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QUALITY OF LIFE AFTER PREOPERATIVE HOME-BASED EXERCISE TRAINING IN PATIENTS WITH LUNG CANCER: A RESPONDER ANALYSIS

Mestrado em Fisioterapia

SARA PEDROSA PIMENTA

DISSERTAÇÃO ORIENTADA POR JOANA PATRÍCIA DOS SANTOS CRUZ E PEDRO FILIPE ANDRÉ MACHADO

Leiria, março de 2024

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Quality of life after Preoperative Home-based Exercise Training in patients with Lung Cancer: a Responder Analysis

Dissertação apresentada por Sara Pedrosa Pimenta à Escola Superior de Saúde do Instituto Politécnico de Leiria para obtenção do grau de Mestre em Fisioterapia, realizada sob a orientação de Joana Patrícia dos Santos Cruz, da Escola Superior de Saúde do Instituto Politécnico de Leiria, e de Pedro Filipe André Machado, do Centro de Inovação em Tecnologias e Cuidados de Saúde (ciTechCare) do Instituto Politécnico de Leiria.

Leiria, março 2024

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Dissertação de Mestrado Em Fisioterapia

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Título dissertação: Quality of life after Preoperative Home-based Exercise Training in patients with Lung Cancer: a Responder Analysis

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Resumo

Introdução e objetivos: Anteriormente, um programa de exercício físico pré-operatório (PEP) domiciliário mostrou ser eficaz na melhoria da qualidade de vida relacionada com a saúde (QVRS) em utentes elegíveis para ressecção cirúrgica de cancro do pulmão. No entanto, foi observada variabilidade inter-individual na resposta ao PEP na QVRS. Esta análise secundária teve como objetivo explorar as características dos '*responders'*/ '*non-responders*' e os preditores de resposta ao PEP na QVRS. O objetivo secundário foi determinar se a resposta ao PEP (ou seja, '*responders*' e '*non-responders*') está associada a mudanças clinicamente relevantes na QVRS após a cirurgia.

Material e métodos: Os dados de um estudo de viabilidade e de um RCT foram analisados e incluíram dados sociodemográficos e clínicos [comorbidades; teste de marcha com carga progressiva (*Incremental Shuttle Walk test)*; 5 vezes sentar e levantar; força de preensão manual]; e o *European Organization for Research and Treatment of Cancer Quality of Life Questionnaire* C30 (EORTC-QLQ-C30) para avaliar a QVRS. Os '*responders'* vs. '*non-responders'* foram classificados através da diferença mínima clinicamente importante (5 pontos) na escala *Global QoL do* EORTC-QLQ-C30 após PEP (1-5 dias antes da cirurgia). As diferenças entre grupos foram analisadas através de testes *t* para amostras independentes, testes U de Mann–Whitney, testes qui-quadrado/exato de Fisher dependendo do tipo/distribuição dos dados. Os preditores da resposta ao PEP foram analisados através de regressões logísticas.

Resultados: Foram incluídos 32 utentes (63% homens, 67,1±7,8 anos), 56% (n=18) foram '*responders*' ao PEP na QVRS Global. Os '*responders'* apresentavam valores mais baixos na *Global QoL*, Função Emocional e *Summary Score* ($p<0,05$) do que os '*non-responders'*, e 50% tinham DPOC ($p=0,019$). Não foram encontradas diferenças significativas nas variáveis de desempenho físico ($p>0,05$). No modelo de regressão logística que incluiu as variáveis DPOC e *Summary Score* (R^2 de Nagelkerke=0,511), a DPOC foi o único preditor significativo: os utentes com DPOC tinham 13,4 vezes maior possibilidade de serem '*responders'* (OR=13,4; IC 95% 1,4; 132,2).

Conclusões: Os resultados sugerem que os utentes que respondem ao PHET apresentam menor QVRS antes do programa e diagnóstico de DPOC, embora apenas a presença de DPOC seja um preditor da resposta ao PHET na QVRS. Os utentes que respondem ao PEP tendem a manter ou melhorar a QVRS 1 mês após a cirurgia, embora esta relação ainda não seja clara. Outros preditores de resposta devem ser investigados em amostras maiores.

Palavras-chave: Cancro do pulmão; Pré-habilitação; *Responder analysis*; Qualidade de vida relacionada com a saúde

Abstract

Introduction and aims: Previously, a preoperative home-based exercise training (PHET) program proved to be effective in improving health-related quality of life (HRQoL) in patients awaiting lung cancer surgery, yet inter-individual variability was observed. This secondary analysis aimed to explore characteristics of responders/non-responders and predictors of response in HRQoL to PHET. A secondary goal was to determine whether the response to PHET (i.e., 'responders' and 'non-responders') was associated with clinically relevant changes in HRQoL following lung cancer surgery.

Methods: Data from a feasibility study and a randomized controlled trial (experimental group) were analyzed and included sociodemographic/clinical data (comorbidities; Incremental Shuttle Walk test; 5 times sit-to-stand; handgrip strength), and the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC-QLQ-C30) to assess HRQoL. Responders vs. non-responders were classified using the minimal important difference (5 points) in the Global QoL scale of the EORTC-QLQ-C30 after PHET (1-5 days before surgery). Between-group differences were analyzed through independent samples t-tests, Mann–Whitney U tests, Chi-square/Fisher exact tests depending on data type/distribution. Predictors of response to PHET were analyzed through logistic regressions.

Results: 32 patients (63% male, 67.1±7.8 years old) were included, from which 56% (n=18) were responders to PHET in Global QoL scale of the EORTC-QLQ-C30. Responders had lower scores in Global QoL and Emotional Function scales, and in the Summary Score ($p<0.05$), compared to 'non-responders'. 50% of responders had COPD ($p=0.019$). No significant between-group differences were found in performance variables ($p>.05$). In a regression model including the Summary Score and COPD (Nagelkerke $R^2=0.511$), COPD was the only significant predictor of response: COPD patients were 13.4 times more likely to be responders (OR=13.4; 95% CI 1.4; 132.2).

