My-PEP: a prehabilitation intervention in oesophageal cancer patients.

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Background

Oesophageal cancer is the seventh most commonly occurring cancer (572 000 new cases in 2018) and the sixth leading cause of cancer death (509 000 deaths in 2018) worldwide (Bray et al., 2018). Whenever possible, oesophageal resection and reconstruction (oesophagectomy) is currently the recommended treatment modality (Best, Mughal, & Gurusamy, 2016), but carries a high risk of postoperative complications that impact patient quality of life, cancer recurrence/survival, hospital costs and resources. Most of the complications in patients undergoing oesophagectomy (e.g. atrial fibrillation, pneumonia) affect the cardiopulmonary system (Oxenberg, 2018).

Exercise results in a greater cardiac output, improved respiratory muscle strength and skeletal muscle adaptations (Rivera-Brown & Frontera, 2012). Exercise as part of prehabilitation (i.e. the process of providing patients with a reserve to withstand the stress of major cancer surgery; Wynter-Blyth & Moorthy, 2017) has been proposed to counteract the surgical consequences of anaesthesia, tissue trauma and bed-rest (Vermillion et al., 2018). Several studies on prehabilitation in patients undergoing thoracic and gastrointestinal cancer resection have demonstrated an increase in preoperative physical fitness and physical activity, as well as decreased postoperative complications with shorter hospital stay (for some recent reviews see Doganay & Moorthy, 2019; Vermillion et al., 2018).

Many potentially effective prehabilitation interventions may not succeed, simply because patients fail to adopt and maintain the prescribed behaviour (viz. regular exercise). The development of a theoretical understanding of the likely process of change, drawn on

existing evidence and theory, has been advocated as an integral step in complex intervention (i.e. interventions that contain several interacting components; Craig et al., 2007) design and evaluation by the UK Medical Research Council (Craig et al., 2007; Glanz & Bishop, 2010). However, choosing a relevant theory (among many theories) can be a challenging task. Despite controversial (see Odgen, 2016), a comprehensive supra-theory model of behaviour applicable across contexts might be useful in behavioural intervention design and evaluation.

According to COM-B model (Michie, Campbell, West, Brown, & Gainforth, 2014), for any behaviour to occur (*B*) at a given moment, there must be the capability (*C*; i.e. psychological and physical abilities to perform a behaviour) and opportunity (*O*; i.e. physical and social environmental factors that facilitate engagement in the behaviour), and the strength of motivation (*M*; i.e. reflective and automatic brain processes that energise and direct behaviour) to engage in it must be greater than for any competing behaviours. The model was developed to guide understanding of behaviour in context and to present behavioural determinants targets for intervention design. Moreover, it sits at the centre of the Behaviour Change Wheel (BCW; Michie, Atkins, & West, 2014) which is a framework proposed to help intervention designers move from a behavioural analysis of the problem (i.e. what needs to shift in order for the desired behaviour to occur?) to intervention design (i.e. how can it be effectively done: relevant intervention functions, behaviour change techniques, mode of delivery?). The application of BCW to the development of complex interventions has increased in popularity over recent years (e.g. Barker, Atkins, & Lusignan, 2016; McEvoy et al., 2018).

My-PEP description. A preoperative personalised programme (*my-PEP*)[1] was designed by a multidisciplinary team (e.g. physiotherapists, clinicians, psychologists) to increase physical fitness in adults with oesophageal adenocarcinoma during the preoperative phase (a

[1] A more detailed description of *my-PEP* can be found in the *ExPO Trial Protocol* (available from the corresponding author).

period of approximately 14-16 weeks). This prehabilitation intervention was theoretically grounded in BCW and comprised two major components: exercise and psychological support to adopt and maintain the prescribed exercise. The exercise component consisted of home-based inspiratory muscle training with a device (up to 20 min per day), during and after neoadjuvant chemotherapy, and hospital-supervised sessions of aerobic exercise and muscle strengthening (60 to 90-min sessions, 2 sessions per week for 4 weeks), after neoadjuvant chemotherapy. The psychological component was operationalised through behaviour change techniques and delivered before and during hospital-supervised exercise sessions. In addition, both components were tailored to patient's capability (e.g. knowledge, skills, stamina), opportunity (e.g. time, social support) and motivation (e.g. desires, reflex responses, evaluations, self-conscious planning) needs, formally assessed by questionnaire and interview at baseline. Therefore, for instance, a frail patient with low self-efficacy and a discouraging environmental context to exercise was offered a prehabilitation intervention with suitable intensity and duration levels of exercise, as well as a set of behaviour change techniques aimed at creating more positive self-beliefs about capabilities (e.g. focus on past success, social comparison, verbal persuasion about capability) and increasing opportunity (e.g. restructuring physical environment, use of prompts/cues).

