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Research Article

Multimodal Exercise in Older Patients with Advanced Pancreatic Cancer Undergoing First-Line Chemotherapy: A Case Series Examining Feasibility and Preliminary Efficacy

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Purpose. Exercise is emerging as an adjunct therapy to cancer treatment; however, its role in older patients with advanced pancreatic cancer undergoing first-line chemotherapy is unclear. The aim of this study was to primarily provide evidence on feasibility with an exploratory examination of the initial efficacy of exercise in this clinical setting. *Materials and Methods*. Six patients aged 60–75 years with *de novo* or recurrent advanced pancreatic cancer undergoing first-line chemotherapy consented to participate in twice-weekly exercise that included resistance and aerobic training and boxing-related activities for up to 12 weeks. Patients were monitored for attendance, adherence, and adverse events. Body composition, muscle strength, functional ability, patient-reported outcome measures, and patient-reported experience measures were assessed at baseline and/or postintervention. *Results*. Of the 6 patients, 1 withdrew after baseline testing and 5 attended 42%–95% of planned sessions and adhered to 28%–83% of the prescribed exercise. There were no serious exercise-emergent adverse events. All 5 patients increased or maintained lean mass (0.1%–4.4%) and 4 reduced fat mass (−0.4%−−8.6%). Improvements were observed in 4 or all 5 patients for muscle strength (7.1%–75%), 5 times sit-to-stand (1.3%–21.4%), 6-m backward walk (16.5%–35.8%), and patient-reported outcomes. Furthermore, all patients perceived exercise as very helpful in managing their cancer and expressed a strong willingness to continue exercise in the future. *Conclusion*. A multimodal exercise program appears feasible with potential physical and psychological benefits for older patients with advanced pancreatic cancer undergoing first-line chemotherapy. Further research including a larger sample size is warranted.

1. Introduction

Pancreatic cancer is a highly aggressive malignancy with an overall 5-year survival rate globally of less than 10%, though it remains relatively uncommon [1, 2]. The poor prognosis of pancreatic cancer is to a great extent attributable to the lack of specific symptoms and effective screening at an early stage, resulting in over 80% of patients at diagnosis presenting with advanced-stage disease where surgery is largely precluded due to extensive local blood vessel involvement and/or distant metastases [2]. In the absence of curative options, chemotherapy is the primary treatment in patients with advanced pancreatic cancer with the ultimate goal of prolonging life [3–5]. In current practice, multiagent regimens, such as FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin), have survival advantages over previously approved single-agent regimens (e.g., Gemcitabine) and thus are preferred in the first-line setting [5]. However, these regimens often expose patients to an increased number and severity of toxicities, such as fatigue, neuropathy, diarrhea, and nausea [6–8]. In addition, patients with advanced pancreatic cancer have a high

prevalence of psychological distress due to symptom burden and mental challenges associated with the diagnosis [3]. These disease-related and treatment-related side effects can result in significant declines in physical, physiological, and psychological parameters, collectively leading to poor quality of life (QoL) and, in turn, permanent treatment discontinuation [3, 9]. As such, interventions to minimise toxicities and maximise physical, physiological, and psychological functioning as well as QoL are of clinical significance.

Exercise medicine is increasingly recognised as an adjunct therapy to cancer chemotherapy with robust evidence supporting favourable effects on treatment-related toxicities (e.g., fatigue), cardiovascular fitness, muscle strength, physical function, and QoL [10–12]. However, current evidence of exercise during chemotherapy is predominantly derived from patients with prevalent cancers and comparatively better prognoses (e.g., breast and colorectal) [12]. Clinical data concerning exercise training in pancreatic cancer remain scant [13] with most trials including patients with potentially curable disease (i.e., resectable and borderline resectable) [14, 15], conducted in the postoperative setting [16–20], or during a short preoperative waiting period (~12 days) with no chemotherapy prescribed [21]. To date, there are only 3 case reports investigating exercise in patients with advanced pancreatic cancer during first-line chemotherapy, and these patients were of a relatively younger age (46–55 years) [22–24].

Therefore, in this case series pilot study, we primarily report on feasibility outcomes of a multimodal exercise program in older patients (aged ≥60 years) with advanced pancreatic cancer during first-line chemotherapy, including attendance, adherence, and adverse events (AEs). Further, an exploratory evaluation was undertaken of efficacy of the intervention on physical, physiological, and psychological health outcomes as well as overall QoL. Lastly, we report findings of patients' perceptions of and experience with the exercise program.

2. Materials and Methods

This case series included 6 older patients (aged ≥60 years) with advanced pancreatic cancer undertaking a multimodal exercise program during first-line chemotherapy at the Edith Cowan University (ECU) Exercise Medicine Research Institute (EMRI) in Perth, Australia. A prospective case series design is advocated for a pilot study in the clinical setting and particularly for uncommon diseases to assess the need for a controlled trial with a larger sample size and thus was used in this study [25, 26]. Ethics approval was obtained from the ECU Human Research Ethics Committee, and all patients provided written informed consent before participation.

2.1. Patients and Procedures. The cases were accrued from consecutive patients with pancreatic cancer treated by the study clinician (CT) and referred to EMRI for clinical exercise services between June 2021 and May 2022. A study investigator or accredited exercise physiologist approached patients over the telephone about their interest in participating in the study. Interested patients were provided with study documentation and asked to obtain medical clearance from their physician before enrollment.

