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ORIGINAL ARTICLE

Effects of a prescribed, supervised exercise programme on tumour disease progression in oncology patients undergoing anti-cancer therapy: a retrospective observational cohort study

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Key words
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Abstract

Background: Exercise promotes numerous advantages in both health and disease, and is increasingly being acknowledged to improve overall survival in cancer patients. Preclinical studies indicate a direct effect on tumour behaviour, but human data on the effect of exercise on tumour progression are lacking.
Aims: To capture preliminary clinical data regarding the impact of a prescribed, supervised exercise programme on cancer disease progression.
Methods: Retrospective cohort study of 137 matched pairs of patients. All patients referred to LIFT Cancer Care Services (LIFT) supervised exercise programme between 2018 and 2019 were matched with non-LIFT patients from the oncology practice database. Disease progression via staging computed tomography scans ± tumour markers was compared for each match. Secondary outcomes were changes in neutrophil-to-lymphocyte ratio (NLR) and death. Results were analysed by logistical regression and adjusted for potential confounders.
Results: Patients from the LIFT group had a 66% (OR = 0.34, 95% CI 0.19 to 0.61) decreased odds of disease progression and 76% (OR = 0.24, 95% CI 0.12-0.47) decreased odds of death compared with the non-LIFT group. No effect on the number of LIFT sessions on disease progression was demonstrated. The LIFT group had a mean final NLR reading 3.48 (−5.89 to −1.09) lower than the non-LIFT group.
Conclusion: Supervised exercise programmes have the potential to significantly improve outcomes in cancer patients due to an effect on tumour progression.

Introduction

Exercise has well established benefits in both health and disease.[1–3] A number of international organisations including the Clinical Oncology Society of Australia have recommended that exercise should be prescribed to all patients with cancer as part of their treatment regimen.[4,5] These endorsements are based on a growing body of evidence for the benefits of physical activity to counteract many of the adverse physical and psychological effects of cancer and its treatment.[4] Many of these beneficial effects are linked to the general health-promoting properties of exercise. However, it is increasingly being recognised that exercise training may have direct effects on cancer biology itself.[6]

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In the oncology setting, it is known that exercise can improve symptom outcomes as well as important quality of life measures.[1–3,7,8] A systematic review by Fuller *et al.*[9] reported that out of the 140 meta-analyses published on the therapeutic effects of exercise for cancer survivors, the majority (75%) showed statistically significant and clinically relevant benefits of exercise on a range of treatment-related side-effects and physical, functional and psychosocial outcomes.

Importantly, post-diagnosis exercise has been suggested in observational data to enhance survivorship in cancer patients by up to 60% via both cancer-related and all-cause mortality.[10–14] The way in which physical activity is undertaken appears to be relevant to its effect magnitude. An analysis of 34 randomised controlled trials (RCT) found that the effects of supervised exercise were twice as large as those of unsupervised exercise in patients with cancer.[8] Supervised exercise is performed under the guidance of a trained health professional, performing specific, sometimes individualised, exercises with the goal of improving the participants health-related outcomes.

The exact mechanisms for these significant benefits are unclear but may be due to systemic or direct effects on the tumours itself.[15,16] Recent research has focused on molecular and cellular mechanisms by which exercise might directly alter tumour cell behaviour.[6,17] Data from murine models are showing that exercise training can affect tumour initiation, progression and metastasis.[3,18]

The ways by which exercise can directly alter cancer disease progression have largely been investigated using animal or *in vitro* models, while human trials are limited. Therefore, this study aims to capture preliminary clinical data regarding the impact of a prescribed, supervised exercise programme on cancer disease progression in a population of patients undergoing anticancer treatment.

It was hypothesised that participation in a supervised exercise programme could reduce the rate of disease progression. This was tested by matching oncology patients attending LIFT Cancer Care Services (LIFT) exercise programme in addition to usual cancer care, with similar patients who just received usual care from the same cohort of treating oncologists. The primary outcome was evidence of disease progression according to staging computed tomography (CT) images. A secondary end-point of neutrophil-to-lymphocyte ratio (NLR), a known marker of inflammation and prognostic indicator in cancer,[19,20] was also measured.