The purpose of this paper is to present feasibility data of *my-PEP* that will potentially justify and inform a future randomised controlled trial to determine if this prehabilitation intervention decreases postoperative cardiopulmonary complications.

Methods

Design. A single centre, parallel group, single-blinded, randomised controlled trial (NCT02962219) was carried out to produce primary (viz. patients' eligibility; trial recruitment and retention; *my-PEP* adherence and safety) and secondary (viz. reasons for non-

participation in the study; group differences in physical activity, physiological fitness, quality of life, postoperative cardiopulmonary complications[2]) outcomes and conducted in the department of Upper Gastrointestinal Surgery at the Norfolk and Norwich University Hospitals Foundation Trust (NNUH), Norwich, United Kingdom.

Participants. Adult patients with histology proven oesophageal adenocarcinoma planned for both neoadjuvant chemotherapy and oesophagectomy, capable of giving informed consent and complying with trial procedures (e.g. without concomitant illness or disability that would make them unsuitable for exercise).

Materials. In order to determine any changes in physical activity, physiological fitness and quality of life over time, measurements were taken both prior to commencement of neoadjuvant chemotherapy and one week prior to surgery, using a few questionnaires – International Physical Activity Questionnaire short version (IPAQ), European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core-30 (EORTC QLQ-C30), EORTC QLQ Oesophago-Gastric module (EORTC QLQ-OG25) – and a cardiopulmonary exercise (CPEX) test that would provide measures of fitness[3]. For the purpose of comparing groups of patients (viz. willing vs. not willing to join the trial, intervention vs. control) sociodemographic and clinical data were collected by a pseudo-anonymised form – ExPO Patient Recruitment Identification Form (PRIF) – at recruitment. Determinants of Physical Activity Questionnaire (DPAQ) was used at baseline so that patients allocated in the intervention arm could have their personal barriers and facilitators to perform physical activity addressed or encouraged during *my-PEP*. A diary was also given to these patients to record home-based exercise sessions adherence and adverse reactions. Thirty-day postoperative morbidity was measured by hand review of the medical notes.

[2] This measure was used to provide information about *my-PEP* safety rather than its efficacy.
[3] Fitness was operationalised as VO_{2peak} (the maximal oxygen consumed at peak exercise) and VO_{2AT} (oxygen consumed at estimated anaerobic threshold).

Procedures. Patients were identified at weekly NNUH oesophagogastric cancer specialist multidisciplinary team meetings between October 2016 and June 2017. Written informed consent was obtained from the patients who met the inclusion criteria. Consenting participants were asked to complete PRIF, IPAQ, EORTC QLQ-C30 and -OG25, and to perform a CPEX prior to commencement of neoadjuvant chemotherapy. Based on CPEX results, participants were stratified into *high* and *low* fitness score groups (to help equally distribute those with a *low* level of fitness between trial arms, reducing the risk of selection bias) and randomised afterwards. Randomisation was done by a statistician on a 1:1 basis into intervention and control arms using random block sizes (known only to the statistician) generated by computerised randomisation. Both arms received usual standard care advice (in written form) to exercise at home during the preoperative phase. In addition to this, patients allocated in the intervention arm were offered *my-PEP* components (based on DPAQ results) and given the exercise diary. One week prior to surgery, all participants were asked to complete the second IPAQ, EORTC QLQ-C30 and -OG25, and to perform another CPEX. After oesophagectomy 30-day postoperative morbidity measurement was taken for all patients.

All statistical analyses were performed using a standard software package (Stata v.15.0). Descriptive statistics were generated for participants in each of the two arms (absolute frequencies and percentages for categorical variables; means and standard deviations or medians and interquartile ranges for continuous variables, depending on their distributions). Equivalence between groups, regarding sociodemographic and clinical data, was attested by means of Fisher exact test (or its Freeman-Halton extension, for 2x3 contingency table) and Student test. Mean differences between groups, concerning pretest to post-test changes, were compared using Student test. All tests were two-tailed and the significance was set at $p \leq .05$.

Results

Primary outcomes. During the recruitment period, 20 eligible patients were approached but only 11 were recruited (recruitment rate: 55%) because 7 did not want to participate for different reasons (e.g. unwilling to travel for hospital sessions, no need of additional support to engage in exercise, dislike for exercise) and 2 patients who were willing to participate were excluded as CPEX testing was unable to be arranged. The sociodemographic and clinical characteristics of both willing and non-willing patients were similar[4].

Table 1. Baseline sociodemographic and clinical characteristics of the allocated participants.