2.2. Exercise Intervention. Patients were asked to perform supervised exercise twice weekly for up to 12 weeks in ECU exercise clinics provided that their tumors remained unresectable over this time period. Each session was ~60 minutes, including 20–30 minutes of resistance training and a maximum 20 minutes of aerobic-based exercise. In addition, a 5-minute warm-up (treadmill walking) and cool-down (static stretching) were completed at the beginning and end of each session. The program was progressively overloaded and autoregulated based on the patient's readiness to train at the start of each session [10].

Resistance training included 6 exercises that targeted the major muscle groups of the upper body and lower body using predominantly machine-based equipment (overhead press, pull-down, chest press, seated row, leg press, and leg curl). Each exercise was performed in 2-3 sets at 8–12 repetition maximum (RM). The training load was increased by 5–10% when a patient successfully completed two additional repetitions on the last set of an exercise for two consecutive sessions.

Aerobic-based training comprised continuous cycling on a cycle ergometer (upright or recumbent) and intermittent boxing-related drills at a moderate-intensity to vigorous-intensity, which were alternated from session to session to provide greater variety and training stimulus. Exercise intensity was manipulated from ~65% to 85% of estimated maximum heart rate (MHR = 220-age), corresponding to a rating of perceived exertion (RPE) of 4–6 (moderate–hard) on the 10-point Borg scale [27]. For continuous cycling, patients were asked to pedal at a cadence of 50–80 rpm with pedalling resistance and speed adjusted to elicit target intensity [28]. Intermittent boxing-related training included 4–8 bouts of 45–60 seconds repeated punches at a boxing heavy bag or focus mitts with 60-second rest intervals between adjacent bouts. Various punch combinations (e.g., jab-straight-jab) with or without the addition of footwork (e.g., forward/backward stepping) and defence moves (e.g., ducking) were used, and patients were asked to wear standardised boxing gloves during training.

2.3. Outcome Measures. Feasibility was assessed by attendance rate (ratio between attended and prescribed sessions), permanent discontinuation (end of the program before week 12 without completing the posttest), exercise interruption (missing ≥3 consecutive sessions), and exercise modification (sessions deviating from the original prescription, e.g., reduction in exercise intensity and/or volume, and end of a session earlier than the planned duration). Reasons were recorded when the occurrence of discontinuation, nonattendance, or nonadherence to original prescriptions. The incidence of serious (events that are life-threatening or lead to hospital admission or death) [29] and nonserious AEs

were documented by a study investigator and patients in a logbook (e.g., training log). An AE was defined as any unfavourable experience that occurred over the time course of the study and was recorded until dropout for whatever reason.

Measurement of efficacy outcomes was performed at baseline and postintervention. Whole-body lean mass and fat mass were examined using dual-energy X-ray absorptiometry (DXA; Hologic Discovery A, MA, USA) [30]. Upper body and lower body muscle strength was assessed using 1 RM (the maximum weight that can be lifted only once) chest press and leg press, respectively (Cybex International Inc., Medway, MA, USA) [30]. Functional ability was assessed using the 400-m walk, the 6-m backwards tandem walk, and 5 times sit-to-stand [31].

Self-administered questionnaires were used for fatigue (Functional Assessment of Chronic Illness Therapy-Fatigue) [32], psychological distress (Brief Symptom Inventory-18) [33], other cancer-related and treatment-related symptoms and overall QoL (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module [EORTC-QLQ C30]) [34], and physical activity level (Godin Leisure-Time Physical Activity Questionnaire) [35]. In addition, patients' views regarding the exercise prescription, perceived facilitators and barriers to exercise during the study, and intentions towards exercise after the intervention were examined using a semi-structured questionnaire survey at postintervention.

2.4. Statistical Analysis. Data are presented at an individual-patient level for baseline characteristics and outcomes measures at each time point, as recommended in relevant guidelines [36, 37]. Descriptive statistics were used to summarise data regarding attendance, adherence, AEs, and responses to a semi-structured questionnaire survey. The percentage change between baseline and postintervention of individual cases was calculated for efficacy outcomes. The sample size of this study was not prespecified given no published literature or anecdotal clinical evidence available in this clinical setting [38]. However, to evaluate the recruitment potential and strategies used, patients that could be recruited over a planned recruitment time frame of 12 months were analysed [39]. Considering the study clinician's historical caseloads, we anticipated recruiting at least 10 participants within this period. All analyses were performed using R 4.2.1 (https://www.r-project.org).

3. Results

Thirteen patients with pancreatic cancer referred to EMRI were invited to participate in the study. Of them, 6 patients (46%) with advanced disease provided informed consent and undertook the baseline assessment. Reasons for declining to participate included uninterested in the research ($n = 3$), time constraint/travel difficulty ($n = 3$), and feeling exhausted from treatment ($n = 1$).

Baseline demographic and clinical characteristics of enrolled patients are provided in Table 1. These patients (including 5 male and 1 female) ranged in age from 60 to 75 years, had a BMI <31 kg/m^2, and were considered insufficiently or moderately active with a Godin Leisure Score Index ≤16 [40] at study entry. Of the 6 enrolled patients, 4 had a diagnosis of *de novo* or recurrent metastases (hepatic/lung) from the primary adenocarcinoma of the pancreas or the ampulla of Vater; the other 2 were considered locally advanced due to partial or complete encasement of major arterial (including superior mesenteric artery and hepatic artery) and venous (superior mesenteric vein) structures. All but 2 patients had already commenced first-line chemotherapy before study entry with time since chemotherapy ranging from 3 to 29 weeks.

