Final Report
Executive Summary

HSC Public Health Agency
Research and Development

HSC R&D Division Final Progress Report

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HSC Public Health Agency
Research and Development

HSC R&D Division Award Details

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HSC Public Health Agency
Research and Development

Evidence Brief

(1 page: which may be used for dissemination by HSC R&D Division)

Why did we start?

(The need for the research and/or Why the work was commissioned)

People living with and beyond cancer experience numerous disease and treatment toxicities. Exercise training has been shown to be an effective strategy in disease management, leading to physiological and psychological benefits that can prevent inevitable decline and attenuate the severity of several toxicities. However, to date, most evidence has been collected in the most common cancers e.g. breast and colorectal, and in the early stages of the disease. There is little consensus around key delivery parameters such as the optimal exercise dose and the level of supervision that is required.

What did we do?

(Methods)

We undertook an extensive programme of work in exercise oncology. This programme involved delivering a number of exercise trials in various cancer populations: a global trial of high intensity interval training in advanced prostate cancer (INTERVAL-MCRPC); a home-based moderate intensity programme for men with prostate cancer who were ineligible for the INTERVAL study; and a supervised exercise trial for individuals with pancreatic cancer undergoing chemotherapy post-surgery. The research fellow also delivered the NI component of moderate intensity training in colon cancer survivors (CHALLENGE-UK).

What answer did we get?

(Findings)

This programme of work has demonstrated individuals with advanced cancer can undertake an individualised, prescribed exercise programme.

Home-based exercise training, with weekly remote monitoring, was feasible and safe for men with metastatic prostate cancer.

In addition, concurrent exercise training during adjuvant therapy for pancreatic cancer is safe, feasible and well tolerated and may prevent expected declines in functionality, muscular strength and quality of life.

What should be done now?

(Practice/Policy Implications and/or Recommendations)

An implementation project designed to understand how exercise can be successfully embedded into the cancer patient pathway throughout Northern Ireland is needed.

This would involve a screening and triaging process to identify those individuals with cancer who should be referred to three levels of exercise intervention: low risk self-managed home-based exercise, moderate risk (symptoms or co-morbidities) group-based supervised exercise, and high risk one to one supervision.

Final Report

(no more than 20 pages)

Please structure the report using the headings below

The team received funding from the PHA to deliver two prostate cancer exercise trials (INTERVAL GAP4 (study 1) and EXACT (study 2)). There was an expectation and allowance that the Research Fellow would also contribute more broadly to the exercise oncology programme based in QUB, this was successfully implemented with funding secured from Pancreatic Cancer UK (PCUK) for a trial of exercise in pancreatic cancer (PRECISE, study 3), the Research Fellow was involved in the grant application and led the delivery of this trial. Further detail of additional activities and capacity development are described at the end of the report (including the delivery of CHALLENGE-UK, a global trial of exercise in colorectal cancer survivors; co-design of an exercise intervention for individuals with prostate cancer immediately prior to radiotherapy; successful grant applications; publications; PhD/Masters supervision and teaching).

Background

Early detection and advances in cancer treatment, alongside conventional therapies have improved survival outcomes for the most prominent cancers. As such, there is now a greater proportion of survivors living with and beyond their cancer. The National Cancer Research Institute (NCRI) report that by 2030, four million people in the UK will be living with the long-term effects of cancer[1]. Managing this patient population poses a unique challenge, given many will suffer the ongoing burden of treatment-related toxicities. The priority in this phase is to improve the overall quality of their survivorship and attempting, where possible, to offset cancer-related consequences. In recent years, physical activity (any bodily movement involving skeletal muscular contraction that results in energy expenditure above rest) or indeed exercise training (planned, structured and repetitive activity to improve or maintain physical fitness) has garnered growing recognition as an effective therapy in cancer care. Exercise oncology research has exponentially increased over the past two decades, with accumulating evidence-based findings advocating exercise training throughout the cancer continuum[2]. Cancer-specific guidelines suggest patients should be as active as possible, with a minimum recommendation of 30 mins aerobic exercise 3 days weekly and 2 days of resistance training[3]. Exercise training has been shown to be a safe, feasible and effective therapeutic strategy in disease management, invoking several physiological and psychological benefits that can prevent inevitable decline and attenuate the severity of several toxicities. Aerobic, resistance and mindfulness-based interventions, either in isolation or combined, have proved effective in various cancer populations[4-6], in improving cardiorespiratory/functional fitness; muscular strength and lean body mass; bone health; sleep and fatigue and mental health. There is also a reduced risk of disease recurrence, risk of comorbidities and improved survival[7].

Prostate cancer

Prostate cancer (PC) is the most diagnosed male malignancy in Europe[8]. Approximately 20% of cases present with advanced disease characterised by metastatic progression. Androgen deprivation therapy (ADT) alongside androgen receptor pathway inhibitors (e.g. abiraterone acetate; enzalutamide) is standard of care for metastatic castrate resistant prostate cancer (mCRPC) and confers significant survival benefits. Despite this mCRPC remains incurable[9] and men endure a

substantial number of treatment-related toxicities (i.e. fatigue; increased fat mass; decreased fitness; depression), impacting their quality of life. With the increasing incidence and improved overall survival rates, more men are now living with mCRPC and its treatment-related toxicities. Thus, managing this population is complex and poses a significant challenge for clinicians, with a strong emphasis placed on delaying progression, counteracting side effects and improving the quality of survivorship.

Accumulating evidence suggests that exercise training is an effective adjuvant therapy for men with PC. Clinical trials have shown exercise is safe and effective in improving cardiorespiratory fitness, muscular strength, quality of life and fatigue, in men with PC actively receiving treatment[10-12]. However, evidence in advanced PC remains limited. Preliminary evidence shows supervised exercise training for patients with metastatic disease confers similar benefits, to those with localised disease[14-15]. Importantly, exercise training in this advanced group is safe and well tolerated, with high compliance and retention rates[14].

Study 1

Movember GAP4: INTERVAL – MCRPC: INtense Exercise for survival with Metastatic Castrate-Resistant Prostate Cancer: a multicentre, randomised, controlled, phase III study.