Conclusions: Findings suggest that patients who respond to PHET have lower baseline HRQoL and COPD diagnosis, although only the presence of COPD predicts response to PHET in HRQoL. Patients who respond to PEP tend to maintain or improve HRQoL 1 month after surgery, although this relationship is still unclear. Other predictors of response should be investigated in larger samples.

Keywords: Lung cancer; Prehabilitation; Responder analysis, Health-Related Quality of Life

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List of abbreviations

CCI – Charlson Comorbidity Index

COPD – Chronic obstructive pulmonary disease

CI – Confidence Intervals

EORTC-QLQ-C30 – European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30

5STS – Five-Times Sit-to-Stand Test

HRQoL – Health-related uality of life

ISWT – Incremental shuttle walk test

LC – Lung cancer

MID – Minimal important difference

PHET –Preoperative home-based exercise training

RCT – randomized controlled trial

RPE – Rating perceived effort

Introduction

Globally, lung cancer (LC) is one of the most common types of cancer, with 2.2 million new cases estimated in 2020, accounting for 11.4% of all cancer diagnosis (1-3). Additionally, LC is the most lethal type of cancer worldwide, representing 18% of all cancer-related deaths in 2020 (1-3). This pattern has also been observed in Portugal, where LC is the third more incident type of cancer and the leading cause of cancer-related death (4).

Surgical resection of the tumor is the cornerstone of curative treatment, suitable for patients with early-stage LC and sufficient cardiopulmonary reserve to tolerate the surgery (5). Although it offers the best survival outcomes for early-stage LC, with five-year survival rates for people with localized disease at approximately 60% (6, 7), surgery leads to short- and long-term impairments on health-related quality of life (HRQoL) (8).

HRQoL can be defined as a "multidimensional construct encompassing perceptions of both positive and negative aspects of dimensions such as physical, emotional, social, and cognitive functions, as well as the negative aspects of somatic discomfort and other symptoms produced by a disease or its treatment" (9). Together, these dimensions provide a comprehensive understanding of individual's global health status and its impact on their quality of life (9, 10). Therefore, it is now considered a crucial endpoint in oncology care (11).

Patients awaiting LC resection experience poor HRQoL compared to the general population (12), which is further impaired by surgery, leading to functional limitations and symptoms of pain, fatigue and dyspnea (8, 13, 14). There is consistent evidence showing that patients experience a significant decline in the physical and role functions 1 month after surgery. Furthermore, the deterioration in physical function and symptoms of dyspnea and fatigue persist up to 2 years after surgery, even in patients without recurrent disease [8]. This deterioration in HRQoL is of clinical significance since poor preoperative HRQoL is associated with extended postoperative length of hospital stay and an increased risk of postoperative cardiopulmonary complications (15, 16).

The long-term negative impact of surgery on HRQoL is also a concern for patients. In a recent qualitative study, all patients surgically treated for LC were concerned about their physical

function after surgery and 96% about symptoms of fatigue and pain (17). Thus, there is a need for effective interventions to improve pre and postoperative HRQoL. In current clinical guidelines, exercise training has been strongly recommended to improve cancer-related health outcomes such as depressive symptoms, anxiety, HRQoL and self-reported physical function (18, 19). Additionally, there is growing evidence supporting the effectiveness of preoperative exercise training in improving exercise capacity and decreasing the risk of postoperative pulmonary complications in LC patients (20-24). However, this evidence emerged from studies focused on center-based interventions (23, 25-28). This modality of interventions implies frequent travels that may hinder patients' adherence due to transportation-related accessibility barriers (29). Furthermore, the preoperative period is itself a stressful and busy period for patients (30), which may decrease patients' willingness to participate in such programs. Indeed, transportation issues are the main barrier for participating in center-based prehabilitation programs (29), and patients awaiting oncology surgery express a strong preference for home-based interventions (29, 31, 32).

Thus, to meet patients' preferences and minimize adherence problems to prehabilitation, home-based exercise programs may be a promising alternative. In previous studies, a preoperative home-based exercise training (PHET) program was implemented in patients awaiting LC surgery and it was considered safe, feasible and well accepted (33). It was also found to be clinically effective in improving preoperative HRQoL and preventing its deterioration after surgery (34).

Despite these beneficial effects, inter-individual variability in response to PHET was observed (33), which may be related to patients' characteristics and/or clinical status before surgery. Although this topic has not yet been explored among LC patients, in previous clinical trials involving breast and prostate cancer patients, baseline demographic, clinical and psychosocial variables explained the heterogenous effects of exercise training on postoperative HRQoL (35, 36).

Indeed, one of the current challenges in the field of exercise research is how to address the inter-individual variability in response to exercise training interventions (37). The evaluation of the mean change in an outcome set indicates a strong and positive impact of exercise training

within a population level. However, the clinical relevance of these effects on an individual level can vary significantly (37, 38) which should be properly considered to establish clinical meaningfulness, for example through a "responder analysis". This analysis provides insights that enable clinicians to tailor the intervention to the individuals' characteristics and identify the "best candidates" for a given intervention, which further optimizes individuals' outcomes. Moreover, in a recent international Delphi study, the identification of cancer patients who respond to surgical prehabilitation was established as a top research priority (39).

The main aim of this study was to investigate whether baseline characteristics of LC patients undergoing PHET can account for the variability of the response in preoperative HRQoL (i.e., "responders" and "non-responders") and predict a clinically meaningful response to PHET. A secondary goal was to determine whether the response to PHET (i.e., 'responders' and 'non-responders') is associated with clinically relevant changes in HRQoL following LC surgery.