3.1. Attendance, Adherence, and Adverse Events. An overview of session attendance and program adherence is provided in Figure 1. Case #5 withdrew from the study (due to no longer wishing to participate in the study) after the baseline assessment without initiating the intervention. The remaining 5 patients attended 12, 20, 19, 8, and 18 sessions, corresponding to 50%, 83%, 95%, 42%, and 75% of the sessions prescribed. The occurrence of nonattendance (missing 1 or 2 consecutive sessions) in cases #3, #4, and #6 was mainly due to health-related reasons (e.g., diarrhea) (Supplemental Table 1). Furthermore, exercise interruption (missing ≥3 consecutive sessions) occurred in cases #1, #2, and #4 due to health-related (e.g., swollen legs) and non-health-related reasons (e.g., holiday). All complete cases required modifications to the original prescriptions with the number of sessions affected being 2, 10, 8, 2, and 13, corresponding to 17%, 50%, 42%, 25%, and 72% of the sessions attended by cases #1, #2, #3, #4, and #6, respectively. The occurrence of nonadherence mainly resulted from health-related reasons (e.g., fatigue).

Various AEs were recorded over the study period with the most frequent type of event being fatigue (21 episodes) that was noted in all complete cases. However, none of the AEs were serious except for 1 episode of sepsis (leading to hospitalisation) in case #4, which was recorded outside of exercise. Three patients reported 7 episodes of muscle soreness/pain (cases #1, #4, and #6) and 7 episodes of dizziness (cases #2, #3, and #6) in 58 and 57 attended sessions (~12%), respectively. Further, case #3 reported 1 episode of tight chest in 19 attended sessions (5%) and case #6 reported 1 episode of muscle cramp in 18 attended sessions (6%). All AEs observed during or immediately after an exercise training session resolved without medical attention, though modifications to the original prescription of the affected session were required. No AEs occurred as a result of exercise testing except for 1 episode of lower back pain for case #3 during the 5 time sit-to-stand test.

3.2. Objective Measures and Patient-Reported Outcomes. Compared with baseline, body weight (−0.9%–1.9%) and total lean mass (0.1%–4.4%) were improved or stabilised in all complete cases (Figure 2). In addition, there was a decrease in visceral (−1.1%−−8.6%) and total fat mass (−0.4%−−5.5%) in 4 out of the 5 cases.

Table 1: Baseline characteristics of enrolled patients.

Variables	Case #1	Case #2	Case #3	Case #4	Case #5	Case #6
Age (years)	73	60	66	63	72	75
Gender	Male	Male	Male	Male	Male	Female
BMI (kg/m^2)	26.9	26.7	30.8	22.4	18.8	23.6
Marital status	Divorced	Married	Married	Divorced	Married	Divorced
Education level	Bachelor's degree	Higher degree	Higher degree	Bachelor's degree	Bachelor's degree	Not disclosed
Employment status	Part-time	Full-time	Retired	Retired	Retired	Full-time
Cigarette smoking	Never	Never	Past	Never	Never	Past
Current drinker	No	No	Yes	No	Yes	No
Godin leisure score index[a]	16	0	3	9	Unknown	15
Clinical stage	Metastatic (liver)	Metastatic (liver)	Locally advanced	Metastatic (liver)[b]	Metastatic (lung)[b]	Locally advanced
TNM classification	T2N2M1	T4N2M1	T1bN0M0	T3bN1M0[c]	T3N1M0[c]	T4N1M0
Time since diagnosis (weeks)	33	23	13	4[d]	23[d]	3
Tumor histology	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma	Adenocarcinoma
Primary tumor location	Tail of the pancreas	Head of the pancreas	Head of the pancreas	Ampulla of vater	Head of the pancreas	Body of the pancreas
Time since starting first-line therapy (weeks)	29	20	10	3[e]	0	0
Comorbid conditions						
Hypertension	No	No	Yes	Yes	Yes	Yes
High cholesterol	No	No	Yes	No	Yes	Yes
Heart disease	No	No	Yes	No	No	No
Diabetes	No	No	No	Yes	No	Yes
Parkinson's disease	No	No	No	Yes	No	No

[a]A Godin leisure score index of 14–23 units or less than 14 units is classified as moderate active or insufficient active [40]. [b]Distant relapse from the pancreatic primary. [c]At the time of the initial diagnosis. [d]Time since diagnosis of recurrent metastases. [e]Time since starting the initial chemotherapy for recurrent metastases. BMI, body mass index.