	Male gender	Age (years)	Smoking status	BMI (Kg/m^3)	T staging	N staging	CAD	Ht
Intervention	4(80)	66.3±9.4	N: 3(60) F: 1(20) C: 1(20)	27.1±4.4	T3: 5(100) T4: 0(0)	N0: 3(60) N1: 1(20) N2: 1(20)	1(20)	1(20)
Control	6(100)	65.4±9.1	N: 1(17) F: 3(50) C: 2(33)	27.0±4.4	T3: 5(83) T4: 1(17)	N0: 1(17) N1: 2(33) N2: 3(50)	0(0)	1(17)

Note. $n_{intervention}$ = 5 and $n_{control}$ = 6. N = Never, F = Former, C = Current, BMI = Body Mass Index, CAD = Coronary Artery Disease, Ht = Hypertension. Data shown are *f* (%) or *M*±*SD*.

All recruited patients were randomised (5 to the intervention group, 6 to the control group; see Table 1) after providing consent for participation and completed the trial (retention rate: 100%). The hospital-supervised exercise sessions offered (Mdn = 5, IQR = 4-5) were fully attended (attendance rate: 100%) by the intervention group who adhere completely to the personalised aerobic and muscle strengthening exercises (adherence rate: 100%). It was not feasible to offer the maximum 8 sessions to any of the patients, due to the earlier than anticipated scheduling of either surgery or second CPEX test. Adherence to home-based exercise sessions (i.e. inspiratory muscle training and exercise according to standard care advice) in the intervention group was low (adherence rate: 25% to 49%), owing to the side effects of chemotherapy (viz. fatigue; nausea and vomiting; mouth problems such as "dry mouth", "mouth ulcers", "cold sores"). No adverse reactions to exercise were reported.

[4] The details of this comparison can be found elsewhere (Lam, 2018).

Secondary outcomes. Despite promising gains in intervention group's physical activity, physiological fitness and quality of life (see Table 2), there were no statistically significant differences between arms regarding these variables ($.12 \geq p \geq .61$). The 30-day postoperative cardiopulmonary complication rates were also similar between arms (viz. intervention group: 60%; control group: 67%). No deaths occurred at 30 days.

Table 2. Baseline values and changes in secondary outcome variables of the allocated participants.

		Intervention		Control	
		Baseline	Δ	Baseline	Δ
Physical activity (MET-min/week)		819±1446	+883±1893	1600±1549	-432±315
Fitness (mL/Kg/min)	VO_{2peak}	21.4±6.4	+2.0±1.4	22.6±6.4	+0.3±3.2
	VO_{2AT}	12.8±1.7	+1.5±1.1	13.3±1.6	-1.2±2.3
Quality of life	QLQ-C30	78.2±14.0	+2.0±1.5	75.0±13.0	-3.0±2.9
	QLQ-OG25	34.4±14.9	+5.0±15.0	34.9±13.8	-13.0±7.4

Note. $n_{intervention} = 5$ and $n_{control} = 6$. MET = Multiples of the resting metabolic rate. Data shown are *M*±*SD*.

Discussion

These findings provided 'proof of concept' for a larger feasibility randomised controlled trial. Firstly, all patients referred for neoadjuvant chemotherapy and oesophagectomy were eligible for the trial, could be recruited in reasonable numbers and engaged easily until the end of the study period. Secondly, *my-PEP* exercise sessions were safe and well tolerated, with no significant adverse effects reported during the intervention or after the oesophagectomy, and patients adhered particularly well to the hospital-based sessions. At last, whilst there were important improvements in intervention group's physical activity, physiological fitness and quality of life, this study was unable to demonstrate statistically significant differences due to small patient numbers.

Strengths of this study included the design of a programme tailored to each patient's (physical, psychological and environmental) needs, which also had the input of both professionals and patients. Weakness of this study comprised a small sample size (due to a much lower than anticipated number of oesophagectomies over the recruitment period and

logistic problems with arranging baseline CPEX testing for potential participants who wanted to join the trial) and its single centre nature (i.e. patients from Norfolk may not be representative of those in other areas of the UK, particularly from more urban areas, limiting generalisation of the study conclusions).

On that account, a larger sample from several centres will be required in a definitive feasibility randomised controlled trial. Additional measures to improve recruitment in future work could include (1) the capacity to offer supervised exercise sessions closer to patients' homes (e.g. in primary care centres), as a long travel distance was the commonest reason for non-participation, and (2) an alternative method of measuring physiological fitness (e.g. 6-minute walk test; American Thoracic Society, 2002) to avoid CPEX laboratory logistic issues. Also, adherence to home-based exercise sessions may also benefit from a more regular support or contact from the trial team – through weekly telephone calls, for example (Wynter-Blyth & Moorthy, 2017).

In sum, it was demonstrated that *my-PEP* is viable, safe and well adhered to, but needs a larger feasibility study in patients with oesophageal adenocarcinoma undergoing chemotherapy to investigate whether their fitness can be improved in the short time between neoadjuvant chemotherapy and surgery by the intervention. Such feasibility data is required prior to a full randomised controlled trial investigating whether *my-PEP* can reduce the incidence of postoperative complications.

Acknowledgements

The author would like to thank Dr S. Lam for the valuable contribution he has made to the manuscript.

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