Methods

Study design

This study is a secondary analysis of data from a feasibility trial (33) and a randomized controlled trial (RCT) (34). These studies were part of a larger project (OncoEnergy) that aimed to explore the feasibility, safety, and effectiveness of a PHET program on HRQoL in patients undergoing LC resection. Ethical approval was previously obtained from the Ethics Committees of the institutions where patients were recruited (Appendix 1). Data were collected between February 2022 and May 2023, at the Portuguese Oncology Institute of Coimbra, Leiria Hospital Center, Santarém Hospital Center, and Figueira da Foz Hospital Center (Portugal).

Participants

Consecutive adult patients (≥ 18years), candidates to surgery for confirmed or suspected lung malignancy (clinical stage IIIA or less), who had medical approval to exercise, and surgery scheduled for at least two weeks from study enrolment, were considered for inclusion. Exclusion criteria were: (i) metastatic tumor (ii) contraindications for exercise training or physical testing (iii) inability to speak/understand Portuguese (iv) being already involved in regular exercise training (aerobic and resistance training over the past month for ≥2 days/week, ≥30 minutes/session). Potential participants were identified during routine

appointments of Pulmonology or Thoracic Surgery and invited to participate by their medical staff. If eligible and willing to participate, patients were contacted by the research team who provided oral and written information about the trial. Patients who agreed to participate signed a written informed consent (Appendices 2 and 3) prior to any assessment.

Data collection

Assessments were conducted at baseline (T0), after the PHET (1-5 days prior to surgery – T1), and 4-5 weeks after surgery (T2). Sociodemographic (age, sex, education), anthropometric data (height, weight), clinical data (smoking status, lung function, cancer diagnosis, histological subtype, tumor stage) were first collected using a structured questionnaire. Comorbidities were assessed and scored according to the Charlson Comorbidity Index (CCI) which classifies comorbidities as mild (CCI scores of 1-2), moderate (CCI scores of 3-4) or severe (CCI scores≥5) (40).

HRQoL was assessed using the Portuguese version (41) of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30) version 3.0 (42), following the recommendations of the international consensus on patient-centered outcomes for lung cancer (11). The QLQ-C30 includes a global QoL scale, five functioning scales, three multi-item symptom scales, six single-item symptom scales, and a financial impact scale (43). Scores range from 0 to 100 points, with a higher score in the global QoL and functioning scales indicating better QoL/higher level of functioning and a higher score in the symptom scales indicating a higher level of symptomatology. In this study, the Global QoL scale of the EORTC-QLQ-C30 was chosen as the main outcome of HRQoL, as previously recommended (43). Additionally, following the recommendations of the EORTC Quality-of-Life Group, the QLQ-C30 Summary Score (SumSc) was used to supplement the 15-outcome profile generated by the QLQ-C30 (44).

Exercise capacity was assessed using the incremental shuttle walk test (ISWT) following the protocol described by Singh et al. (45). Handgrip strength was assessed using the Jamar Plus+ Dynamometer (Performance Health, Nottinghamshire, UK) following the standardized method recommended by the American Society of Hand Therapists (46). Five-Times Sit-to-Stand Test (5STS) was also used, where patients were instructed to rise from a standardized armless chair (0.41–0.45 m high) to a standing position five times as quickly as possible without using their

hands for support. The test was completed after the fifth repetition, and the time needed to perform the test was recorded using a stopwatch to the nearest 0.01s (47).

Intervention

The PHET program was previously tested for its feasibility, acceptability, and safety in a feasibility trial (33) and for its effectiveness on a multicenter RCT (34). The intervention duration was adjusted based on the waiting times for surgery (3.6 ± 0.2 weeks (34)) and comprised three main components presented in table 1. Details of the program have been published elsewhere (33) and trials were registered in ClinicalTrials.gov (NCT01772082 and NCT05469425).

Table 1 - Preoperative Home-based Exercise Training (PHET) program description.

<table>
<tr><th>PHET Component</th><th colspan="6">Description</th></tr>
<tr><td>Educational Session
(first day of the PHET program)</td><td>Themes</td><td colspan="2">Importance of exercise training before LC surgery</td><td colspan="2">Demonstration of the home-based exercise program</td><td colspan="2">Instruction on training intensity monitoring using the Borg Category Ratio (Borg CR-10)</td></tr>
<tr><td rowspan="3">Home-based exercise program
(5 days/week,
3.6 ± 0.2 weeks)</td><td rowspan="2">Aerobic training</td><td>F</td><td colspan="2">I</td><td>T</td><td>T</td><td>P</td></tr>
<tr><td>3x week</td><td colspan="2">RPE of 3–5 (moderate to strong)</td><td>Walking</td><td>30 min/session</td><td>40 min/session (2nd week)</td></tr>
<tr><td>Resistance training</td><td>2x week</td><td colspan="2">RPE of 3–5 (moderate to strong)</td><td>Sit-to-stand; calf raise; step up; glute bridge; biceps curl; shoulder press</td><td>2 sets 15 repetitions</td><td>3 sets 15 repetitions (2nd week)</td></tr>
<tr><td>Telephone supervision
(weekly basis)</td><td colspan="6">Purposes:
Monitor exercise adherence
Identify adverse events
Overcome exercise barriers
Adjust planned exercise program</td></tr>
</table>

Legend: LC, lung cancer; PHET, Preoperative home-based exercise training; REP, Rating of perceived exertion. Parameters of the training components: F, frequency; I, intensity; T, type; T, time/volume; P, progression.

Data Analysis

Analyses were performed using SPSS Statistics (v27, IBM). Plots were created using GraphPad Prism (v7, GraphPad Software). Descriptive statistics were computed for baseline characteristics – data are presented as means ± standard deviations or median [interquartile range] for continuous variables, depending on data distribution, and as numbers (proportions) of patients for categorical and ordinal variables.

