial ovarian cancer (EOC) is the seventh most common cancer in women and the main cause of death among gynaecological cancers in developed countries [1]: the risk of developing ovarian cancer gets higher with age. Ovarian cancer is rare in women younger than 40. Most ovarian cancers develop after menopause. Half of all ovarian cancers are found in women 63 years of age or older [2]. Environmental and lifestyle-related factors are thought to have a role in the development of EOC; these include use of talcum powder in the genital area, asbestos, pelvic irradiation, viruses (particularly mumps) and obesity. Other factors are associated with significantly increased risk of EOC are the use of post- menopausal hormones and fertility drugs. However, genetic factors, including BRCA-1 or -2 mutations, represent the most important risk factor for EOC. [3]. Tumour growth and metastasis depend on angiogenesis triggered by chemical signals from tuomour cells in a a phase of rapid growth. [4] Bevacizumab is a monoclonal antibody that binds the vascular endothelial growth factor (VEGF), leading to a prevention of the activation of its receptor (VEGFR), thus determining a reduced angiogenesis. Bevacizumab seems to be tolerated and active in the second and third-line treatment of patients with EOC/PPC and [5, 6] randomized

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phase III trials showed that the addition of bevacizumab to standard first-line chemotherapy followed by maintenance bevacizumab improves progression-free survival (PFS) compared to standard chemotherapy [7, 8]. However, bevacizumab is associated with toxicities that are occasionally life-threatening [9]. In GOG 0218 trial the rate of hypertension requiring medical therapy was significantly higher in the bevacizumab followed by maintenance bevacizumab group (22.9%) compared to the control group (7.2%)[7]. Other adverse events of particular interest are gastrointestinal perforations, wound healing complications, proteinuria, haemorrhages, venous thromboembolism and heart failure. Consequently, HRQoL becomes a major consideration in treatment choice when differences in survival rates are small or negligible and when treatments are expensive and toxicities common. QoL is important in advanced ovarian cancer, where treatments can be effective but are only rarely curative [10]. The GOG 0218 -trial evaluated the impact of bevacizumab on QoL as measured by the Trial Outcome Index (TOI) of the Functional Assessment of Cancer Therapy-Ovary (FACT-O). In this placebo-controlled randomized phase III-trial, bevacizumab compromised QOL, as measured by the FACT-O-TOI, to a mild extent during chemotherapy, but had no prolonged effect after chemotherapy completion [11].Conversely, ICON7 trial, while demonstrating a prolongation in PFS and OS in high-risk patients compared with standard chemotherapy and chemotherapy and bevacizumab, showed a poorer (rather than equivalent) HRQoL with bevacizumab continuation treatment in patients with EOC.[8]. Exercise has been proposed as a promising strategy for the management of some of these physical and psychological complaints and evidence is currently available for breast, prostate, colon and haematological cancers. For instance, it was demonstrated that physical exercise enhances HRQoL during active treatment in people with breast [12], myeloma [13], head and neck [14], colorectal cancer, [15] and multiple myeloma [16].

Moreover, physical activity has been identified as one potential non-pharmacological intervention, which can help to ameliorate fatigue during cancer treatment. Apart from the psychological effect, aerobic exercise may be a promising strategy to reduce also physical adverse events, not limited to fatigue. It is well known that the mean systolic and diastolic blood pressure is reduced by regular physical activity. Even if studies investigating the effect on the cardiotoxicity of physical exercise during bevacizumab therapy does not exist, some evidence, on animal models, demonstrated that physical exercise may antagonize the toxic effects caused by anthracycline on the heart [17]. During a recent meta-analysis by Haykowsky MJ et al, fourteen randomized trials in non-oncologic heart failure patients were identified, demonstrating a consistent benefit in ejection fraction improvement of aerobic training (WMD =2.59%; 95% CI 1.44% to 3.74%, I2= 17.2%) [18]. However, the aetiology of heart failure in cancer survivors may differ from that of a person without a history of cancer and thus the effect of physical exercise on treatment-induced heart failure may not be the same. Finally, physical exercise may have also an impact on cancer-specific survival, as demonstrated in breast and colorectal cancer. Regarding EOC, only three previously published reports have investigated the role of physical activity on ovarian cancer survivorship and there are no data from randomized control trials. In the first study with 635 ovarian cancer patients conducted in Sweden, the investigator showed there was no evidence of reduced risk of survival in any of the physical activity categories measured in over different periods of life (childhood, early adulthood, etc.) and before diagnosis. Anyway, they found that 2hours a week during young adulthood, in patients with stage I and II ovarian cancer, reduced the mortality [19].The second study is a prospective cohort study, that showed a modest 31% lower mortality in non-obese women who reported more than 2hr/week regular physical activity (HR = 0.69, 95% CI = 0.47 to 1.00); overall HR for the entire sample was not statistically significant [20].