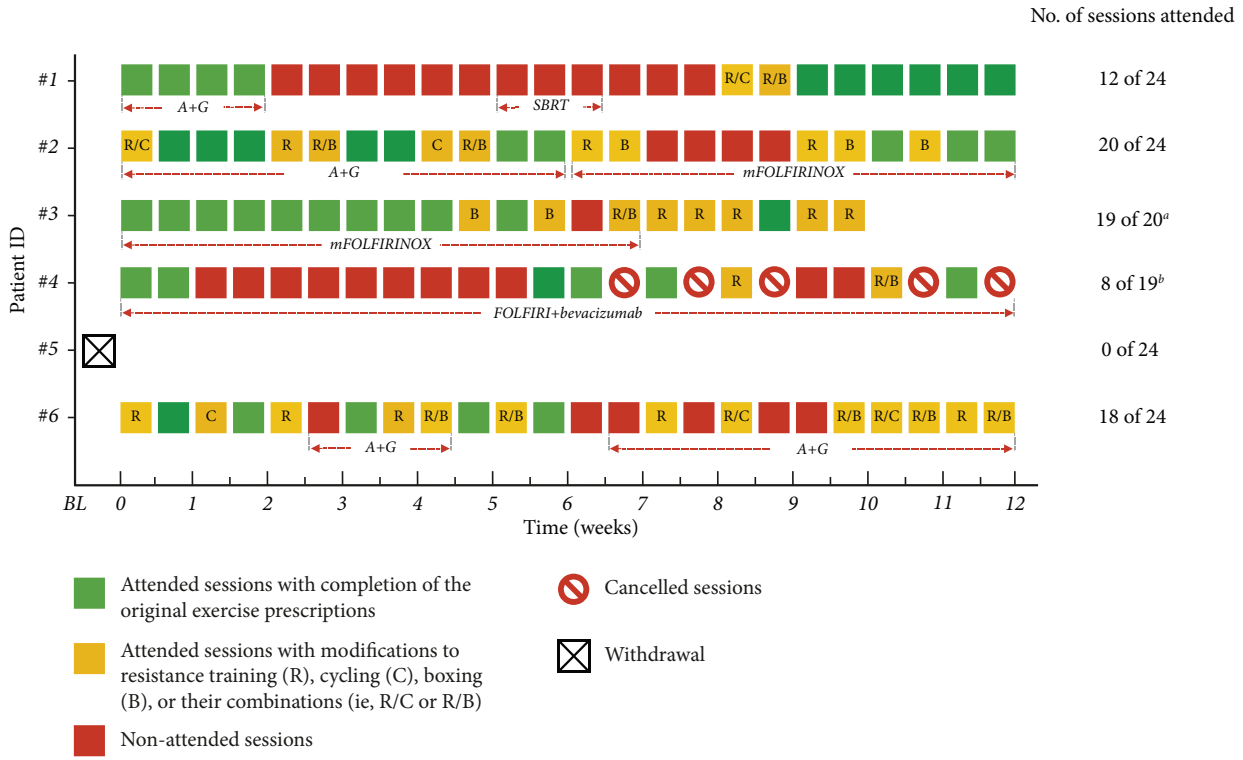

Figure 1: Overview of exercise attendance and adherence. [a]Only 20 sessions were prescribed due to patient eligible for surgical resection. [b]Only one session per week was prescribed since week 7 to accommodate the patient's preference. *A + G*, nab-paclitaxel plus gemcitabine; BL, baseline; FOLFIRI, fluorouracil, leucovorin, and irinotecan; mFOLFIRINOX, modified FOLFIRINOX (leucovorin, fluorouracil, irinotecan, and oxaliplatin); SBRT, stereotactic body radiation therapy.

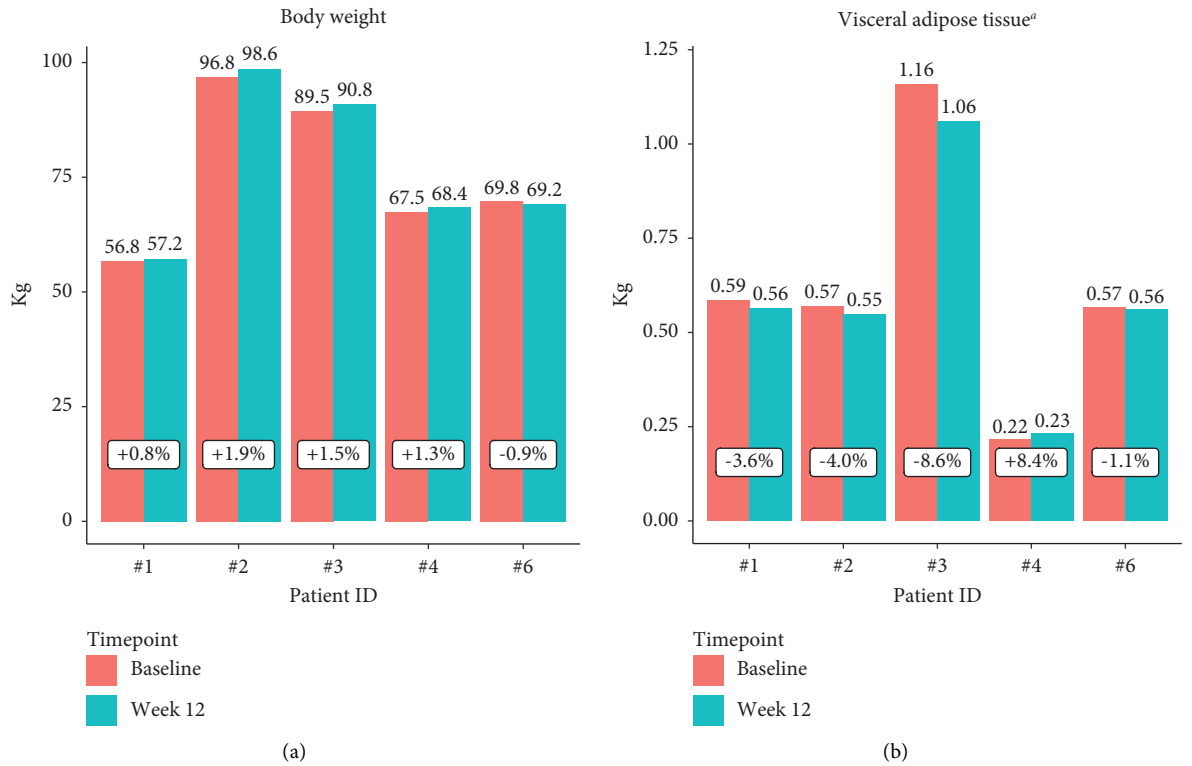

Figure 2: Continued.