Through a global collaboration, Movember executed a large-scale multi-centre trial designed to test the effects of exercise on prostate cancer progression and treatment side effects. QUB and the Northern Ireland Cancer Centre (NICC) was provided with the opportunity to act as a recruitment site to contribute to this global study and was tasked with recruiting 45 men with mCRPC.

There were significant delays in gaining approvals for the trial to open due to the need for a four-way contract between QUB, Guys and St Thomas', the Belfast Trust and Movember. The project opened to recruitment in February 2019 with the first person randomised in March 2019.In 12 months, 9 potential participants were screened, but 7 of these were screen fails. This pattern was reflected globally and to manage this Movember extended the inclusion criteria to hormone sensitive prostate cancer in 2020. The UK faced a protracted period to gain ethical approval to amend the inclusion criteria to the hormone sensitive group (was still not granted in 2022). COVID-19 halted recruitment globally in 2020 and once restrictions permitted, there were many challenges to reopening due to the aerosol generating procedures required for screening (CPET). Despite extensive work from the team to secure additional funding, numerous risk assessments to allow CPET testing to recommence, Movember made the decision to close the trial globally to recruitment in November 2022. The trial was therefore not reopened in Belfast following the lifting of COVID-19 restrictions.

In spite of the challenges encountered with the INTERVAL-MCRPC study, the team were successful in delivering a number of other exercise trials throughout the COVID-19 pandemic. These are detailed in this report (EXACT, PRECISE and CHALLENGE-UK).

Study 2:

Exercise for advanced prostate cancer: a multicomponent, feasibility, trial for men with metastatic castrate-resistant prostate cancer (EXACT)

EXACT consisted of a 12-week exercise programme, comprising home-based aerobic and resistance training, and acted as a parallel alternative to the INTERVAL-MCRPC trial. The exercise

programme aimed to offer the benefits of participating in physical activity to those men with mCRPC who were ineligible for the INTERVAL programme i.e. high intensity exercise. We wished to ensure all men had the opportunity to capitalise on the benefits of increased physical activity by offering a lower intensity lifestyle physical activity intervention. This was the first of its kind in this advanced and unwell population.

Aims and objectives

The primary objective of this study was to establish the feasibility of delivering a prescribed exercise intervention to men with advanced PC. As part of this primary objective, we collected data on patient eligibility and recruitment rates, adherence to the programme and attrition rates, the rate of exercise-induced adverse events (if any). Secondary objectives focused on the feasibility of data collection processes, collecting changes in body composition, functional ability, physical fitness, physical activity levels and patient-reported outcome measures (cancer-related fatigue, pain and quality of life).

Methods

This single site, single arm feasibility study (NCT03658486) examined the effects of 12-weeks of a home-based/remotely supervised exercise training in men actively receiving ADT + an androgen receptor pathway inhibitor (ARPI) for mCRPC. Patients were identified by their clinical oncologist while attending their routine clinic appointment at The Northern Ireland Cancer Centre between January 2019 – February 2022. Following confirmation of eligibility, patients attended three testing sessions at baseline, post-intervention and 3-month follow up. Initially planned as onsite, face-to-face visits, the COVID-19 pandemic and associated restrictions necessitated a protocol modification to enable remote assessments under strict mitigation measures.

Participants

Men with mCRPC received medical clearance to participate from their clinical oncologist. Inclusion criteria specified that all men: had testosterone levels <50 ng/dL; were currently receiving ADT; were prescribed an ARPI (abiraterone acetate or enzalutamide); had an ECOG performance status of 0-1; and were at least 4-weeks removed from any surgery and fully recovered. Exclusion criteria included: patients currently exceeding exercise recommendations for cancer[17]; brain metastases; current, active secondary malignancy; congestive heart failure or recent cardiovascular event; unstable angina; uncontrolled metabolic disease; and pain with exertion. All patients provided informed consent to participate after reviewing the patient information sheet and having had the opportunity to ask any questions. PC diagnosis and treatment history were extracted from medical records. Ethical approval was obtained from the Office for Research Ethics Committees Northern Ireland (REC B, Reference: 18/NI/0108). Research Governance permissions were granted by the Belfast Health and Social Care Trust (Reference: 18049GP-SS). All trial procedures were performed in accordance with the Declaration of Helsinki.

Exercise intervention

The 12-week, home-based intervention consisted of progressive, moderate intensity walking and resistance exercise, 2-5 times per week. This intervention was designed in consultation with the ACSM exercise guidelines for oncology patients[17], with the aim of achieving these by week nine. Participants had flexibility to complete walking and resistance exercises consecutively or separately

based on readiness (e.g. symptom burden on any given day) or preference and modifications were prescribed if necessary (e.g. metastatic bone lesions). Resistance training was performed using body mass and dumbbells (or weighted household items depending on dumbbell accessibility). Participants were provided with a guided warm up and stretching exercises prior to completing exercise training. During the initial assessment, all exercises were demonstrated, and participants were provided with a pedometer (Digi-Walker, Yamax) to determine step count during exercise, an exercise booklet with further instructions and an exercise diary, to log each training session. Participants reported rate of perceived exertion (RPE) during each session, to ensure they maintained an appropriate exercise intensity, using the 6-20-point scale, with each aiming for 12-14 during exercise[18]. Participants were encouraged to work beyond prescribed exercise if treatment-related side effects permitted but equally they could reduce and catch up missed exercise when toxicities have subsided (i.e. autoregulation[19]). Weekly telephone contact between the exercise professional and participants acted as behavioural support and enabled remote monitoring, query resolution and guidance on exercise selection and progression. Exercise adherence was extracted from each exercise diary upon completion. Interruptions to the programme were documented if patients missed three consecutive sessions.

Feasibility outcomes

Feasibility was determined by the number of patients recruited, as well as retention and adherence rates and the response rates to patient-reported outcomes. All variables are expressed as percentages, with adherence reflecting the number of sessions prescribed versus attended. Intervention fidelity (i.e. the prescribed dose and any deviations / escalations from the protocol) was determined and the rate of adverse events in response to exercise or treatment, from the point of informed consent. Intervention-related adverse events were graded and coded according to the Common Terminology Criteria for Adverse Events (CTCAE).