Responders and non-responders were classified based on the minimal important difference for improvement (MID = 5 points) of the Global QoL scale of the EORTC-QLQ-C30 (48) in T1 (i.e., after PHET and before surgery). Baseline differences between responders/non-responders were analyzed through independent samples t-tests, Mann–Whitney U tests, Chi-square/Fisher exact tests depending on data type/distribution. A statistical significance level of 0.05 was used. To identify potential predictors of response in T1, univariate regression models between each independent variable from baseline assessment (sociodemographic and clinical variables, physical performance assessment – ISWT, 5TSTS, handgrip strength –; HRQoL EORTC QLQ-C30 subscales) and the dichotomized variable of the difference (T1-T0) in Global QoL scale of the EORTC-QLQ-C30 (dependent variable) were computed. Predictor variables presenting a significant univariate association ($p<0.10$) (49) were examined in a binary logistic regression using the backward stepwise method to identify the main predictors. The logistic regression assumptions were verified.

Chi-square tests were performed to determine whether the response to PHET (i.e., 'responders' vs 'non-responders') was associated with clinically relevant changes in HRQoL ('deterioration' vs 'non-deterioration') following LC surgery (T2). 'Deterioration' vs 'non-deterioration' consists of the dichotomization of the difference between Global QoL in T2 and T0 using the MID for deterioration in Global QoL scale (-5 points) (48).

Results

Sample characteristics

Thirty-two participants were included in the analysis. Baseline characteristics of participants are presented in Table 2. Most participants were male (62.5%), had a mean age of 67.1±7.8 years, had a diagnosis of adenocarcinoma (75%) and underwent lobectomy (84.4%) via video-assisted thoracoscopic surgery (65.6%). Sociodemographic and clinical characteristics of participants are presented in Table 2.

Responders, Non-responders, and predictors of response

After PHET, 56.3% (n=18) of patients were responders in Global QoL. Baseline characteristics of responders and non-responders are presented in Table 2. The responders' group had a higher proportion of patients with COPD compared to the non-responders' group (50% vs.

7.1%, respectively; p=0.019). There were no other significant differences regarding sociodemographic variables and clinical variables including pulmonary function, type of surgery and type of cancer (p>0.05, Table 2). Results from physical performance assessments are presented in Table 3. There were no significant differences regarding physical performance outcomes (p>0.05).

Differences were found in EORTC-QLQ-C30 sub-scales (Table 4), with responders presenting lower scores in Global QoL (p=0.002), Emotional Function (p=0.0041) and Summary Score (p=0.04) when compared to non-responders. There were no other differences in EORTC-QLQ-C30 sub-scales, including symptom sub-scales (p>0.05).

Table 2 – Sociodemographic, clinical characteristics and differences between responders and non-responders according to Global QoL Scale of the EORTC-QLQ-C30 (n=32).

Variable	All participants (n=32) n (%)	Responders (n=18)	Non-Responders (n=14)	p- value
Mean Age (years)	67.1±7.8	65.2±8.1	69.5±6.9	0.120
Median BMI (Kg/m^2) [Q1-Q3]	25.8 [23.5-28.4]	25.7 [22.7-28.8]	26.3 [25-29.9]	0.301
Sex (male)	20 (62.5%)	10 (55.6%)	10 (71.4%)	0.157
Educational level (years)				0.077
< 10 years	21 (65.6)	11 (61.1%)	10 (71.4)	
≥ 10 years	11 (34.4)	7 (38.9%)	4 (28.6%)	
Smoking Status				0.149
Current	6 (18.8%)	2 (11.1%)	4 (28.6%)	
Former	15 (46.9%)	9 (50%)	6 (42.9%)	
Never	11 (34.4%)	7 (38.9%)	4 (28.6%)	
Comorbidities				
Hypertension	16 (50%)	9 (50%)	7 (50%)	1.000
COPD	10 (31.3%)	9 (50%)	1 (7.1%)	0.019*
Diabetes	4 (12.5%)	2 (11.1%)	2 (14.3%)	1.000
History of myocardial infarction	4 (12.5%)	2 (11.1%)	2 (14.3%)	1.000
Previous cancer	7 (21.9%)	3 (16.7%)	4 (28.6%)	0.669
Other	7(21.9%)	5 (27.8%)	2 (14.3%)	0.426
Mean Charlson Comorbidity Index (CCI) score	4.5±1.5	4.6±1.4	4.3±1.7	0.237
Mild comorbidities (CCI 1-2)	4 (12.5%)	1 (5.6%)	3 (21.4%)	
Moderate comorbidities (CCI 3-4)	11 (34.3%)	8 (44.4%)	3 (21.4%)	
Severe comorbidities (CCI≥5)	17 (53.1%)	9 (50%)	8 (57.1%)	
Mean Pulmonary Function				
FVC (% predicted)	94±11.8	91.8±11.7	96.7±11.8	0.275
FEV_1(% predicted)	82.3±18.9	76.8±20.9	89.4±13.7	0.071
DLCO (% predicted)	69.6±18.4	68.5±17.2	71.3±20.7	0.694
Type of Lung Cancer				0.142
NSCLC	84.4%	17 (94.4%)	71.4%	
Neuroendocrine	15.6%	1 (5.6%)	28.6%	
Histological Subtype				0.06
Adenocarcinoma	75%	15 (83.3%)	9 (64.3%)	

(continued)

Squamous cell carcinoma	6.3%	2 (11.1%)	-	
Typical carcinoid	9.4%	-	3 (21.4%)	
Atypical carcinoid	9.4%	1 (5.6%)	2 (14.3%)	
Resection degree				0.203
Lobectomy	84.4%	14 (77.8%)	13 (92.9%)	
Bi-lobectomy	3.1%	1 (5.6%)	-	
Segmentectomy	3.1%	-	1 (7.1%)	
Wedge resection	9.4%	3 (16.7%)	-	
Surgical Approach				0.446
VATS	21 (65.6%)	13 (72.2%)	8 (57.1%)	
Open thoracotomy	10 (31.3%)	4 (22.2%)	6 (42.9%)	
RATS	1 (3.1%)	1 (5.6%)	-	

Data are presented as mean ± standard deviation, median [interquartile range], or numbers (proportions). Legend: BMI, body mass index; COPD, chronic obstructive pulmonary disease; CCI, Charlson Comorbidity Index; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; DLCO, diffusion lung capacity for carbon monoxide; NSCLC, Non-small cell lung cancer; VATS, video-assisted thoracoscopic surgery; RATS, robot-assisted thoracoscopic surgery. *Significant at p<0.05

Table 3 - Physical performance outcomes and differences between responders and non-responders according to Global QoL Scale of the EORTC-QLQ-C30.