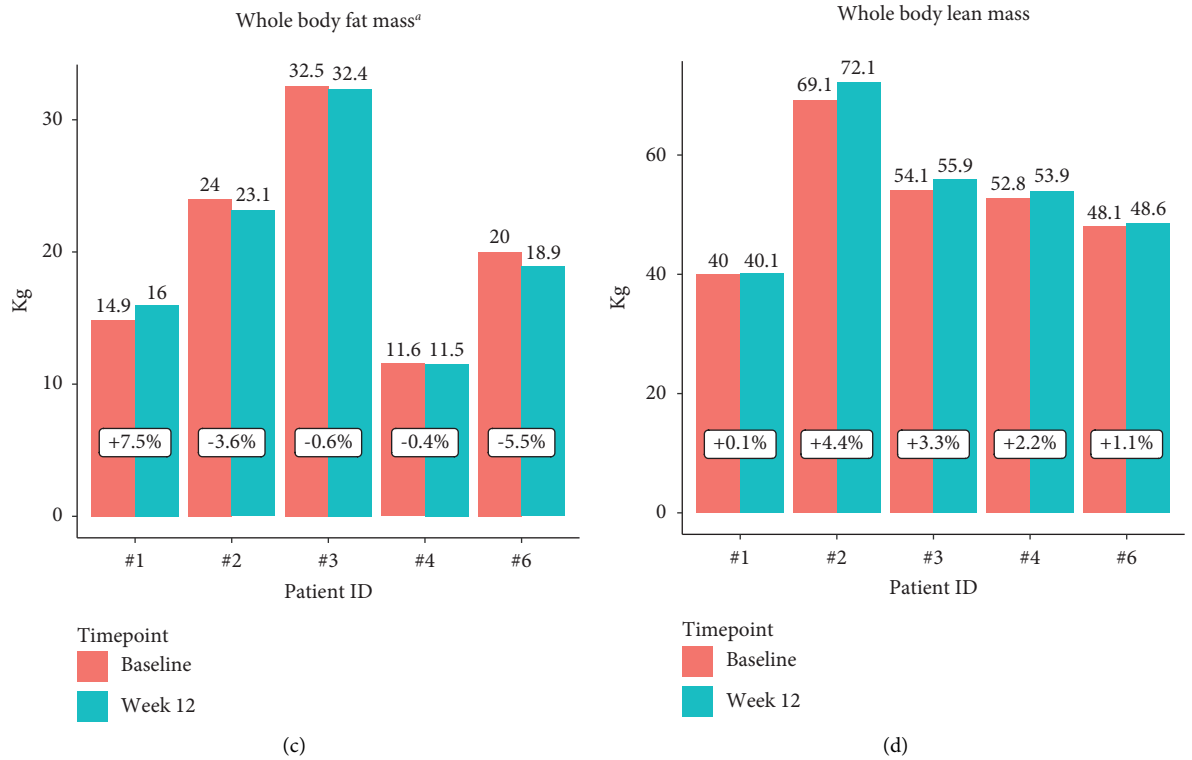

Figure 2: Changes in body weight and body composition from baseline to postintervention. [a]Negative change (given as %) represents an improvement.

Chest press strength improved (8.3%–12.0%) in 4 of the 5 patients, and all cases improved leg press strength (7.1%–75.0%) over the intervention (Figure 3). In addition, 3 or 4 patients showed an improvement or maintenance in 6-m backward tandem walk (up to −35.8%), 400-m walk (up to −9.1%), and 5 times sit-to-stand (up to −21.4%). Given the magnitudes of changes in these measurements, 3 patients, 2 patients, and 1 patient met or exceeded the threshold for clinically important improvements for the 400-m walk (20 seconds) [41], 5 times sit-to-stand (1.7 seconds) [42], and 1 RM chest press (6 kg) [43], respectively.

All complete cases demonstrated maintenance of or a decline in psychological distress based on the depression, anxiety, and somatisation symptom scales as well as the global score on the Brief Symptom Inventory-18 (Table 2). In addition, 4 cases (except for case #6) reported higher global health as well as improvement in the functional scales and reduction in symptom scales of the EORTC QLQ-C30. For patients who demonstrated an improvement in EORTC QLQ-C30, the degree of changes was all beyond the threshold for clinical importance (≥5 points) [44]. Furthermore, the improvements of fatigue level in 4 of the 5 patients based on the Functional Assessment of Chronic Illness Therapy-Fatigue were also of clinical importance (≥3 points) [45].