Body composition

Height and weight were determined using a free-standing stadiometer and calibrated laboratory scales, respectively. Body mass index was derived from these measurements (kg/m2). Hip and waist circumference was measured in centimetres using a tape measure. Anthropometric assessments were captured by the same investigator throughout the trial.

Functional outcomes

To provide an indication of functional fitness, patients completed a timed six-minute walk test on a flat, indoor, 20-metre walkway. The six-minute walk test is a valid and reliable assessment in clinical populations and a surrogate measure of aerobic fitness[20]. Patients were instructed to walk briskly for the duration of the test. Heart rate response was monitored throughout, with perceived exertion rated at the end of the test. To provide an indication of lower extremity strength a timed sit-to-stand test was used. This 30-second sit-to-stand test is a valid and reliable measure of lower extremity strength[21]. Patients were instructed to rise from a seated position to standing upright and return to seating, without assistance, as many times as possible within 30 seconds.

Patient-reported outcomes

The severity and impact of pain on daily living, over a recall period of 24 hours, was measured using the Brief Pain Inventory Short Form[22]. HRQoL was measured using the EuroQOL 5-dimension 5-

levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy-Prostate (FACT-P) questionnaires. The EQ-5D-5L questionnaire assesses HRQoL across five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and provides a visual analogue scale for patients to self-assess their own health status[23]. The FACT-P is a 39-item HRQoL questionnaire assessing five domains (physical well-being, social/family well-being, emotional well-being, functional well-being; and additional concerns), in the previous 7-days, with higher scores indicating improved quality of life[24]. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-fatigue) with higher scores indicating less fatigue[25]. Patients recalled and self-reported their physical activity levels (frequency and duration of vigorous intensity, moderate intensity, walking and sitting) during the previous 7 days, using the International Physical Activity Questionnaire (IPAQ)-Short Form[26].

Data analysis

For feasibility, the number of patients screened, those accrued and not willing to participate with reasons were recorded. Attendance (for outcome assessments), compliance and retention rates for the intervention was analysed using descriptive statistics and reported as a percentage of their expected overall involvement. The acceptability of functional capacity and patient-reported outcomes was reported using completion rates. All measures were scored according to standard practice and analysed using paired sample t-tests to detect any changes. Effect size (Cohen's d) was calculated for each with small, medium and large effects defined as 0.2, 0.5 and 0.8, respectively. Outcome data is presented as mean and standard deviation (95% confidence intervals), with clinically meaningful differences (according to normative data) noted. Data analysis was performed using SPSS version 29. Statistical significance was set at $p < 0.05$.

Personal and Public Involvement (PPI)

The study was supported by the Northern Ireland Cancer Research Consumer Forum. A stakeholder group was identified for the duration of the project to include service user involvement from the beginning. They were involved in all stages of the process from conception and design to evaluation. Bringing their experiential expertise from the beginning of the project, their input ensured the programme was designed to meet the end users' needs. Two PPI representatives were heavily involved throughout the duration of the project, attending all steering group meetings and were part of the authorship team who wrote the full results paper[27].

Findings

Eligibility and recruitment rate

In our 3-year recruitment window, one hundred and seventeen patients with advanced PC were assessed for eligibility by their treating clinician. Forty-five percent (n = 53) were excluded due to not meeting the eligibility criteria or alternatively at the discretion of the oncologist due to contraindications (e.g. comorbidities; frailty; disease progression; potential for non-compliance), while 13% (n = 15) were excluded for having a disease state other than mCRPC (e.g. hormone-sensitive). Within the men that declined (n = 19), the most common reasons were uninterested (58%) or too busy lack of time (26%). Of those eligible and approached (n = 49), thirty patients were consented with 93% (n = 28) completing baseline testing and enrolling in exercise training. Thus, the recruitment rate (the proportion enrolled versus eligible) for this trial was 61%. It should also be noted that recruitment to this trial was severely impacted by several waves of the COVID-19 pandemic and associated restrictions within the UK, including a suspension to recruitment for all clinical trials (23-

March-2020 – 15-Sept-2020). No demographic differences (i.e. age, sex or race) existed between those that agreed to participate and those that declined the invite to participate.

Participant characteristics

The mean age of participants was 71 years (range: 55 – 82 years). Mean BMI was 29.4 kg/m2 (range: 23.4 – 39.3 kg/m2), with 86% overweight (> 25 kg/m2) at baseline. Eighty-two percent of participants were married, 75% completed formal education and 71% were retired at trial entry. Most participants had received at least one prior treatment modality (86% radiotherapy; 32% chemotherapy), half had at least one comorbidity (57%), while 71% reported they had never smoked. All participants identified as white (British, Irish or European).

Retention and adherence rates

Eighty-six percent (n = 24) of patients that completed baseline outcomes went on to complete the 12-weeks of exercise training and post-intervention outcomes. Positively, 79% (n = 22) attended the 3-month follow-up. All (100%) of participants attempted and completed anthropometric and physical testing as well as patient-reported outcomes at baseline and post-intervention (no missing data). Task completion for the 6-min walking test at 3-months decreased slightly (96%), due to a single patient suffering ankle pain from an industrial-related accident. Aside from this, task completion for the remaining outcomes at 3-months (body composition and patient-reported outcomes) remained high (100%). The total number of outcome assessments through the duration of this trial was 74 (59% completed at treatment site, while 41% were completed remotely under identical conditions). Self-reported adherence to the overall intervention was 81.9%. Adherence to the aerobic component (i.e. brisk walking mins per week versus prescription) was 80.8%, while resistance training was 83% (based on minimum threshold of repetitions per exercise).

Intervention fidelity

Exercise training was interrupted on nine occasions during the intervention. The most common reason for interruption was disease or treatment-related toxicities including fatigue and bone pain (33%), followed by viral infection (22%). Of the 288 total training weeks the intended weekly dose of aerobic exercise was modified on 98 occasions (34%), but encouragingly escalated on 162 weeks (56%) allowing patients to recover the missed exercise. In terms of the aerobic component, patients were prescribed a cumulative dose of 1190 mins and completed 1613 ± 1128 mins. Fifty-four percent (n = 13) of patients exceeded the planned dose of aerobic exercise during the 12-week intervention, while six (25%) were unable to achieve at least 1000 mins due to a combination of work / lack of time (n = 3) and disease or treatment-related factors (n = 3). Overall, 96% of patients attempted to complete aerobic exercise during the intervention. For resistance training, patients were prescribed a minimum cumulative dose of 2304 repetitions and completed 4092 ± 4030 repetitions. Seventy-one percent (n = 17) attempted all prescribed resistance exercises, with all patients completing at least half of those prescribed. Comparable with aerobic exercise, 67% (n = 16) completed more repetitions than prescribed during the intervention.