Variable		All participants (n=32)	Responders (n=18)	Non-Responders (n=14)	p-value
ISWT (m)		459.7 ± 184.9	480.8 ±229.4	432.5 ±106.2	0.472
5TST (s)		8.89±3.1	8.5±3.3	9.4±3	0.410
Handgrip strength (Kg)	**Left hand**	31.6±9.6	30.7±9.4	32.7±10.2	0.565
	Right hand	32.7±8.8	32.3±8.9	33.1±9	0.788

Data are presented as mean ± standard deviation. Legend: ISWT, Incremental Shuttle Walking Test; 5TST, 5 times sit-to-stand test; m, meters; s, seconds; kg, kilograms. *Significant at p<0.05

Table 4 - Baseline scores of the EORTC-QLQ-C30 scales and differences between Responders and Non-responders according to Global QoL Scale of the EORTC-QLQ-C30.

Variable	All participants (n=32)	Responders (n=18)	Non-Responders (n=14)	p-value
EORTC-QLQ-C30 scale				
Global QoL	62.33 [50-83]	50 [42-60.3]	83 [72.9-83.1]	0.002*
Physical Function	90 [80-93]	87 [78.3-100]	93 [80-93]	0.866
Emotional Function	75 [60.2-83.3]	67 [48-83]	83 [75-94]	0.0041*
Role Function	100 [83-100]	91.67 [79-100]	100 [100-100]	0.135
Cognitive Function	100 [83-100]	100 [83-100]	91.67 [79-100]	0.722
Social Function	100 [83-100]	100 [67-100]	100 [95.8-100]	0.235
Dyspnea	0 [0-24.8]	0 [0-33]	0 [0-0]	0.357
Fatigue	11 [0-30.3]	16.50 [0-24.9]	5.50 [0-33]	0.587
Pain	0 [0-17]	0 [0-17]	8.50 [0-17]	0.866
Nausea and vomiting	0 [0-0]	0 [0-0]	0 [0-0]	0.808
Insomnia	33.33 [0-33.3]	33.3 [0-75.3]	0 [0-33]	0.059
Appetite Loss	0 [0-0]	0 [0-0]	0 [0-0]	0.613
Constipation	0 [0-0]	0 [0-0]	0 [0-8.3]	0.925
Diarrhea	0 [0-0]	0 [0-0]	0 [0-0]	0.955
Financial Impact	0 [0-33]	0 [0-33]	0 [0-33]	0.896
Summary score	90.11 [82.3-93]	85.4 ±8	91.1± 6.4	0.04*

Data are presented as mean ± standard deviation or median [interquartile range]. *Significant at p<0.05

Predictors of response

The presence of COPD (p=0.009) and the variables FEV_1 (p=0.071), Emotional Function (p=0.036) and SumSc (p=0.04) were significantly associated with being a responder to PHET in Global QoL, in the univariate analysis. Since multicollinearity was found between COPD and FEV_1 and between Emotional Function and SumSc, the independent variables included in the model were SumSc and COPD.

The logistic regression model containing SumSc and COPD as independent variables was statistically significant ($\chi 2(4) = 12.1$, $p < 0.05$). The model explained 42.1% (Nagelkerke R^2) of being a responder in Global QoL and correctly classified 72% of the cases. In this model, COPD was the only significant predictor of being a responder to PHET (p=0.026). Patients with COPD were 13.4 times more likely to be a responder to PHET in preoperative Global QoL (OR=13.4; 95% CI 1.4; 132.2).

One month after surgery (T2), 62.5% (n=20) of patients maintained or improved Global QoL in relation to baseline (i.e., 'non-deterioration'). From these, 65% were responders in Global QoL to PHET in T1. In 37.5% of patients (n=12), a deterioration in Global QoL was observed after surgery, and 58.3% of these were patients who did not respond in Global QoL to PHET in T1.

There was no significant association between the response to PHET (i.e., 'responders' and 'non-responders') in T1 and Global QoL change in T2 ('deterioration' vs 'non-deterioration') (p=0.198). However, patients who responded to the PHET in the pre-surgical assessment tended to be those who maintained or improved Global QoL scores 1-month after surgery (Figure 1).