3.3. Patients' Perceptions of and Experience with the Program. Responses to a semi-structured questionnaire survey for perceptions of and experience with the intervention are summarised in Supplemental Table 2. Overall, all patients were satisfied with the program and considered the prescribed exercise frequency, duration, and intensity suitable, though case #4 indicated "*once per week*" as a preferable frequency due to his Parkinson's disease burden. Of the prescribed exercise components, resistance training was mostly liked followed by intermittent boxing, while 2 patients disliked continuous cycling. The most cited facilitator to the initiation and continuation of the program was the desire to address chemotherapy-induced physical and psychological deterioration, whereas the most frequently reported barriers were time commitment and the side effects involved in chemotherapy. In addition, all patients felt the intervention very helpful by making them physically and

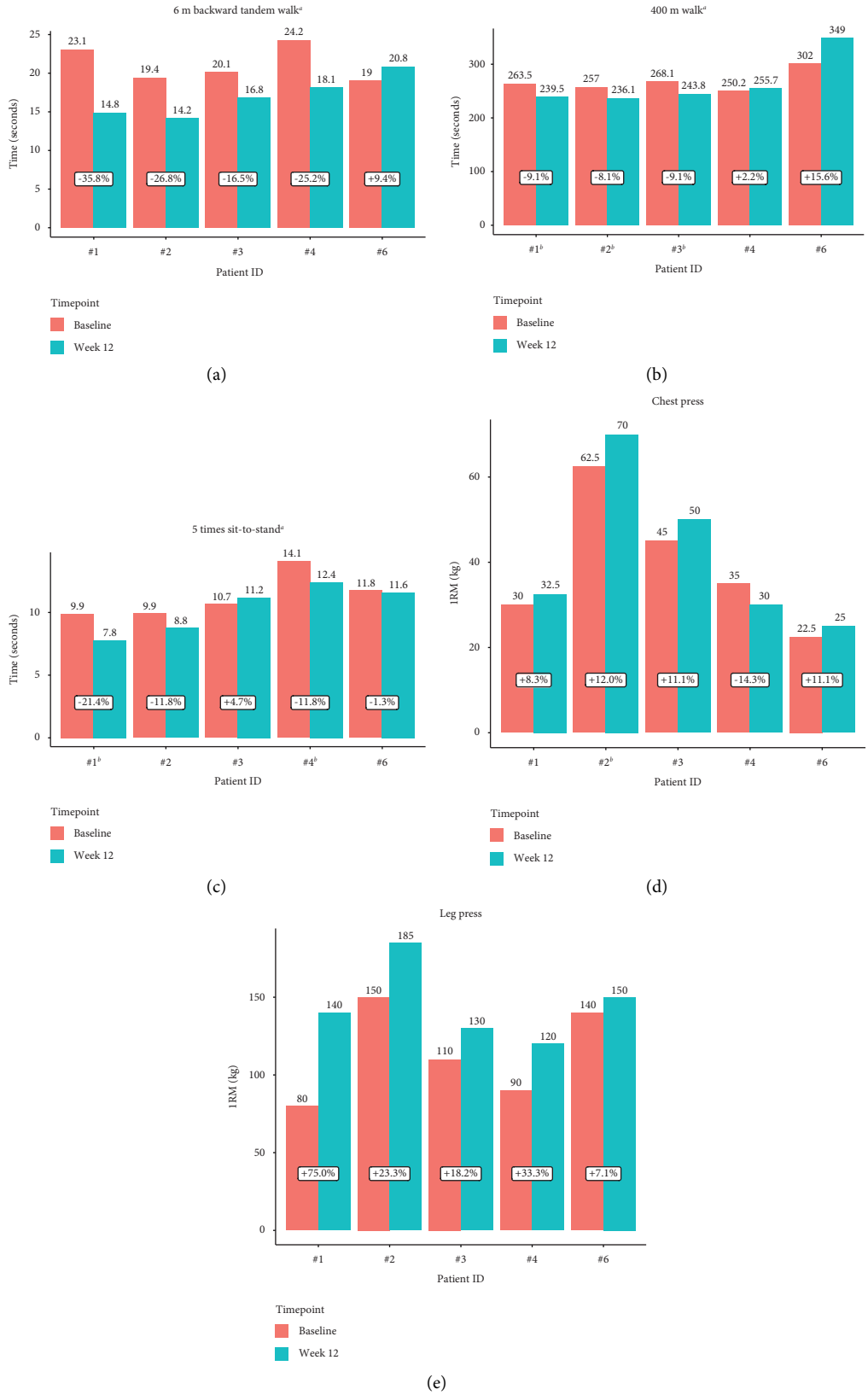

FIGURE 3: Changes in functional ability and muscle strength from baseline to postintervention. [a]Negative change (given as %) represents an improved performance. [b]Patients whose magnitude of change in the measurement met or exceeded the threshold for clinically important improvements.

Table 2: Changes in patient-reported outcomes.