Adverse events

No safety concerns related to the exercise intervention were identified during the trial. One incident was reported outside of the exercise training, whereby a participant fractured his metatarsal during his daily routine (gardening). This occurred during week 2, however he was able to resume exercise

with a modified exercise programme at the start of week 9. Seventeen acute or ongoing disease or treatment-related AEs were reported, resulting in missed exercise training. The most commonly cited treatment-related side effects were fatigue, bone pain and infection. Exercise training was permitted with fatigue, at a reduced level, but paused with more severe side effects until they subsided or completely resolved.

Anthropometric outcomes

Exercise training decreased body mass post-intervention ($p = 0.044$; 95% CI = 0.39 – 2.51; Cohen's $d = 0.44$). A mean decrease of 1.3 kg (-1.5%) was recorded post-intervention. No changes were detected at 3-months follow up ($p = 0.841$; 95% CI = 1.18 – 1.44; Cohen's $d = 0.04$). Similarly, BMI decreased post-intervention ($p = 0.045$; 95% CI = 0.01 – 0.81; Cohen's $d = 0.43$) but returned to baseline levels at 3-months. Waist and hip circumferences remained unchanged from baseline.

Physical outcomes

Exercise training improved 6-min walking distance post-intervention (+13.3%) ($p < 0.001$; 95% CI = 34.15 – 85.14; Cohen's $d = 0.99$) and at 3-months follow up (+11.1%) ($p < 0.001$; 95% CI = 30.99 – 63.41; Cohen's $d = 1.32$). Similar improvements in lower extremity muscular strength were detected, with increased repetitions for the timed sit-to-stand test at post-intervention (+25%) ($p < 0.001$; 95% CI = 2.17 – 4.08; Cohen's $d = 1.39$) and 3-months (+25%) ($p < 0.001$; 95% CI = 1.23 – 3.77; Cohen's $d = 0.87$).

Patient-reported outcomes

Exercise training improved fatigue at 3-months follow up, compared to baseline ($p = 0.042$; 95% CI = 0.16 – 7.84; Cohen's $d = 0.46$). Following the intervention, the anxiety / depression dimension of EuroQoL decreased at 3-months follow up, compared to post-intervention ($p = 0.015$; 95% CI = 0.12 – 0.97; Cohen's $d = 0.57$). No changes were detected between baseline and 3-months for anxiety / depression ($p = 0.057$) or the remaining four dimensions. Self-reported physical activity levels (number of days) increased for both vigorous ($p = 0.01$; 95% CI = 0.39 – 2.53; Cohen's $d = 0.58$) and moderate exercise ($p = 0.012$; 95% CI = 0.45 – 3.29; Cohen's $d = 0.56$) at post-intervention, while sitting hours decreased ($p = 0.015$; 95% CI = 0.29 – 2.36; Cohen's $d = 0.55$). The duration of moderate intensity minutes also increased at 3-months follow up, compared to baseline ($p = 0.021$; 95% CI = 8.49 – 91.5; Cohen's $d = 0.55$). Finally, no changes were detected in pain severity, pain interference or overall scores for the FACT-G / FACT-P.

Conclusion

We have shown that home-based, concurrent exercise training is safe and feasible for men with mCRPC. To our knowledge, this trial recruited, retained and completed the largest sample of advanced PC patients to a home-based exercise intervention to date, in the UK and globally. Exercise training has been shown for the first time to result in improved body mass, functional fitness and patient-reported outcomes, particularly fatigue, in a sample of UK patients with mCRPC. This trial served as a parallel alternative to the INTERVAL-MCRPC trial in Belfast, highlighting that if men were deemed ineligible, then they could still participate and complete a moderate intensity exercise programme. This is important from a patient care perspective, as they could avail of the benefits of being active (i.e., improved fitness, reduced fatigue and improved HRQoL), albeit at a moderate intensity and while at home.

Practice and Policy Implications/Recommendations

Home-based exercise training could prove an effective and viable alternative to supervised exercise for men with mCRPC. Given that the number of men living with mCRPC is expected to rise because of new and emerging therapies extending survival, understanding their complex needs and the best supportive care strategies to improve outcomes is crucially important. Home-based exercise training is accessible and scalable and should form part of this care pathway in the future. A definitive, sufficiently powered RCT is now required to replicate these findings and establish the chronic effects of training. This feasibility study provided preliminary evidence that men with very advanced cancer, and who are not able to participate in high intensity exercise can still take part in physical activity and should set the benchmark for all other cancer patients.

PANCREATIC CANCER

Study 3:

PancREatic Cancer and Individualised Supervised Exercise (PRECISE): a feasibility trial protocol for patients with resectable pancreatic ductal adenocarcinoma

Background

Pancreatic cancer is an aggressive malignancy with poor survival outcomes. In 2020, 495,773 new cases of pancreatic cancer were reported globally, with 466,003 deaths[28]. Incidence and mortality rates have remained stable or slightly increased in many countries, to the extent that pancreatic cancer is projected to surpass breast cancer as the third leading cause of cancer death in Europe by 2025[29]. Pancreatic ductal adenocarcinoma (PDAC) is the most commonly diagnosed neoplasm, accounting for more than 90% of cases[30]. Surgical resection remains the only curative treatment, with adjuvant chemotherapy administered as standard of care to improve survival rates. Although, these available treatment methods for PDAC are associated with chronic toxicities that impose a considerable physical and psychological burden[31]. Patients often experience debilitating side effects including reduced physical functioning, decreased skeletal muscle mass, heightened fatigue, gastrointestinal issues, pain and nausea[32]. Coupled with treatment-related toxicities, PDAC patients are at risk of developing associated comorbidities in sarcopenia and cachexia. In fact, cancer cachexia will affect up to 80% of pancreatic cancer patients during their disease course, with a significant proportion meeting cachexia criterion at diagnosis[33]. Even those eligible for resection can exhibit signs of cachexia, with reduced adipose tissue and muscle atrophy associated with poorer treatment responses to chemotherapy[33]. Ultimately, cancer cachexia impairs mobility and is strongly associated with morbidity and mortality[34]. Such toxicities and the risk of debilitating comorbidities, demands a need for adjunct therapies that counteract these complications.