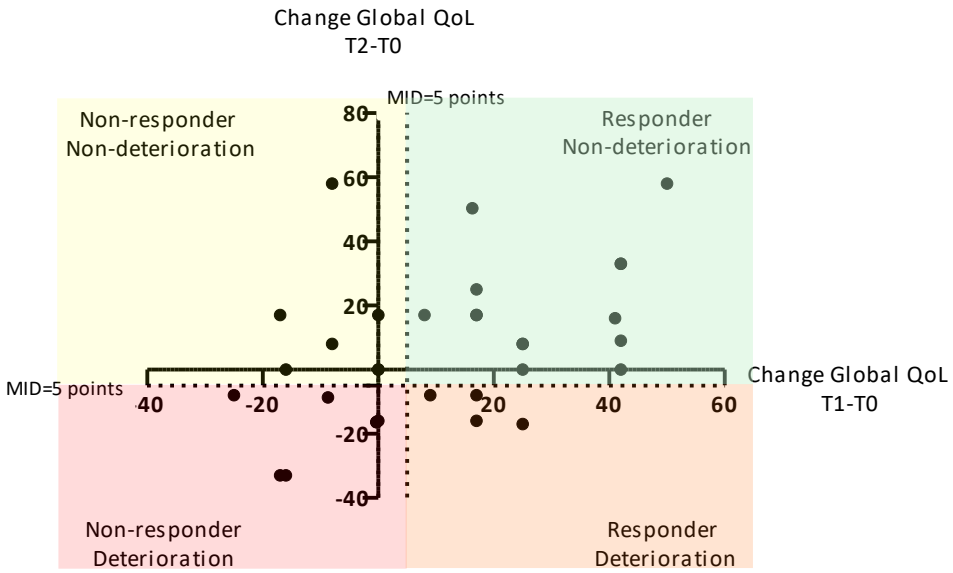

Figure 1 - Scatter plot with the distribution of responders vs. non-responders in Global QoL scale to the Preoperative Home-based Exercise Training (PHET) program (T1-T0), and patients who deteriorated vs. non-deteriorated in Global QoL scale score 1 month after surgery (T2-T0). X-axis – difference between T1 and T0 in the Global QoL scale scores; Y-axis – difference between T2 and T0 in the Global QoL scale scores. Dotted vertical line represents the minimal important difference for improvement (MID 5 points) of the Global QoL scale at T1. Dotted horizontal line represents MID for deterioration (-5 points) of the Global QoL scale at T2. Green shadow represents "responders" in T1 who maintained or improved Global QoL score in T2 compared to T0. Red shadow represents "non-responders" who deteriorated. Orange represents "responders" in T1 who deteriorated in T2. Yellow shadow represents "non-responders" who did not deteriorate at T2.

Discussion

This is the first study aiming to identify "responders" and "non-responders" and predictors of response to PHET in HRQoL among patients with LC awaiting surgery. Findings from this study suggest that there is a considerable proportion of patients who do not respond to the PHET in terms of Global QoL. Furthermore, we found significant between-group baseline differences in Global QoL, Summary Score and Emotional Function score, with responders presenting lower scores than non-responders. This group also had a higher proportion of patients with COPD than the non-responder group. Despite these baseline differences, only the presence of COPD was a significant predictor of response to PHET in Global QoL. Regarding the secondary aim of the study, there was no significant association between being a "responder" to PHET before surgery and not deteriorating Global QoL 1-month after surgery. However, there was a

trend indicating that patients exhibiting a positive response to PHET tended to not deteriorate in HRQoL at 1-month postoperative assessment.

Similarly to our findings, Huang et al. (2016) found that half of the subjects included in their study were defined as 'responders' to the individual exercise prehabilitation program, which included aerobic and resistance training. However, when comparing baseline characteristics between the 'responder' and 'non-responder' groups, no statistically significant differences were observed. It is important to note that the sample included patients with other types of cancer in addiction to LC. Moreocer, response to the exercise program was defined according to the cardiopulmonary exercise testing results and there were three different modes of delivery of the exercise program, according to patients' preference (home-, community- or hospital-based), which limits comparisons with the present study.

The results from our analysis suggest that patients awaiting LC surgery with COPD diagnosis are more likely to experience significant improvements in Global QoL after PHET. In fact, COPD and lung cancer frequently co-occur, with 40% to 70% of people with LC also being diagnosed with COPD (50). Treatment for LC coexisting with COPD is challenging, as COPD may increase postoperative morbidities and decrease survival (51). The present study showed that this group of patients may benefit more from a PHET in terms of QoL – this is a new finding that deserves further investigation in future studies.

The results obtained in our study suggest that functional performance and sociodemographic variables did not predict the response of HRQoL to the PHET. In previous clinical trials involving breast and prostate cancer patients, baseline demographic, clinical and psychosocial variables explained the heterogeneous effects found in HRQoL after an exercise training program (35, 36). Specifically, in the study of Buffart et al. (2015) found that beneficial effects of a 12-month exercise program on HRQoL in older long-term survivors of prostate cancer could partially be explained by exercise-induced improvements in lower body functional performance (35). In the study of Courneya et al (2008) with patients with breast cancer, marital status influenced the response in QoL to an exercise training intervention. However, these patients were in different stages of cancer (not in the surgical period) which may impact functional status and HRQoL. This hinders comparisons with findings from our study.

This study also showed a tendency to patients who exhibited a positive response to PHET not to deteriorate in HRQoL at 1-month post-surgery. Evidence on the field of prehabilitation for cancer resection has been growing, but it is still in the beginning. Most of the existing literature in this field is from small, underpowered trials, implementing heterogenous protocols and interventions, and there is still a lack of studies exploring predictors of response to prehabilitation exercise interventions (39).

Thus, identifying cancer patients most likely to benefit from prehabilitation is now one of the research priorities (39). Responder analysis through dichotomization of the interest outcome into “responders” and “non-responders” is a common methodology used to explore this topic of inter-individual response to exercise interventions (38). However, some caution should be taken when interpreting results, and some arguments can be made. One issue relates to the inherent variability of intra-individual adaptive responses, as it remains unclear whether exercise responsiveness is a permanent or temporary phenomenon. Therefore, it may be preferable to label patients who exhibit no measurable improvement in each variable as those who “did not respond” rather than “non-responder”, since it is more coherent with the time frame of evaluation – i.e. the patient “did not respond” on that assessment timepoint, however, it could be changeable, not permanent as the connotation given by “non-responder” (52). Another issue is related to the measurement errors inherent to the instruments and the random within-subject variation. Such confounders might represent “false” individual variation which potentially leads to the misidentification of individuals as “non-responders”. It has been proposed to compare standard deviations of the intervention group to a control/comparator group and thus a “true” individual variation could be acknowledged (52).

Additionally, future studies should explore exercise dose since this is a potential factor influencing not only Global QoL response but also other important outcomes to the preoperative exercise program. Adopting metrics that capture the actual exercise dose achieved during each session (e.g., intensity, time, volume) across a program may have important moderating effects on outcomes.