More recently, a prospective study, which examined an association between physical activity and ovarian cancer survival reported that women who performed vigorous-intensity exercise had a 26% lower risk of ovarian cancer-specific mortality, respectively, compared to women who reported moderate-intensity physical 111 activity (HR=0.74; 95% CI, 0.56-0.98) [21]. One important limitation of all these studies is the utilization of self-reported physical activity data collected at (or soon after) the time of ovarian cancer diagnosis, without continuing to track physical activity after diagnosis. In short, while survival data are limited, there appears to be some evidence supporting an association between physical activity and improved survival. However, evidence from survival studies are too scarce to draw meaningful conclusions and additional studies, including follow-up with +-regard to physical activity behaviour, are necessary to further elucidate the association between exercise and HRQol in ovarian cancer.

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Materials and methods

The main aim of our study is to evaluate if a regular and structured exercise will be able to improve HRQoL in EOC patients eligible for bevacizumab treatment. Secondary aims are to assess the safety of exercise in patients treated with bevacizumab and chemotherapy, and to assess treatment-related adverse events in both arms. Moreover, an exploratory analysis of the predictive factors, like global methylation of cell-free DNA, VEGF, VEGFR, Ang1 and Tie2, of response to bevacizumab and exercise will be performed. This study is a multicentre pragmatic randomised controlled trial with two study arms that aims to include patients with histologically confirmed EOC, fallopian tube or OC. A group will be randomized to an exercise programme in addition to usual care and a control group receiving usual care while maintaining their habitual physical activity pattern. The exercise programme is a 12-week supervised group programme. Potential study participants will be recruited if they meet the following criteria: female patients ≥18 years of age, patients with histologically confirmed EOC, fallopian tube carcinoma or OC, including mixed Mullerian Tumours, patient with RECIST progression, with either measurable or non-measurable disease, ECOG Performance Status of 0–1, Life expectancy of ≥24 weeks, Patients will be excluded if they underwent surgery (including open biopsy) within 4 weeks before the first bevacizumab dose, inadequate bone marrow function (ANC: <1.5 x 109/l, or platelet count <100 x 109/l or Haemoglobin <9 g/dl), inadequate coagulation parameters, renal or liver function (APTT >1.5 x upper limit of normal (ULN) or INR >1, serum (total) bilirubin >1.5 x ULN, AST/SGOT or ALT/SGPT >2.5 x ULN, serum creatinine >2.0 mg/dl or >177 mmol/l). Will be also be excluded patients with a history or evidence of brain metastases or spinal cord compression, pregnant or lactating, history or evidence of thrombotic or haemorrhagic disorders; including cerebrovascular accident (CVA) / stroke or transient ischemic attack (TIA) or subarachnoid haemorrhage within ≤6 months prior to the first study treatment), uncontrolled hypertension (sustained systolic >150 mm Hg and/or diastolic >100 mm Hg despite antihypertensive therapy) or clinically significant (i.e. active) cardiovascular disease, including myocardial infarction or unstable angina within ≤6 months prior to the first study treatment; New York Heart Association (NYHA) grade II or greater congestive heart failure (CHF); serious cardiac arrhythmia requiring medication (with the exception of paroxysmal supraventricular tachycardia); peripheral vascular disease ≥grade 3 (i.e. symptomatic and interfering with activities of daily living requiring repair or revision). History of abdominal fistula, gastrointestinal perforation, or intra-abdominal abscess, or with signs of impending bowel obstruction within 6 months before the first study treatment, non-healing wound, ulcer or bone fracture, will be not eligible to bevacizumab treatment and thus to the trial. Again, severe (>G2) peripheral neuropathy will be not permitted to enter in the study. Other known malignant neoplastic diseases in the patient's medical history with a disease-free interval of fewer than 5 years (except for previously treated basal cell carcinoma and in situ carcinoma of the uterine cervix), evidence of any other medical conditions (such as psychiatric illness, peptic ulcer, etc.), physical examination or laboratory findings that may interfere with the planned treatment, affect patient compliance or place the patient at high risk from treatment-related complications, participation in another clinical trial with any investigational agents within 30 days prior study screening will determine the ineligibility of the patient.