As previously detailed, conventional exercise, particularly moderate to vigorous/high intensity aerobic and resistance training, delivered as part of rehabilitation or adjuvant therapy provokes numerous physical and psychological benefits that can alleviate several treatment-related toxicities and improve disease outcomes[31,35-37]. Accumulating evidence suggests exercise training improves aerobic fitness, functional capacity, muscular strength and lean muscle mass[38-40]. The benefits of exercise training also extend to improving overall quality of life, pain, inflammation and cancer-related fatigue[41]. Thus, delivering exercise as a supportive therapy to adjuvant care could positively impact prognosis, given quality of life is an independent predictor of cancer survival and the associated

treatment toxicities (e.g. fatigue) affects the vast majority of PDAC patients receiving chemotherapy[42,43]. However, whilst the evidence favours exercise training as an important part of care, unlike other gastrointestinal cancers epidemiological evidence of the association between PDAC risk and/or progression and exercise remains limited, although some suggest greater volumes might decrease risk[44,45]. The complexity of this disease, its treatment pathway and associated side effects/risk of comorbidities, provide a unique opportunity to test the effects of exercise training during treatment.

At present, clinical exercise trials in PDAC within the adjuvant setting are limited to a small selection of studies[46-50]. None of these trials included representation from the UK within their sample, so it was unclear how an exercise intervention might be implemented within the UK National Health Service. Concurrent exercise training has been shown to improve physical capacity, HRQoL, fatigue, sleep quality and importantly prevented muscular atrophy in a case sample[47]. Given body composition has been cited as a predictor of toxicity[51] and PDAC patients commonly suffer post-surgical weight loss and cachexia, this might prove clinically relevant. Recently, in a larger sample of 22 patients, supervised concurrent exercise training during adjuvant therapy proved safe and enhanced functional ability alongside muscular strength[50]. Clinically relevant individual changes were also noted for cancer-related fatigue and QoL, although body composition outcomes remained unchanged[50]. Such physiological improvements with exercise training could aid treatment tolerance, mitigate toxicities and arguably facilitate dose intensity, thus impacting the hard to shift endpoint of survival. Though speculative this downstream mechanism could arise from the direct biological effects of exercise on the tumour microenvironment[52] or from improved cardiovascular and metabolic functions, however the evidence base remains limited. In ESPAC4 trial, during adjuvant chemotherapy (Gem/Cap) only 54% of patients completed chemotherapy and a large proportion (47%) stopped treatment due to toxicity, with fatigue being the most commonly reported[53]. Exercise may help alleviate this and hence tolerability to treatment and therefore potentially survival. On the other hand, it could be argued that the fact that only 54% of patients completed chemotherapy highlights the need for a feasibility study in this disease. We proposed that supervised, non-linear, concurrent training founded in the 'principles of training' could unlock the full therapeutic potential of exercise within this heterogenous population of PDAC patients. This approach involved manipulating intensity, duration and occasionally the frequency of training sessions to allow the training volume to continually progress across the entire programme. As there is considerable heterogeneity in this population, exercise programming should be equally individualised, to promote safety and optimise the efficacy of treatment for the individual.

Aims and Objectives

The aim of this trial was to establish the feasibility of delivering a prescribed, personalised, supervised exercise programme in PDAC patients undergoing adjuvant therapy, to improve outcomes and reduce symptom burden.

Methods

Participants

Participants diagnosed with PDAC, post-surgical resection and scheduled for adjuvant chemotherapy were screened for eligibility by clinicians within the Northern Ireland Cancer Centre, Belfast Health and Social Care Trust. Participants had no evidence of metastatic disease and no

active prior malignancies (other than PDAC) within the last 3 years. Clinicians identified suitable participants and provided participant information packs at their chemotherapy planning clinic, with a view to enrolling in the exercise intervention after completing two cycles. The rationale for introducing exercise at this point, was to ensure participants tolerated chemotherapy well prior to commencing exercise training. Participants were screened for recent and historical comorbid conditions that might contraindicate them from the exercise intervention. Clinicians provided medical clearance to participate prior to chemotherapy cycle 3. Participants provided written informed consent to participate. At the time of exercise programming, all participants were treated with adjuvant gemcitabine / capecitabine or FOLFIRINOX (fluorouracil, irinotecan, leucovorin and oxaliplatin), bi-weekly for 12 cycles. Ethical approval for this trial was granted by the East of Scotland Research Ethics Committee (22-October-2019; Ref: 19/ES/0125). All the methods were conducted in accordance with relevant guidelines and regulations.

Exercise intervention

Exercise training commenced following two cycles of adjuvant chemotherapy. Each participant received a personalised, supervised, progressive exercise programme for 16-weeks, running concurrently with chemotherapy. The programme comprised aerobic and resistance exercises, completed twice weekly under supervision by clinical exercise physiologists. Participants were also encouraged to supplement supervised exercise with additional bouts of home-based aerobic exercise weekly. Prior to and following exercise, basic observations (i.e. blood pressure, oxygen saturation), self-rated fatigue and pain were obtained. The trial adhered to the principle of autoregulation[19]. Upon entry participants completed 4-weeks of gradually progressive resistance exercise to familiarise then progressed to undulated exercise. The resistance exercise progressed in load from 12 to 6 repetitions, and 2 to 4 sets per exercise. Participants were encouraged to work beyond the prescribed exercise if treatment-related side effects were manageable. Typically, each supervised session commenced with a 10-min cardiovascular warm up, followed by 60 min of combined aerobic and resistance exercises. Aerobic exercise was performed on a cycling ergometer during supervised sessions, with brisk walking the preferred mode of exercise at home. Resistance exercise involved body weight, free weights and pin-loaded resistance machines to target the upper and lower extremities. Heart rate was monitored continuously throughout, using a Polar M200 watch, to ensure participants remained within the required heart rate zone (50–75% heart rate reserve). Onsite supervised resistance sessions were completed at a percentage of each participants 1-repetition maximum (1-RM) and separated by at least 48hrs. Participants reported sessional rate of perceived exertion (RPE) using a 10-point scale. To minimise cross-interference between training modalities and to maintain variety, compliance and enjoyment, aerobic and resistance exercise timing alternated monthly. Each session was scheduled individually with reasons for cancellations or rescheduling noted, thus enabling intervention adherence to be calculated. Interruptions to the programme were documented if participants missed three consecutive sessions. To accommodate the COVID-19 pandemic, participants were offered a remotely supervised option using Zoom, but with obvious limitations in progression (e.g. dumbbells; resistance band exercises).