Strengths and Limitations of the Study

This study has some limitations that need to be acknowledged. Specifically, the small sample and the exclusion of patients who received neoadjuvant treatment, which limit the generalization of findings to these subgroups of individuals. The strengths of this study include the definition of the "response threshold" based on a stablished value, the MID for improvement in Global QoL for patients with LC, instead of an arbitrary measure of improvement (either absolute or relative). However, arguments could be made for the most appropriate subscale and respective MID. Specifically, the study aimed to explore the response of HRQoL to PHET using the Global QoL Scale, which is only one measure provided by the EORTC QLQ C30 – it was chosen given its overall assessment of patient's perceived health and QoL, considering physical, emotional, and social aspects. However, the Summary Score has been reported to be more sensitive than the Global QoL Scale score for assessing QoL decline during the 3 months after surgery for lung cancer (53). Nevertheless, to the best of authors' knowledge, the MID of the SumSc has not been yet determined which limits its use to identify clinically meaningful response to interventions.

Conclusion

The current study showed most patients respond to the PHET, yet there are still non-responders. Patients with LC and COPD seem to be more likely to respond to the intervention in terms of Global QoL. Future studies should explore other predictors of response to PHET in larger samples, and include patients who received neoadjuvant treatment, as a large proportion of patients may receive this intervention in addition to surgery. This study also showed a tendency for responders to (at least) maintain baseline values of HRQoL at 1 month after surgery. Future studies should explore the longitudinal trajectory of HRQoL in patients who respond and do not respond to prehabilitation in order to identify the best candidates for this type of intervention. The exercise training dose and mode of delivery should also be explored to improve healthcare access and quality.

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Appendices

Appendix 1. Ethical approval

IPO COIMBRA

Qualidade
Um Compromisso

Parecer Final da Comissão de Ética

Trabalho de Investigação nº: TI 36/2021

Data: 08/11/2021

Apreciado na reunião da Comissão de Ética de 18/11/2021, o projeto *OncoEnergy*: Efeito de um programa de exercício físico pré-operatório na qualidade de vida após a cirurgia de cancro do pulmão e cancro colorretal foi aprovado por unanimidade dos/as presentes.....

PEL'A COMISSÃO DE ÉTICA

(*) Indicar o resultado da votação de **aprovação** ou **rejeição** e se por unanimidade ou maioria, assinalando e juntando as declarações de voto que houver.

CENTRO HOSPITALAR LEIRIA

CI - Centro de Investigação
Ref.ª 04/2022

DELIBERAÇÃO DO Conselho de Administração Acta nº 12022/01/05
Aprovado
22.01.05

Para CA.
Alexandra Borges
Vogal Executiva
2022/01/04

Exmo. Senhor
Presidente do Conselho de Administração
Centro Hospitalar de Leiria, E.P.E.

O Conselho de Administração
...nio de Carvalho
...Presidente
...Alexandra Borges
...gal Executiva
...Ilvato Feijó
...etor Clínico
...ília Fael
... Diretora
...Vogal Executiva

Leiria, 04 de janeiro de 2022

Assunto: Estudo intitulado "OncoEnergy: Effect of preoperative home-based exercise programo n quality of life after colorectal and lung cancer surgery." submetido pela Dra. Joana Patrícia dos Santos Cruz, Professora Adjunta da ESSLEI – IPL do Centro de Inovação em Tecnologias e Cuidados de Saude (ciTechCare), a desenvolver no serviço de Pneumologia e Cirugia Geral.

De acordo com o Procedimento Interno "Aprovação de estudos e projetos de Investigação", em vigor desde 2016.03.07, informa-se que o estudo mencionado em epígrafe está devidamente instruído de acordo com os elementos assinalados na Listagem de Documentos e Validação, em anexo.

Considerando que o estudo pretende desenvolver um programa de exercícios que é aplicado em formato home-based aos participantes, que todo o acompanhamento destes participantes será realizado através de questionários ou consultas programadas nos cuidados de saúde e são aplicados os pressupostos das Boas Práticas para a Investigação Clínica, o mesmo não colide com as medidas do Plano de Contingência, para a COVID-19, atualmente em vigor no CHL.

Mais se informa que o presente estudo obteve o parecer favorável pela Comissão de Ética, de acordo com a Ata n.º 10 de 2021.12.14. Neste sentido, submete-se o pedido anexo para decisão final do Conselho de Administração.

Com os melhores cumprimentos,

O COORDENADOR DO CENTRO DE INVESTIGAÇÃO

(JOÃO MORAIS)

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Revisão 2022.01.04 Psc

Original e Investigador
2022.01.06 Elisabete

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

HDFF Hospital Distrital da Figueira da Foz, E.P.E.

COMISSÃO DE ÉTICA

DECLARAÇÃO

Para os devidos efeitos declara-se que, após análise dos documentos do **Estudo OncoEnergy**, referencia CiC - **OBS_CIC.12 |2022**, do aluno de Doutoramento Pedro Filipe André Machado, do IP de Leiria, em que o Investigador responsável no HDFF é a Dra. Maria Vitória Martins de Pneumologia, esta Comissão considerou não haver qualquer impedimento para a sua execução, uma vez que se encontra no estrito cumprimento das normas internas instituídas.

A Presidente da Comissão de Ética

Mª Teresa Simões Pereira

REPÚBLICA PORTUGUESA
SAÚDE

SNS SERVIÇO NACIONAL DE SAÚDE

HDS Hospital Distrital de Santarém

Santarém, 22 de abril de 2022

Apreciação e Votação do Parecer

A Comissão de Ética apreciou o pedido de autorização para a realização da investigação a desenvolver no HDS, no Serviço de Pneumologia, com o título "**Efeito de um programa de exercício físico pré op na qualidade de vida após o tratamento cirúrgico de cancro do pulmão (oncoEnergy)**", pelo Técnico Pedro Filipe André Machado. A Comissão de Ética apreciou o pedido de autorização para realização do estudo depois de reunida toda a documentação necessária. Na sua análise não identificou matéria que ofenda os princípios éticos e morais, sendo de parecer que o estudo em causa pode ser aprovado.