An oncologist will recruit patients during a regular outpatient clinical visit. The clinician will assess the patient eligibility and will provide each patient and/or a legal representative with relevant, comprehensive, verbal and written information regarding the objectives and procedures of the study as well as their possible risks. If eligible, patients will be asked to sign informed consent upon which they will be randomly allocated to the intervention or the control group. Work described will be carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Recruitment and allocation strategy summarised in Fig.1. After completing the eligibility screen, consent process and all baseline assessments, eligible, consented women will be equally assigned to the intervention or control arms using the Biostatistics and Clinical Trials Unit of IRST.(Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori.vedi inglese) Patients will be randomized on a 1:1 allocation rate using mixed block sizes (blocked randomization). The randomization clinic visit (baseline) will include a physical examination and vital signs, tumour evaluation and tumour marker (CA-125), echocardiogram, physical activity assessment, blood and urine samples and QoL evaluation with EORTC-C30 questionnaire. (Tab. 1). Treatment administration will start within 30 days after the date of randomization.

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Physical activities

The pre-exercise screening will be performed before each training session. If one of the following criteria will be found, the participant will be excluded from the physical training component of the program on that specific day: diastolic blood pressure <45 mmHg or >95mmHg; pulse at rest >100 beats per minute; temperature >38°C; respiration frequency >20 per minute; infections requiring treatment with antibiotics; ongoing bleeding; fresh petechiae; bruises; thrombocytes <50×109/l; leucocytes <1.0×109/l. During the training sessions, the participants' heart rate will be continuously monitored by means of a wireless heart rate transmitter and the participants will be advised to respect their own physical limitations.

The following exercise programme consists of about 1 hour of supervised group-based training two times aweek for 12 weeks combining aerobic and resistance training. In addition, the participants of the intervention group are encouraged to be physically active for at least 30 min at home. The 60-min exercise classes included a warming-up (5/10 min), aerobic and muscle strength training (40/50 min) and a cooling down (5/10 min) period that will be included respiratory, joint mobilisations and stretching. The intensity of the aerobic training (AT) will be initially at 60% to 65% of the age-predicted max HR (220-age) for 20 minutes.; after 4 weeks at 65% to70% of the age-predicted max HR (220-age) for 25minutes and then will be increased at 75% of age-predicted max HR for 30minutes. The intensity of the activity will remain less than 85% of the age-adjusted maximal heart rate (220-age). Heart rate and the Borg scale of perceived exertion are monitored during the aerobic training. The aerobic activity includes cardiovascular machine: treadmill, bike etc. Muscle strength training will be performed for all major muscle groups: arms, legs, shoulder and trunk.The resistance training (RT) will start with 3sets × 10 repetitions (65 % one-repetition maximum) separated by one-minute; after 4 weeks increased at 3sets × 10 repetitions (65 % one-repetition maximum) to reach gradually to two series of eight repetitions at 80% 1RM. During RT will be using small free weights and gym equipment (small rubber and gym ball, sticks, elastic bands). During each training session, the exercise intensity will be controlled by expert professional (STAMPA), using a heart rate monitor and 6-20 Borg Rating of Perceived Exercitation (RPE). All session will be conducted in a local fitness centre with good access to equipment. Patients will be able to carry out the third session after that the practitioner will have checked that the patient has below the correct walking. Participants will be instructed to begin each session with a 5-min gradual warm-up and walk the correct intensity (HR and speed) which will be planned in advance with expert professional and 5 min cool down. These sessions will be unsupervised and completed in any location convenient to the participant (e.g. within their own neighbourhood, park etc.). To verify attendance in the programme, the exercise will be recorded by an appropriate instrument. Participants assigned to the control group will receive conventional medical care and complete outcome measures in parallel with the intervention group. The control group will be invited to maintain activity if already in an exercise program or to increase the level of physical activity if sedentary, following the American Cancer Society Guidelines on physical activity [22], but no specific prescriptions will be given.