Methods

Study design and data sources

This was a retrospective cohort study, using available data from patients who attended LIFT between 2018 and 2019, and patients attending the Adelaide Cancer Centre (ACC) between 2010 and 2019. The data retrieved were available within the participants electronic case file and were de-identified by a staff member at the ACC assigning each participant a randomly generated study participant number. Data sources included medical imaging, blood tests and the number of LIFT sessions attended for prescribed, supervised, exercise medicine.

Exercise intervention

The LIFT exercise intervention was a personalised, supervised exercise programme, individualised to each patient. The exercise programmes were designed by trained physiotherapists and were based on the patient's goals and availability of the patient to attend the clinic. The exercise programmes are predominately vigorous in intensity and incorporate a combination of resistance, cardiovascular, balance and flexibility exercises. The number of sessions per week range from one to five and are approximately 1 h in duration based on the patient's individual tolerance. There was no defined treatment period.

Ethics

This study was approved by the Bellberry Human Research Ethics Committee (approval number 2019-10-870) and a waiver of informed consent was granted.

Study population

The study cohort consisted of patients older than 18 years with a solid tumour cancer diagnosis. All patients who participated in at least one exercise medicine session at LIFT, while also receiving treatment for their cancer from ACC, were included in the intervention cohort. Each patient was then individually matched to a comparable control participant who had also received treatment through ACC but had not attended LIFT for exercise medicine. The matching process utilised the ACC cancer registry, which contained diagnostic information about all patients who had been treated at ACC. The patients were matched by as many of the criteria listed in Table 1 as possible, with 'gender' and 'cancer diagnosis' being a requirement for matching. Pairs were assigned a matched concordance percentage based on the number of criteria that were met in the matching process.

Outcome measures

The primary outcome of the study was tumour progression as stated by the authorised reports of staging CT

Table 1 Participant matching criteria

Matching criteria
Cancer diagnosis (ICD-10 Code)†
Gender†
Age at diagnosis (±10 years)
Cancer histology (ICD-0-3 Codes)
Stage (TNM classification)
Grade
Treatment match by at least one agent/modality
Oncologist
Date of diagnosis (±5 years)
Presentation date (±5 years)

†Required for matching. ICD, International Classification of Disease coding system designed by World Health Organization; ICD-10, latest revision of ICD; ICD-0-3, International Classification of Disease for Oncology, 3rd edition – further classifies neoplasms based on site (topography) and histology (morphology); TNM, cancer staging system whereby T refers to size/extent of primary tumour, N refers to the number of nearby lymph nodes and M refers to whether the cancer has metastasised.

scans completed by independent consultant radiologists, based on standard Response Evaluation Criteria in Solid Tumours (RECIST) criteria. In patients with prostate cancer where no CT was available, the tumour marker prostate-specific antigen (PSA) was used as a surrogate end-point. Secondary outcomes included the effect of treatment on the neutrophil-to-lymphocyte ratio (NLR) and death. The trial period for each match was determined by the most recent staging CT scan prior to the commencement of LIFT attendance for each LIFT participant. This was identified as 'Scan A'. The trial period was calculated between 'Scan A', and the last available staging scan (or tumour marker measurement) for that patient. This period was then transposed to the control non-LIFT patient by back-dating from their last available staging scan (or tumour marker). 'Scan A' for the non-LIFT patient was then determined as the most recent staging scan prior to the commencement of the matched trial period.

Statistical analysis

Logistic regression models were fitted to estimate the association between the treatment group and disease progression. Models were adjusted for the potential confounders: sex (male/female), age (<50, 50–70, 70+ years), duration from scan A to final scan, cancer type (breast cancer, prostate cancer, all other cancers), cancer stage (I, II, III, IV) and match concordance. Due to the large number of categories in the cancer diagnosis fields (ICD-10 and ICD-0-3), models could not be fitted that included these variables as confounders. For this reason, ICD-10 values were combined into three categories: 'Breast and female genital organs' (ICD-10 codes C50-C58, n = 86) of which all but one had breast cancer (C50), 'Male genital organs' (ICD codes C60-C63, n = 74) all of whom had prostate cancer (C61) and all other ICD-10 categories.