O processo foi votado pelos Membros da Comissão de Ética do HDS

RESULTADO DA VOTAÇÃO: **PARECER FAVORÁVEL**

O Presidente da Comissão de Ética

Dr. Paulo Sintra

Mod. HDS – 134-A.21

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Appendix 2. Informed consent of the feasibility trial

CONSENTIMENTO INFORMADO,
LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM INVESTIGAÇÃO

Por favor, leia com atenção a seguinte informação. Se concordar com a proposta, queira por favor assinar este documento.

Título do estudo: Efeito de um programa de exercício físico pré-operatório na qualidade de vida após a cirurgia de cancro do pulmão e cancro colorretal (OncoEnergy)

Somos um grupo de investigadores que está a desenvolver um estudo no âmbito de um projeto de doutoramento (Universidade de Coimbra) que **tem como principal objetivo** avaliar o impacto de um programa de exercício físico pré-operatório na recuperação após a cirurgia em pacientes diagnosticados com cancro do pulmão ou cancro colorretal. Este programa de exercício físico será realizado em casa, nas 3 a 4 semanas que antecedem a cirurgia e terá supervisão telefónica semanal de um fisioterapeuta.
Assim, e para atingir o objetivo do estudo, solicitamos-lhe que realize os exercícios que lhe serão explicados pelo fisioterapeuta numa consulta médica pré-operatória. Além disso, ser-lhe-á pedido que responda a dois questionários e efetue alguns testes físicos, que serão realizados por profissionais devidamente treinados para o efeito. A resposta aos questionários e testes físicos será realizada em três momentos: 1º) antes de iniciar o programa de exercício físico, 2º) após o programa de exercício físico, 3º) um mês após a cirurgia.
Este estudo mereceu parecer favorável da Comissão de Ética e da Direção da instituição onde está a ser recrutado. A sua participação é voluntária e todas os dados obtidos são anónimos e confidenciais, serão apenas utilizados para fins da investigação (tese de doutoramento, comunicações em congressos e artigos científicos), estando em todos os momentos assegurada a sua privacidade. Neste sentido, em qualquer momento pode interromper a sua participação, sem qualquer tipo de prejuízo. Caso necessite de algum esclarecimento adicional, não hesite em contactar:

Joana Cruz (Investigadora Principal), E-mail: joana.cruz@ipleiria.pt, Telemóvel: 969 196 218
Pedro Machado (estudante de doutoramento), E-mail: pedro.machado@ipleiria.pt, Telemóvel: 912967214

Obrigado pela sua colaboração.
Nome do Investigador(a): _____

Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pela(s) pessoa(s) que acima assina(m). Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências. Desta forma, aceito participar neste estudo e permito a utilização de dados, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pelos investigadores.
Nome:_____
Assinatura:_____
Data:_____/_____/_____

Appendix 3. Informed consent of the randomized controlled trial

CONSENTIMENTO INFORMADO,
LIVRE E ESCLARECIDO PARA PARTICIPAÇÃO EM INVESTIGAÇÃO

Por favor, leia com atenção a seguinte informação. Se concordar com a proposta, queira por favor assinar este documento.

Título do estudo: Efeito de um programa de exercício físico pré-operatório na qualidade de vida após a cirurgia de cancro do pulmão e cancro colorretal (OncoEnergy)

Somos um grupo de investigadores que está a desenvolver um estudo no âmbito de um projeto de doutoramento (Universidade de Coimbra) que **tem como principal objetivo** avaliar o impacto de um programa de exercício físico pré-operatório na recuperação após a cirurgia em pacientes diagnosticados com cancro do pulmão ou cancro colorretal. Este programa de exercício físico será realizado em casa, nas 3 a 4 semanas que antecedem a cirurgia e terá supervisão telefónica semanal de um fisioterapeuta.

Para atingir o objetivo do estudo, todos os pacientes serão divididos aleatoriamente, num grupo que realizará o programa de exercício pré-operatório de 3 a 4 semanas ou num grupo que receberá os cuidados pré-operatórios usuais na instituição onde será operado. Todos os participantes receberão uma chamada telefónica semanal com o objetivo de supervisionar o pograma de exercício físico ou, no caso de integrar o grupo que receberá os cuidados pré-operatórios usuais, a chamada visará a monitorização de sintomas (dor, fadiga e dispneia). Além disso, ser-lhe-á solicitado que responda a algumas perguntas e efetue alguns testes físicos, que serão realizados por profissionais devidamente treinados para o efeito. Os questionários e os testes físicos serão aplicados em quatro momentos: 1º) quatro semanas antes da cirurgia, 2º) na última consulta antes da cirurgia, 3º) um mês após a cirurgia, 4º) três meses após a cirurgia.

Este estudo mereceu parecer favorável da Comissão de Ética e da Direção da instituição onde está a ser recrutado. A sua participação é voluntária e todas as informações obtidas através desta entrevista são anónimas e confidenciais e serão apenas utilizadas para fins da investigação (tese de doutoramento, comunicações em congressos e artigos científicos), estando em todos os momentos assegurada a sua privacidade. Neste sentido, em qualquer momento pode interromper a sua participação, sem qualquer tipo de prejuízo. Caso necessite de algum esclarecimento adicional, não hesite em contactar:

Joana Cruz (Investigadora Principal), E-mail: joana.cruz@ipleiria.pt, Telemóvel: 969 196 218
Pedro Machado (estudante de doutoramento), E-mail: pedro.machado@ipleiria.pt, Telemóvel: 912967214

Obrigado pela sua colaboração.
Nome do Investigador(a): _____

Declaro ter lido e compreendido este documento, bem como as informações verbais que me foram fornecidas pela(s) pessoa(s) que acima assina(m). Foi-me garantida a possibilidade de, em qualquer altura, recusar participar neste estudo sem qualquer tipo de consequências. Desta forma, aceito participar neste estudo e permito a utilização de dados, confiando em que apenas serão utilizados para esta investigação e nas garantias de confidencialidade e anonimato que me são dadas pelos investigadores.

Nome:_____
Assinatura:_____
Data:_____/_____/_____