Measures	Case #1			Case #2			Case #3			Case #4			Case #6		
	T0	T1	%	T0	T1	%	T0	T1	%	T0	T1	%	T0	T1	%
BSI-18															
Depression, [a]T-score	42.0	42.0	0.0	42.0	42.0	0.0	50.0	50.0	0.0	48.0	48.0	0.0	57.0	48.0	−15.8
Anxiety, [a]T-score	39.0	39.0	0.0	39.0	39.0	0.0	39.0	39.0	0.0	60.0	60.0	0.0	48.0	48.0	0.0
Somatisation, [a]T-score	47.0	47.0	0.0	58.0	58.0	0.0	66.0	66.0	0.0	58.0	58.0	0.0	62.0	57.0	−8.1
Global severity index, [a]T-score	41.0	41.0	0.0	50.0	50.0	0.0	57.0	57.0	0.0	57.0	57.0	0.0	58.0	53.0	−8.6
EORTC QLQ-C30															
Global health status/QoL, score (0–100)	66.7	83.3	**25.0**	25.0	83.3	**233.3**	41.7	58.3	**40.0**	50.0	83.3	**66.7**	66.7	58.3	−12.5
Functional scales, score (0–100)															
Physical functioning	93.3	100	**7.1**	60.0	93.3	**55.6**	66.7	80.0	**20.0**	80.0	100.0	**25.0**	80.0	60.0	−25.0
Role functioning	100	100	0.0	16.7	83.3	**400.0**	16.7	66.7	**300.0**	66.7	83.3	**25.0**	100	33.3	−66.7
Emotional functioning	100	100	0.0	100	100	0.0	91.7	100.0	**9.1**	91.7	91.7	0.0	50.0	58.3	**16.7**
Cognitive functioning	100	100	0.0	100	100	0.0	100.0	100.0	0.0	100	100	0.0	83.3	66.7	−20.0
Social functioning	66.7	100	**50.0**	33.3	100	**200.0**	50.0	66.7	**33.3**	50.0	66.7	**33.3**	100.0	100.0	0.0
Symptoms scales/items, score (0–100)															
Fatigue[a]	33.3	22.2	**−33.3**	55.6	11.1	**−80.0**	66.7	33.3	**−50.0**	33.3	11.1	**−66.7**	33.3	77.8	133.3
Nausea and vomiting[a]	0	0	0.0	16.7	0	**−100.0**	33.3	16.7	**−50.0**	33.3	33.3	0.0	0	0	0.0
Pain[a]	0	0	0.0	0	0	0.0	0	33.3	200.0[b]	0	0	0.0	16.7	0	**−100.0**
Dyspnoea[a]	33.3	0	**−100.0**	33.3	0	**−100.0**	33.3	33.0	0.0	0	0	0.0	33.3	66.7	100.0
Insomnia[a]	33.3	0	**−100.0**	66.7	33.3	**−50.0**	33.3	0	**−100.0**	66.7	33.3	**−50.0**	33.3	33.3	0.0
Appetite loss[a]	33.3	33.3	0.0	66.7	0	**−100.0**	0	0	0.0	0	0	0.0	33.3	66.7	100.0
Constipation[a]	33.3	0	**−100.0**	0	0	0.0	0	0	0.0	33.3	0	**−100.0**	33.3	33.3	0.0
Diarrhea[a]	0	0	0.0	0	33.3	100.0[c]	100	0	**−100.0**	0	0	0.0	0	0	0.0
Financial difficulties[a]	33.3	0	**−100.0**	0	0	0.0	0	0	0.0	0	0	0.0	0	66.7	200.0[c]
FACIT-F, total score (0–52)	46.0	49.0	**6.5**	23.0	47.0	**104.4**	19.0	36.0	**89.5**	43.0	49.0	**14.0**	45.0	27.0	−40.0

BSI-18, Brief Symptom Inventory-18; EORTC QLQ-C30, European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core Module; FACIT-F, Functional Assessment of Chronic Illness Therapy-Fatigue; T0, baseline; T1, postintervention; %, percentage change. [a]Negative change represents an improvement. [b]Calculated after adding the smallest possible value greater than 0 for the pain scale (i.e., 16.7) to both baseline and posttest values. [c]Calculated after adding the smallest possible value greater than 0 for the diarrhoea/financial difficulties item (i.e., 33.3) to both baseline and posttest values. Bold type indicates clinically important improvements.

mentally stronger during chemotherapy. Moreover, all patients indicated that they were "*very likely*" to continue regular exercise after the program, and 3 continued exercising at an EMRI exercise clinic under supervision through a standard user-pay model.

4. Discussion

In this case series pilot study, we primarily reported on the attendance, adherence, and AEs in 6 older patients (aged ≥60 years) with advanced pancreatic cancer undertaking a multimodal exercise program during first-line chemotherapy with an exploratory evaluation of the efficacy of the intervention on physical, physiological, and psychological health indicators as well as QoL. Further, we measured patients' perceptions of and experience with the exercise program. Based on the preliminary findings, a supervised program that consisted of conventional forms of resistance and aerobic exercise, and intermittent boxing-related training for up to 12 weeks appears to be feasible and may potentially improve or attenuate declines in body composition, muscle strength, functional ability, cancer-related and treatment-related symptoms, and overall QoL.

The retention rate of 83% in this study is higher or comparable to previous studies that delivered a supervised exercise program with an equal length (12 weeks) to patients with pancreatic cancer during treatment [19, 46]. At an individual-patient level, the attendance rates of cases #2 (83%), #3 (95%), and #6 (75%) are similar to earlier case reports of a 12-week supervised program with an equal frequency (2 sessions/week) in 2 younger patients (≤55 years) with advanced pancreatic cancer undergoing first-line chemotherapy [23, 24]. A greater number of sessions for each case requiring modifications to original prescriptions in this study than the earlier case reports that reported equivalent data is not unexpected, given the prescription of a higher training volume and intensity and the inclusion of older patients [23, 24]. However, the mean adherence rate in this study (59%) is not different from a study researched by our institute that evaluated a supervised program including combined resistance and aerobic exercise at a comparable volume and intensity in patients with different stages (including metastatic) of pancreatic cancer (61%) [46].