Logistic regression models were fitted to estimate the dosage effects of the number of LIFT sessions on disease progression. An adjusted model was fitted adjusting for the confounders listed earlier. Linear regression models were used to determine the effect of the treatment group on final NLR, the model was fitted controlling for the initial NLR values and the listed potential confounders. Logistic regression models were used to determine the effect of the treatment group on death (both unadjusted and adjusted for the potential confounders listed above). Subgroup analyses were also fitted to investigate the association between treatment group and disease progression by cancer diagnosis based on ICD-10 codes. Again, due to case numbers, three categories were used (as described earlier).

Results have been presented as unadjusted and adjusted odds ratios (OR) and 95% confidence intervals (CI) for logistic regression models. Unadjusted and adjusted difference in means and 95% CI are presented for linear regression models.

Results

Data were collected from 137 matched pairs of patients. Table 2 shows the patient characteristics. The most common cancer diagnoses were breast and prostate cancer, and the most frequent age was the 60–70 years age bracket. The average number of LIFT sessions attended was 11 with a range of 5–25 sessions. The average participant attended LIFT 2–3 times per week.

There was a statistically significant decrease in the odds of disease progression for patient from the LIFT group compared to those who did not attend LIFT. Patients from the LIFT group had a 66% (OR = 0.34, 95% CI 0.19-0.61) decrease in the odds of disease progression compared with the non-LIFT group. There was also a statistically significant decrease in the odds of death for patients from the LIFT group compared to the non-LIFT group. Patients from the LIFT group had a 76% (OR = 0.24, 95% CI 0.12-0.47) decrease in the odds of death compared with the non-LIFT group. The analysis showed that there was no statistically significant effect on the number of LIFT sessions on disease progression (Table 3).

There was a statistically significant decrease in the mean final NLR reading for patients from the LIFT group compared with the non-LIFT group. The average NLR at

Table 2 Patient characteristics

	LIFT patients (*n* = 137)	Non-LIFT patients (*n* = 137)	All patients (*n* = 274)
Matched fields			
Gender			
Female	64 (46.7)	64 (46.7)	128 (46.7)
Male	73 (53.3)	73 (53.3)	146 (53.3)
Age range (years)			
20–30	1 (0.7)	0 (0.0)	1 (0.4)
30–40	9 (6.6)	6 (4.4)	15 (5.5)
40–50	15 (11.0)	13 (9.5)	28 (10.2)
50–60	35 (25.6)	33 (24.1)	68 (24.8)
60–70	48 (35.0)	52 (38.0)	100 (36.5)
70–80	28 (20.4)	31 (22.6)	59 (21.5)
80–90	1 (0.7)	2 (1.5)	3 (1.1)
Trial period, median (IQR) (days)	149 (78–225)	149 (78–225)	149 (78–225)
Diagnosis			
ICD 10			
Lip, oral cavity + pharynx (C00-C14)	7 (5.1)	7 (5.1)	14 (5.1)
Digestive system (C15-C26)	21 (15.3)	21 (15.3)	42 (15.3)
Respiratory system (C30-C39)	7 (5.1)	7 (5.1)	14 (5.1)
Connective and soft tissue (C45-C49)	6 (4.4)	6 (4.4)	12 (4.4)
Breast + female genital organs (C50-C58)	43 (31.4)	43 (31.4)	86 (31.4)
Male genital organs (C60-C63)	37 (27.0)	37 (27.0)	74 (27.0)
Urinary organs (C64-C68)	7 (5.1)	7 (5.1)	14 (5.1)
Eye + central nervous system (C69-C72)	8 (5.8)	8 (5.8)	16 (5.8)
Endocrine glands (C73-C75)	1 (0.7)	1 (0.7)	2 (0.7)
Stage			
I	5 (3.7)	5 (3.7)	10 (3.7)
II	24 (17.5)	24 (17.5)	48 (17.5)
III	36 (26.3)	36 (26.3)	72 (26.3)
IV	70 (51.1)	70 (51.1)	140 (51.1)
Not available	2 (1.5)	2 (1.5)	4 (1.5)
Match concordance, mean (SD) (%)	80.5 (12.1)	80.5 (12.1)	80.5 (12.1)
Non-matched fields			
Final scan result			
Disease progression	49 (35.8)	69 (50.4)	118 (43.1)
Disease remission	9 (6.6)	8 (5.8)	17 (6.2)
Stable disease	79 (57.7)	60 (43.8)	139 (50.7)
LIFT sessions, median (IQR)	11 (5–25)		
Time from first to last scan, median (IQR) (days)	274 (147–471)	350 (172–761)	302 (161–539)
Time from first scan to death, median (IQR) (days)	251 (183–442)	309 (189–496)	285 (187–453)
First NLR, median (IQR)	3.0 (2.0–4.7)	2.6 (1.8–4.6)	2.8 (1.9–4.7)
Second NLR, median (IQR)	2.9 (2.0–6.6)	3.3 (1.9–6.8)	3.1 (2.0–6.6)
Change in NLR, median (IQR)	0.3 (−1.1–2.2)	0.4 (−0.4–2.9)	0.3 (−0.7–2.3)
Death			
Yes	27 (19.7)	53 (38.7)	80 (29.2)
No	110 (80.3)	84 (61.3)	194 (70.8)