Study outcomes and assessments

Study assessments

The study protocol includes several assessments beyond those collected as primary and secondary outcomes; Tab1 list the specific measures collected along with the protocol-specified time points for data collection.

Table 1: Physical exercise protocol during the study in exercise group

† Aerobic training include treadmill or bike. ††Resistance training include small free weights and gym equipment HR_{max}= 220-età; RM= repetition maximum;

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2 times a week for 12 weeks supervised training session

	Aerobic traning[+]	Resistance training[++]
0-4 weeks	60-65% HR_{max} for 20min	3sets*10repetitions (65%RM)
4-8 weeks	65-70%HR_{max} for 25min	
8-12 weeks	70-75% HR_{max} for 35min	2sets* 8repetions (80%RM)

Self-report questionnaires of quality of life HRQoL information is obtained through specific endpoints of the EORTC QLQC-30 questionnaire which are changed from baseline in global health status, functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning and social functioning) and fatigue measured by the symptom scale. Objective physical activity assessment Aerobic capacity will be determined using a cardiopulmonary exercise test with continuous breathing gas analysis following Bruce Protocol [23; 24]. CPET will be performed using an electronic cycle ergometer; after a 1-min warm-up at 20 W, cycling workload was increased every minute by a predetermined 10, 15, or 20 W until exhaustion or symptom limitation (dyspnoea and/or fatigue) recommended by American College. The sport of Medicine [25]. Peak oxygen uptake (VO2peak) will be determined by taking the mean of VO2 values of the last 30 s before exhaustion. In addition, VO2 and power output will be assessed at the ventilatory threshold. Blood pressure will be evaluated during the exercise and the Borg Scale 6-20 will assess the rating of perceived exertion, at the end of each stage of exercise. [26] The six-minute walk test (6MWT) is widely used to asses aerobic endurance in both clinical and non-clinical populations. The 6WT was originally developed to assess the functional capacity of patients with cardiorespiratory diseases [27] but has since been validated in several populations including patients with morbid obesity, Down's syndrome, Alzheimer's disease and fibromyalgia amongst others. [28] The test measures the distance covered when participants are instructed to walk as quickly as they can for 6 minutes along 35 m long, flat and straight hospital corridor. The doctor with an expert in exercise (STAMPA) will supervise the test. The total distance walked in six minutes will be recorded in Equation value meter. The muscle strength of the upper and lower limbs and flexibility will be evaluated by the sit and reach test (S&R) [29], the Handgrip [30] and the 30" Chair [31].Handgrip strength will be obtained taking the best score of two attempts provided by a mechanical handgrip dynamometer for both hands. The International physical activity Questionnaire short format (IPAQ –SF) will be used to determine physical activity of the week preceding the assessment [32]. It included seven items. The score responds to energy expenditure in METs. The interpretation of this questionnaire defines the total activity of the week in three categories: low, moderate, and high.

The IPQ-SF is filled at the same time for international comparison.

Bio-sample

Four blood and one urine samples will be collected at the moment of clinical and laboratory testing atbaseline, before therapy, before and after a physical exercise section, after the 3 cycles of therapy, after the 6 cycle of therapy and at disease progression or response. It will analyze the global methylation of cell-free DNA, VEGF, VEGFR, Ang1 and Tie2 expression in plasma samples.
The laboratory procedures will be performed at the Biological Laboratory of IRST.