Outcome measures

Participants completed three outcome assessments at baseline (pre-chemotherapy cycle 3); post-intervention (chemotherapy completion) and at 3-months follow up. All assessments were performed by a clinical exercise physiologist.

Feasibility

Feasibility was determined by the number of participants recruited, retention and adherence rates. All variables were expressed as percentages, with adherence reflecting the number of sessions prescribed versus attended. Intervention fidelity (i.e. the prescribed dose and any deviations or escalations from the protocol) was determined and the rate of adverse events in response to exercise or treatment, from the point of informed consent. Adverse events were graded and coded according to the Common Terminology Criteria for Adverse Events (CTCAE).

Anthropometric outcomes

Height and weight were determined using a free-standing stadiometer and calibrated laboratory scales respectively. Body mass index was derived from these measurements (kg/m2). Hip and waist circumference was measured in centimetres using a tape measure. Anthropometric assessments were captured by the same investigator throughout the trial.

Physical fitness outcomes

Participants completed a timed six-minute walk test on a flat, indoor, 20-metre walkway. The six-minute walk test is a valid and reliable assessment in clinical populations and a surrogate measure of aerobic fitness[20]. Participants were instructed to walk briskly for the duration of the test. Heart rate response was monitored throughout, with perceived exertion rated at the end of the test. Muscular strength was assessed using a timed sit-to-stand test and 1-RM testing. For the timed sit-to-stand test, participants were instructed to rise from a seated position to standing upright and return to seating, without assistance, as many times as possible within 30 seconds. This 30-second sit-to-stand test is a valid and reliable measure of lower extremity strength[54]. 1-RM testing comprised a chest press, seated row and leg extension or leg press (not both). Prior to testing, participants completed a graded warm up, consisting of six and three repetitions at approximately 60% and 80% of their perceived maximum, respectively. For 1-RM testing, pin-loaded equipment was used and participants were instructed on correct breathing and lifting technique. 1-RM was determined within a maximum of five repetitions and sufficient recovery was provided between attempts. 1-RM is defined as the highest load that can be lifted, through the full range of motion, at one time.

Patient-reported outcomes

HRQoL was assessed using a range of questionnaires that have shown to be valid and reliable in the cancer population[55]. The severity and impact of pain on daily living, over a recall period of 24 hrs, was measured using the Brief Pain Inventory Short Form[22]. HRQoL was measured using the EuroQOL 5-dimension 5-levels (EQ-5D-5L) and Functional Assessment of Cancer Therapy Hepatobiliary (FACT-Hep) questionnaires. The EQ-5D-5L questionnaire assesses HRQoL across five domains (mobility, self-care, usual activities, pain/discomfort and anxiety/depression) and provides a visual analogue scale for participants to self-assess their own health status[23]. The FACT-Hep is a 45-item HRQoL questionnaire assessing five domains (physical well-being, social/family well-being, emotional well-being, functional well-being; and additional concerns), with higher scores indicating improved quality of life[56]. Fatigue was assessed using the Functional Assessment of Chronic Illness Therapy - Fatigue (FACIT-fatigue) with higher scores indicating less fatigue[25]. Participants recalled and self-reported their physical activity levels (frequency and duration of vigorous intensity, moderate intensity, walking and sitting) during the previous 7 days, using the International Physical Activity Questionnaire (IPAQ) - Short Form[26].

Data analysis

The number of participants screened, those accrued and those not willing to participate with reasons for ineligibility and non-participation were recorded. Participant attendance, compliance and completion rates for the intervention were analysed using descriptive analysis and reported as a percentage of their expected overall involvement. The acceptability of the measures of functional capacity and of the patient-reported questionnaires was reported using completion rates. Any observed changes in functional capacity and patient-reported outcomes from baseline were reported on an individual basis using descriptive statistics (i.e. mean).

Patient and Public Involvement

At the early stage of study development, we approached the Pancreatic Cancer UK Research Involvement Network to ask for PPI involvement on the study. Four people with pancreatic cancer responded to say they were interested in assisting and inputting into the study development. Via a teleconference, the iterative study design was refined following feedback i.e. the issue of an inherent bias in the study sample of those who decide to participate being more active prior to their diagnosis, the importance of the exercise being individualised and taking in to account some of the issues experienced during chemotherapy such as neurological and gastrointestinal side effects and the severe fatigue that can be experienced, to take in to consideration surgical scars and potential for hernias when designing the exercise intervention, the need for the intervention and the study to be pragmatic and flexible. They also suggested potential avenues for dissemination such as charities and social media, in particular 'UK Whipple Warriors' an online peer led support group for the target population of this study.

Two members joined the steering committee and had direct input into the research design, delivery and dissemination. Their ongoing input informed: protocol development; review of client facing materials, such as information sheets and consent forms. They authored publications arising from the project (protocol and results paper).