IQR, interquartile range; LIFT, LIFT Cancer Care Services.

the start of the trial period was 4 (range 0–53) and 6 at the end (range 1–84). The LIFT group had a mean final NLR reading 3.48 (−5.89 to −1.09) lower than the non-LIFT group, once initial NLR and other potential confounders were accounted for (Table 4).

Table 5 shows subgroup analysis by the ICD 10 category of the effect of treatment group on disease progression. Unadjusted models were presented for all ICD-10 categories except for C73–C75 that did not have enough data to fit a model. Models were fitted for the categories C50–C58 and C60–C63, adjusting for potential confounders. Most ICD-10 categories had no statistically significant difference on disease progression. The exceptions to this were the breast and female genital organs (C50–C58) and the male genital organs (C60–C63) groups. For patients with cancers classified as C50–

Table 3 Logistic regression model results of the effect of the treatment group on disease progression, the number of LIFT sessions on disease progression and the effect of the LIFT exercise programme group on death (adjusted and unadjusted results)

Outcome	Exposure	Unadjusted		Adjusted†	
		OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Disease progression	Treatment group				
	Non-LIFT group	Reference		Reference	
	LIFT group	0.55 (0.34, 0.89)	0.015	0.34 (0.19, 0.61)	<0.001
Disease progression	Number of LIFT sessions	0.99 (0.98, 1.01)	0.480	1.00 (0.98, 1.02)	0.749
Death	Treatment group				
	Non-LIFT group	Reference		Reference	
	LIFT group	0.41 (0.24, 0.72)	0.002	0.24 (0.12, 0.47)	<0.001

†Models adjusted for sex, age, duration from scan A to final scan, cancer stage, cancer type (breast, prostate, other) and match concordance. CI, confidence interval; LIFT, LIFT Cancer Care Services; OR, odds ratio.

Table 4 Results from linear regression models investigating the effect of treatment group on final NLR

Outcome	Exposure	Unadjusted		Adjusted	
		Mean difference (95% CI)	*P*-value	Mean difference (95% CI)	*P*-value
Final NLR	Treatment group				
	Non-LIFT group	Reference		Reference	
	LIFT group	−2.73 (−5.07, −0.39)	0.022	−3.48 (−5.89, −1.09)	0.005

Models adjusted for initial NLR, sex, age, duration from scan A to final scan, cancer stage, cancer type (breast, prostate, other) and match concordance. CI, confidence interval; LIFT, LIFT Cancer Care Services; NLR, neutrophil-to-lymphocyte ratio.

C58 those attending LIFT sessions had decreased odds of disease progression of 82% (OR = 0.18, 95% CI 0.04–0.88) compared with those that did not attend LIFT sessions, once potential confounders are adjusted for. For LIFT patients with cancers classified as C60–C63 there was decreased odds of disease progression of 90% (OR = 0.10, 95% CI 0.03–0.36), once potential confounders are adjusted for.