The absence of serious AEs during or immediately after exercise training suggests a favourable safety profile of the program. This finding is encouraging as a sport-related training component (boxing) was added, which has greater movement variability and higher physical demands compared with conventional forms of resistance and aerobic exercise, suggesting a more dynamic training mode may be considered in a program for a more enjoyable exercise experience of patients [47]. However, the occurrence of nonserious AEs potentially related to exercise uptake, albeit at a low rate (5%–12%), underlines the importance of close supervision during exercise training in this patient group to ensure appropriate and timely adjustment to exercise prescriptions for minimal injury risk. Also, standardisation of methods for definition, collection, and reporting of AEs in future studies remains critical for a more definitive evaluation of the safety of exercise in this clinical setting [48].

Patients with advanced pancreatic cancer undergoing chemotherapy are predisposed to progressive loss of body weight and skeletal muscle mass owing to a variety of disease-related and treatment-related factors, which are frequently accompanied by decreased muscle strength and functional ability and increased treatment toxicities and are associated with poor chemotherapy tolerability, QoL, and survival outcomes [49, 50]. For example, Daly and colleagues reported a loss equivalent to 1 kg in skeletal muscle mass per 100 days in patients with foregut cancer (including advanced pancreatic cancer) undergoing chemotherapy [49]. This magnitude of muscle loss has been reported to be associated with a significant reduction in muscle function and strength [49, 51]. Importantly, current evidence suggests that the weight loss and skeletal muscle atrophy in pancreatic cancer may be aggravated by higher adipose tissue, promoting inflammatory and catabolic responses and in older people due to negative changes in nutritional status and digestive function [52, 53]. Thus, the improved or maintained body weight, body composition (average increase in muscle mass of 1.3 kg and decrease in fat mass of 1.1 kg), muscle strength, functional ability, cancer-related and treatment-related symptoms, and overall QoL in 4 of or all 5 complete cases are highly desirable. The poor performance in 5 times sit-to-stand tests in case #3 may be due to total hip replacement surgery that the patient completed 6 months before the study; the patient experienced a sudden pain in the low back (sacrum) in the second attempt of the test (3 attempts required) and ceased the test. In addition, case #4 had several discrete episodes of weakness, lethargy, and vomiting due to chemotherapy after the program and before the posttest. This may explain the declines in performance in the 400-m walk and 1 RM chest press for this patient. Similarly, case #6 underwent chemotherapy 1 day before the postintervention test and reported a lack of energy when attending the testing session, which possibly affected the performance in the 6-m backward tandem walk and 400-m walk.

Apart from the findings above, the results of patient-reported experience further support the feasibility and acceptability of the program in this patient group during first-line chemotherapy. Given the reported barriers to regular exercise (i.e., time commitment and side effects involved in chemotherapy), future research may consider adding an alternative exercise delivery mode (e.g., telehealth) and using (if possible) a colocated exercise clinic within a cancer treatment facility to facilitate exercise uptake [54]. These measures may also assist in recruitment, as time constraint/travel difficulties were cited as major reasons for those who declined to participate in the study. Our finding that intermittent-based exercise modalities (i.e., resistance training and boxing) were more liked than continuous cycling is interesting and justify further investigations of factors that might affect exercise choices of these patients to assist in the uptake and maintenance of exercise. In addition, a strong willingness to continue exercise after a maximum 12-week program identified in the current study provides a rationale for future studies to use a longer-term intervention. An

ongoing randomised controlled trial (the EXPAN trial) by our institute of a maximum 6-month intervention of this format in patients with borderline resectable or locally advanced pancreatic cancer undergoing neoadjuvant therapy may provide additional information in this regard [55].

The strengths of this study include the delivery of a novel multimodal exercise intervention in older patients (≥60 years) with advanced pancreatic cancer and the use of empirically tested or validated outcome measures. The major limitations of this study are the inclusion of only 6 cases and the lack of controls. As such, the health-related efficacy outcomes reported in this study should be interpreted with caution given the inherent limitations of a case series design. However, as this case series was intended as a pilot study to provide a rationale for future trials with a larger sample size, favourable findings regarding feasibility and acceptability as well as indications of the health benefits of the intervention are of significance. Although the pace of recruitment (on average <1 patient per month) was slower than anticipated, the recruitment rate of almost 50% for a relatively uncommon cancer over a COVID-19 lockdown period is suggestive of the strong interest of some patients in exercise during this treatment phase. Despite this, future trials in this clinical setting should consider including multiple study clinicians and collaborative hospitals to facilitate recruitment.

5. Conclusion

This case series pilot study suggests that the multimodal exercise intervention as implemented may be feasible and potentially improve or attenuate declines in physical structure/capacity, psychological health, and overall QoL in older patients with pancreatic cancer during first-line chemotherapy. Given the encouraging findings, further research with a rigorous design and a larger sample size in this clinical setting is justified.

Data Availability

Deidentified data used and/or analysed in this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Authors' Contributions

HL conceived and designed the analysis of the study, collected and managed the data, interpreted the results, and wrote the first draft of the manuscript. DRT, DAG, RUN, CIT, and NS made important contributions to the conception and design of the analysis of the study and critically revised the manuscript. All authors read and approved the final version.

Supplementary Materials

Supplemental Table 1. Reasons for discontinuation, interruption, nonattendance, and modifications. *Supplemental Table 2*. Responses to a semi-structured questionnaire survey. (*Supplementary Materials*)

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