Findings

Eligibility and recruitment rate

In our 19-month recruitment window, from 3rd August 2020 to 31st December 2021, eleven participants with PDAC were screened, deemed eligible and approached by their treating clinician. Based upon regional statistics (1993–2020), the Belfast Health and Social Care Trust average 48 pancreatic cases per year (stages I-IV), with approximately 50% of these advanced cases and considerably fewer suitable for surgical resection (~ 20%)[57]. Positively, this suggests clinical gatekeepers approached the majority of those suitable for enrolment despite the challenging circumstances presented by the COVID-19 pandemic (e.g. restrictions on non-emergency surgery; suspended clinical trial recruitment). All eleven participants approached received a participant information pack and agreed to follow up. Eight participants (80% of original recruitment target) provided informed consent with five participants (63%) enrolling into the exercise intervention (Fig. 2, patient flow diagram). Three of the initial eight participants were withdrawn from the trial, in the time between consent and commencing the intervention (1 medically withdrawn; 2 withdrawn on their own volition citing personal reasons and proximity). The latter was offered a remote alternative, to enhance accessibility, but declined. Thus, the recruitment rate (the proportion enrolled versus eligible) for this trial was 46%. Three from the original eleven eligible participants declined the invite

to participate citing differing reasons (not interested; travel proximity; family commitments). No demographic differences existed between those that agreed to participate and those that declined the invite to participate. The declining population was mixed in terms of gender (2 males, 1 female) and of similar age (68 ± 10 years). Therefore, the results presented are a case series of the five enrolled participants.

Participant demographics

The age range for participants was 49–77 years. All patients were white, 40% were active smokers and 60% were retired. All five participants underwent surgical resection between June 2020 - August 2021 and were prescribed adjuvant chemotherapy between September 2020 - April 2022. Most cases increased or at least maintained their body mass (80%), with only participant 4 losing weight during adjuvant treatment.

Retention and adherence rates

Five participants (63%) proceeded to the intervention and follow up at 3 months. Intervention delivery commenced on the 7th of December 2020 and ceased on 29th April 2022. Participant 1 completed the trial in August 2021, attending 28 out of 32 supervised sessions during his adjuvant chemotherapy (88% adherence). Participant 2 completed the trial in September 2021 (baseline assessment and follow up outcomes only). This participant became non-contactable after baseline and despite persistent efforts to re-establish contact and seek an alternative method of delivery, participant 2 did not complete any supervised exercise sessions during adjuvant chemotherapy. Participant 2 cited a series of treatment-related toxicities for this absence, consistent with a change in chemotherapy regimen (switched from FOLFIRINOX to gemcitabine/capecitabine after cycle 2). Participant 3 completed the trial in November 2021, attending 28/32 supervised sessions (88% adherence). Participant 4 was the next to complete the trial in July 2022. Due to distance from the facility this participant availed of the hybrid option, predominantly completing remotely supervised exercise via Zoom (n = 17) and in person supervision (n = 5) prior to each chemotherapy cycle. Participant 4 completed 22 / 32 supervised sessions (69% adherence). The final participant completed the trial in July 2022, attending 16 / 32 supervised sessions (50% adherence). Overall, 80% (4 / 5 participants) were able to complete the exercise programme.

Intervention fidelity

Exercise training was interrupted 5 times during the entirety of delivering the intervention, predominantly due to treatment-related toxicities (e.g. low cell counts). In total, participants missed 34 sessions (27%) and the intended programme was modified on 49 occasions (38%). Positively, the exercise dose was escalated on 53 occasions (41%), allowing participants to recover some of the altered dose. In terms of the aerobic component participants were prescribed a cumulative dose of 1080 min and completed 686 ± 362 min. One participant exceeded the planned dose during the 16-week intervention (participants 3: 1142 min), while three participants completed less than the prescribed dose (participants 1, 4 and 5: 410, 380 and 810 min respectively). Regarding resistance training, three participants opted to attend regular supervised sessions at the treatment site and were prescribed a cumulative dose of 150,580 ± 33,936 kg, completing 131,782 ± 42,270 kg. All three participants progressed to completing undulated resistance training and coped well with the requirements, lifting more than 100,000 kg during the 16-week intervention (participant 1–103,177 kg; participant 3–180,336 kg; participant 5–111,834 kg).

Adverse events

No intervention-related adverse events occurred during the trial, however a number of treatment-related adverse events were recorded, resulting in missed exercise training. Common treatment-related side effects included fatigue, low cell counts, nausea and diarrhoea. Exercise training was permitted with fatigue, but carefully managed and encouragingly all four participants were still able to exercise. However, exercise programming was paused with more severe side effects until they subsided.

Physical outcomes

At baseline, all five participants completed a 6-min walking test and a 30-second sit-to-stand test. Participant 2 did not complete post-intervention outcomes, but the remaining four participants all completed the same outcomes following the intervention. At 3-month follow up, all participants completed the same physical tests. Aside from participant 2, who stopped walking prior to the expiration of the 6-min duration, these physical tests were well tolerated. The mean walking distance at baseline, post-intervention and 3-month follow up was 431 ± 110, 483 ± 123 and 501 ± 134 metres respectively (participant 2 outcomes omitted due to incomplete attendance). All four participants that engaged with the intervention improved their aerobic fitness at post-intervention and at 3-month follow up. In terms of the timed sit-to-stand test, all actively engaged participants improved or at least maintained their lower extremity muscular strength at post-intervention and 3-months. Participants 1, 3 and 5 also completed 1RM testing at baseline, post-intervention and 3-months. All three tolerated this testing well and improved their upper and lower extremity muscular strength at post-intervention and again at 3-months.

Patient-reported outcomes

The patient-reported outcomes were acceptable and feasible. All participants understood and completed the questionnaires fully (no missing data), suggesting these measures are suitable. The outcomes vary on an individual basis immediately post-intervention and at 3-months, with some improving and some declining. Participants 1 and 5 reported a meaningful improvement in fatigue post-intervention, while participants 3 and 4 reported heightened fatigue at the same time point compared to baseline. Positively, fatigue levels subsided for participant 3 at follow up. HRQoL (i.e. FACT-G and EQ-5D-5 L scores) followed a similar trend and are equally variable overall, although some positive findings are observed individually for health state and self-rated health outcome. For example, participant 1 reported an improved overall FACT-G score post-intervention (as a result of a meaningful improvement within the functional domain), while participant 3 reduced their overall FACT-G, due to decreased scoring across all 4 domains. Encouragingly, participant 3 reported much improved quality of life at 3-months, outscoring in all 4 domains. Conversely, on the self-rated EQ visual analogue scale, participant 1 reported reduced health at post-intervention and 3-months, while participant 3 reported an improvement at post-intervention and again at 3-months.