Discussion

This study supports the hypothesis that participation in a supervised, prescribed exercise programme can significantly reduce cancer tumour progression and even death. Cancer patients attending the LIFT exercise programme showed statistically and clinically significant reduced odds of disease progression (66%) and death (76%) compared with those receiving usual care only.

Interestingly, the benefits of attending the LIFT exercise programme appeared to be applicable across the disease continuum. The majority of breast cancer patients studied had early stage disease (77% stage III or lower), whereas the patients with prostate cancer had mostly advanced disease (74% stage IV). Yet the effects demonstrated on disease progression in these two groups were almost identical.

These benefits were supported by the secondary endpoint marker of systemic inflammation (NLR). High NLR (>5) is known to be a poor prognostic indicator for patients with cancer.[21] Our study demonstrated a significantly lower final NLR in the LIFT cohort compared with the non-LIFT patients by 3.5 on average (mean final NLR values were 5.14 in LIFT vs 7.71 in non-LIFT cohort).

This is one of the first clinical studies of cancer patients to show specific changes to disease progression related to supervised exercise. The results imply that exercise has tumour-specific effects and that there may be clinical validity to the increasing array of *in vitro* and animal studies reporting favourable changes to the tumour microenvironment.[16,22,23]

This effect may be related to cytokines released from muscles (termed myokines) in response to exercise. Certain myokines have been shown in preclinical trials to inhibit tumorigenesis by stimulating apoptosis,[24] inhibiting tumour cell growth[21] and even enhancing the cytotoxic effect of common antineoplastic agents.[25] Changes in intra-tumoural hypoxia and/or host immunity may also be important.[3,26] A recent and comprehensive preclinical study demonstrated that voluntary exercise can lead to redistribution of natural killer cells to tumour sites, and that this was related to a decrease in the incidence and growth of tumour cells across several mouse tumour models by over 60%.[27]

Table 5 Subgroup analysis by ICD 10 category on the effect of treatment group on disease progression

ICD-10 malignant neoplasm category	Exposure	*N*	Unadjusted		Adjusted	
			OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Lip, oral cavity and pharynx (C00-C14)	Treatment group	14				
	Non-LIFT group		Reference			
	LIFT group		0.16 (0.02, 1.63)	0.121		
Digestive organs (C15-C26)	Treatment group	42				
	Non-LIFT group		Reference			
	LIFT group		1.47 (0.43, 4.95)	0.537		
Respiratory system and intrathoracic organs (C30-C39)	Treatment group	14				
	Non-LIFT group		Reference			
	LIFT group		0.53 (0.06, 4.91)	0.579		
Connective and soft tissue (C45-C49)	Treatment group	12				
	Non-LIFT group		Reference			
	LIFT group		2.50 (0.16, 38.60)	0.512		
Breast and female genital organs (C50-C58)	Treatment group	86				
	Non-LIFT group		Reference		Reference	
	LIFT group		0.59 (0.21, 1.63)	0.310	0.18 (0.04, 0.88)	0.034†
Male genital organs (C60-C63)	Treatment group	74				
	Non-LIFT group		Reference		Reference	
	LIFT group		0.20 (0.07, 0.53)	0.001	0.10 (0.03, 0.36)	<0.001‡
Urinary organs (C64-C68)	Treatment group	14				
	Non-LIFT group		Reference			
	LIFT group		1.78 (0.21, 14.77)	0.594		
Eye, brain and central nervous system (C69-C72)	Treatment group	16				
	Non-LIFT group		Reference			
	LIFT group		0.24 (0.02, 3.01)	0.268		
Endocrine glands and related structures (C73-C75)	Treatment group	2§				
	Non-LIFT group					
	LIFT group					

†Model adjusted for age, sex, duration from scan A to final scan, cancer stage and match concordance; ‡Model adjusted for age, duration from scan A to final scan, cancer stage and match concordance; §Not enough data to fit a model. CI, confidence interval; LIFT, LIFT Cancer Care Services.