Data analysis

The sample size was computed considering an 80% power to detect a standardized effect size (ES) for the Global health status/QoL scale of the EORTC QLQ-C30 questionnaire (at week 12 after chemotherapy initiation) of 0.56 (the difference between study arms of 15 points and standard deviation of 20), and a type 1 error of 5%. ES will be computed as a ratio of the difference between the expected mean value on the scale in the intervention group and the expected mean value on the scale in the control group, with the standard deviation of the outcomes (assumed the same under the null and alternative hypotheses). Considering 10% of dropout, 30 patients per groups will be required. Participants are expected to accrue to the study for 3 years. After completion of the protocol interventions, participants are followed for an additional 5 years to collect disease progression, as routine clinical practice (no

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additional evaluations are requested per protocol).Data from the EORTC QLQ-C30 will be standardized following the procedures of the EORTC scoring manual. In particular, raw scores (RS) for each scale will first be computed as the mean of all items included in a scale. RS will then be standardized in a way the scores could range between 0 and 100 using the following formula: [(RS-1)/range]. The range represents the difference between the maximum and the minimum value of the RS.

Data will be analyzed on an intention-to-treat basis. Continuous variables will be summarized by descriptive statistics (number of cases, mean, standard deviation, median, minimum, maximum). Categorical variables will be summarized using counts of patients and percentages. Two independent sample t-test will be used to assess differences in the global health status/QoL standardized scores between the two study arms. Differences over time of patients' QOL will be assessed by means of repeated measures analysis of variance. An analogous approach will be followed for the analysis of biomarker changes in the two study arms.

Analyses regarding PFS will be addressed by using Kaplan Meier curves and tests for curves comparison (i.e.the log-rank test). Multivariable analyses will be performed by means of the Cox proportional hazards model or the most appropriate survival model.

Discussion

It is well established that physical exercise modulates the function of many physiological systems, such as the musculoskeletal, the cardiovascular and the nervous system, by inducing various adaptations to the increased mechanical load and/or metabolic stress of exercise. Moreover, there exists evidence that exercise improves a variety of mental health outcomes including, anxiety, quality of life, and mood. A large portion of this evidence exists among breast cancer, with a smaller portion distributed among prostate, colon, and hematologic cancer. In a meta-analysis of ten studies, quality of life during treatment improved with exercise training and mood also increased. A meta-analysis on 40 exercise interventions including 2,929 cancer survivors was conducted. Cancer survivors who completed an exercise intervention reduced depression more than controls, with depressive symptoms reduced to the greatest degree among breast cancer survivors. [33] Exercise could also reduce the known bevacizumab-related adverse events, such as hypertension. It is well known, indeed, the capability of reducing blood pressure and the ameliorate the cardiac function induced by aerobic training. [18]To confirm the role of physical exercise on anticancer treatments it is necessary to try to further investigate the biological and biochemical mechanisms that physical activity is able to modulate and how they are interconnected with specific activation of cancer-related pathways. The potential protective effects of physical activity on cancer- and treatment-related worsening on HRQoL need to be further investigated, also because it acts through multiple interrelated pathways that may slow down cancer progression: decrease in adiposity, changes in biomarkers and insulin resistance, improvement of immune function, and reduction of inflammation. Physical exercise leads to epigenetic modifications that can have beneficial effects in cancer patients. Moreover, physical activity induces potent and wide-ranging effects on the immune system, mainly as anti-inflammatory that is associated with the modulation of the production of proinflammatory mediators which are associated with muscle damage such as tumour necrosis factor-a (TNF-a), interleukin-1b (IL-1b), and C-reactive protein. The cytokine profile induced by exercise is classically anti-inflammatory, comprising marked increases in the levels of several potent anti-inflammatory cytokines such as IL-10, IL-1 receptor antagonist (IL-1ra), and IL-6. Taking into all this consideration, the results of this study will provide helpful knowledge and insights into the effects of physical exercise on maintaining and/or improve HRQOL during cancer treatment in EOC patients.