Conclusion

This current case series provides preliminary evidence that concurrent exercise training during adjuvant therapy for PDAC patients is safe, feasible and well tolerated and may prevent expected declines in functionality, muscular strength and HRQoL during chemotherapy. Given the effects of surgical resection and cumulative effect of adjuvant chemotherapy on outcomes, a larger definitive trial of exercise training in this model is necessary, perhaps alongside the inclusion of a home-based

or hybrid alternative. Nonetheless, this trial provides an insight and good starting point in the design of future studies. Including exercise training as a standard of care for surgical rehabilitation and during adjuvant therapy could significantly reduce morbidity and mortality in PDAC and better equip patients to endure further treatment if necessary.

Practice and Policy Implications

This trial was originally planned as a UK-wide, multi-centre intervention, but due to the impact of the COVID-19 pandemic and funding limitations, only one site was successfully opened during the recruitment timeframe. Thus, the single centre limits our ability to generalise the findings UK-wide, but indeed illustrates potential trends with exercise training during treatment for PDAC and highlights a need for scaled up research. A sufficiently powered sample would permit greater analysis that could determine if any changes were statistically significant and clinically meaningful. A potential strategy to increase accessibility, would be to accommodate home-based, remotely supervised exercise as a delivery choice to determine its effectiveness on survival, recurrence and treatment-related toxicities. While this case series did facilitate this option through a hybrid model, it was in response to the COVID-19 global pandemic, which in itself created a unique limitation whereby reduced surgical capacity and reduced in person contact made recruitment more difficult.

A definitive RCT, determining the efficacy of exercise on patient reported outcomes and survival, is the logical next step. On a related note, it would appear that resistance exercise may be more tolerable in this population and should receive increased attention in future investigations. As toxicities persist long into survivorship, outcome measures should be reflective of this and longitudinally followed up to determine the chronic impact of exercise training in this population as well as its impact on the risk of recurrence. Further, forthcoming studies should attempt to assess the differentials of body composition, particularly lean mass, given the risk of sarcopenia and cachexia in this population. Positively, this trial was feasible and effective for the participants involved but requires a suitably qualified and experienced exercise or health care professional to deliver and individualise the prescribed dose and oversee the immediate transition of patients into survivorship, which makes its implementation into routine NHS practice challenging.

Pathway to Impact

This programme of work has demonstrated that exercise is feasible in both prostate and pancreatic cancer populations. To enhance the impact a real-world implementation project designed to understand how exercise can be successfully embedded in to the cancer patient pathway at the Northern Ireland Cancer Centre and other centres throughout Northern Ireland is needed. It is likely that a personalised approach to exercise prescription would need to be adopted. This would involve a screening and triaging process to identify those individuals with cancer who should be referred to three levels of exercise intervention: low risk self-managed home based exercise, moderate risk (symptoms or co-morbidities) group-based supervised exercise, and high risk (e.g. bone metastasis) one to one specialist supervision. The development of such a programme would involve several steps including engaging with service users (individuals with cancer, healthcare professionals and commissioners) to understand the implementation problems and develop strategies and solutions to overcome and then test these solutions in practice.

Other activities the Research Fellow was involved in:

CHALLENGE Trial (PI Prof Vicky Coyle, QUB)

This global randomised controlled trial assessed the impact of moderate intensity aerobic exercise training in high-risk colon cancer survivors. This intervention was supervised and incremental in nature, allowing patients to eventually meet and exceed the physical activity guidelines. Behavioural support was provided throughout. The primary objectives of this trial were to determine the impact of physical activity on disease-free survival, supporting by secondary objectives assessing the impact of exercise on quality of life and exploratory biomarkers. Globally, this trial has recruited over 800 patients, with 30 screened within the UK. In Belfast, we randomised 10 patients, with the first completing the intervention in March 2022. To date, only one patient has had a recurrence (control) with no intervention patients suffering a recurrence (as of December 2023).

Codesign of a novel clinical trial to test the ability of exercise to improve oxygenation and radiotherapy efficacy:

We conducted a series of co-design workshops to gauge stakeholder perceptions of an exercise intervention to be delivered immediately prior to radiotherapy treatment. Three iterative workshops involved 8 men with prostate cancer and carers, 2 radiographers and 2 oncologists. Workshops were recorded, transcribed verbatim and thematically analysed. Findings from workshop 1 were presented at workshop 2 and integrated findings at workshop 3. There was widespread support for the proposed intervention, with exercise recognised as an important part of treatment and recovery. Both generic and prostate-specific barriers were suggested. Generic concerns included: participant motivation and recruitment; managing cancer symptoms; exercise timing and location; a time course of the benefits; exercise boredom. Prostate-specific concerns focused on: pre-radiotherapy bladder filling and exercise, pain and discomfort; suitable surrogate endpoints; scheduling; securing necessary support (e.g. physiotherapists / radiographers); simulation scans replicating treatment conditions; and future proofing against radiotherapy refinements (e.g. stereotactic). Although barriers were articulated, solutions were suggested. It was proposed that aerobic exercise (e.g. treadmill or brisk walking) would be appropriate for men with prostate cancer, as would an exercise 'buddy' to manage monotony. Integrating exercise with water intake may serve as a welcome distraction during bladder filling. Finally, personalisation to each individual was a key recommendation alongside support from treating oncologists.

Capacity development:

Grant applications: Pancreatic Cancer UK, £107,975.00, 2-years. (Co-investigator)
Funding awarded to conduct a feasibility trial (PRECISE: PancREatic Cancer and Individualised Supervised Exercise for patients with pancreatic ductal adenocarcinoma).

Supervision: Co-supervised 2 PhD research students (1 to completion) and a MSc studentship.

Teaching: Applied Life Sciences module, Evidence Based Nursing module and delivered a Research Showcase for postgraduate research students.

Research outputs: published 13 peer-reviewed articles; 10 peer reviewed abstracts; and a blog.

Conferences: presented work at BASES 2018; ISPAH 2018; The Joint Public Health Annual Conference; MASCC 2021 and 2022.

Book chapter: Chapter Lead (Patient Optimisation and Rehabilitation) for a Supportive Oncology Handbook, due to be published in 2024, by the Taylor and Francis Group.

CPD: completed a Level 4 in Cancer Rehabilitation (2019) and obtained Associate Fellowships of the Higher Education Academy (2020).

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