The handful of other clinical studies looking at effects of physical activity on disease progression have mostly been based on retrospective self-report measures of exercise behaviour, a method with well known limitations.[28] In general, these studies have agreed that increasing exercise exposure improves outcomes, but results have varied in their strength of association.[28–30] For example, Richman[29] investigated disease progression in men with clinically localised prostate cancer. They demonstrated an effect with similar magnitude to our study; a reduction (57%) in disease progression in those who 'walked briskly' for over 3 h per week compared with those who walked less.[29]

Trials specifically involving supervised exercise programmes have predominantly focused on cancer health-related outcomes such as quality of life and physical fitness of cancer survivors.[2] The few studies measuring disease progression have been exploratory in nature. Courneya[31] produced data from the first randomised trial to examine the effect of supervised aerobic exercise on cancer disease outcomes.[31] Their secondary analysis of this study of 242 women with breast cancer demonstrated a greater disease-free survival in the exercising group compared to usual care, although the effect was not statistically significant. Similarly, *post hoc* analysis by West[32] found that undergoing a structured exercise programme may augment tumour regression following neoadjuvant chemoradiotherapy for locally advanced rectal cancer.[32]

Other studies investigating the effects of exercise on cancer disease progression have generally been preclinical. Heterogeneity among these data has generally precluded meaningful comparisons and conclusions being drawn.[18,33]

The clear limitation of the study was its retrospective and observational design. This allowed for the encroachment of significant bias, particularly affecting selection in both LIFT and non-LIFT groups. The patients attending the LIFT exercise programme may have been overall healthier individuals with a higher inclination to exercise and may have had a previous history of exercise. We were not able to control for these or other important

variables such as frailty or performance status that may have influenced the results. These unmeasured variables may explain the magnitude of the benefit shown in this study in addition to the lack of dose–response found. Furthermore, the non-LIFT cohort were generally more historical than the LIFT patients. This presents two confounders: (i) due to changes in treatment practices that theoretically should improve over time; and (ii) the duration of follow up available was longer in the non-LIFT group, which means that the trial period would have likely occurred later in their disease trajectory.

Unfortunately, there were not enough pairs to establish a relationship between match concordance and disease progression, nor was there enough data to detect a dose response between number of LIFT sessions and effect on disease progression. This is unusual given the strength of the overall effect found. The study was limited in power to the number of LIFT patients who had attended the facility since its opening in 2018; therefore, much of the sub-analysis was underpowered. For the most part, a dose–response has been indicated by the literature. The effect on survival appears to be dose-dependent with the relationship being 'L-shaped' rather than linear, whereby moderate intensity activity is associated with the greatest survival benefit.[14,34] However, when specifically looking at tumour behaviour and disease progression, there may be a more binary effect. This is yet to be established.

The study was undertaken as an exploratory proof-of-concept trial. Although it allowed patients to be matched by up to 10 important variables (including key indicators of disease severity such as stage and grade), it was not exhaustive as the data were not specifically designed for such a purpose. As a result (and out of necessity), the matching was broad and the patients heterogeneous. However, the considerable effect size demonstrated in this study, in the context of the other available literature, warrants a more rigorous analysis, particularly as exercise programmes have been shown to be safe, well tolerated, accessible and cost-efficient, even in advanced cancer.[35] Randomised controlled studies are essential to confirm these potentially impactful findings. There are currently large-scale multi-site RCT underway looking at the effects of supervised exercise programmes on clinical tumour outcomes in patients with colorectal cancer,[36,37] metastatic prostate cancer[38] and lung cancer.[23]

Despite the retrospective study design, and the limitations that this entails, this study provides strong impetus to explore further the possibility that exercise could function as an adjuvant anti-cancer treatment. There is a number of variables requiring further elucidation with more stringent analysis from RCT, including the effects based on stage of disease, type of disease (i.e. hormonal vs non-hormonal), gender, age and any dose–response effect. The latter would be necessary in order to appreciate an optimum dosage of exercise to prescribe for patients.

Conclusion

This preliminary study contributes to the hypothesis that supervised exercise programmes have the potential to improve significantly outcomes in cancer patients due to an effect on tumour progression.

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