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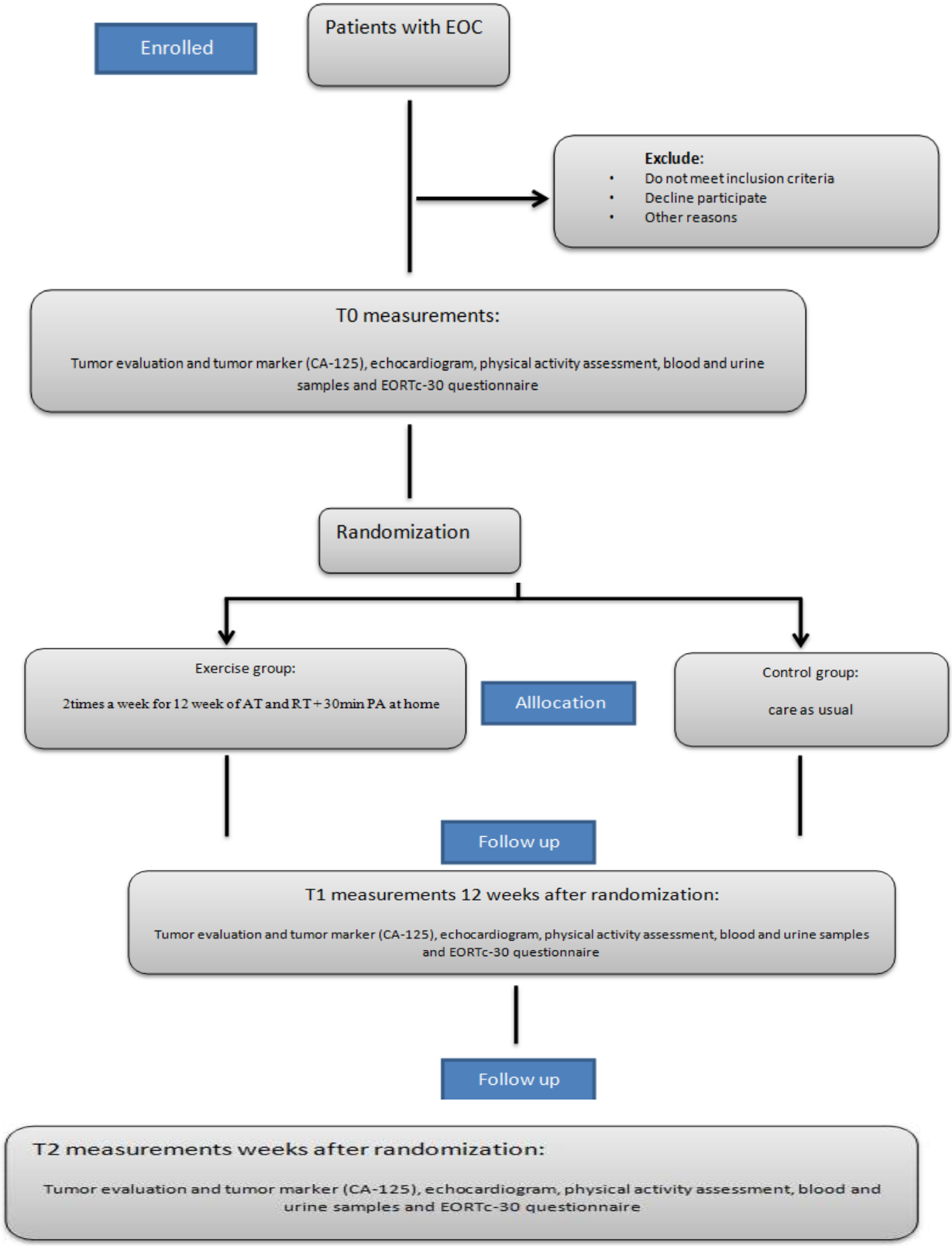

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Abbreviations

EOC: Epithelial ovarian cancer; VEGF: vascular endothelial growth factor; PFS: progression-free survival; TOI:Trial Outcome Index; FACT-O: Functional Assessment of Cancer Therapy-Ovary; AT aerobic training; RT: resistance training; RPE: Borg Rating of Perceived Exercitation; IPAQ –SF: International physical activity Questionnaire short format

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The author(s) declare that they have no competing interests.

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