

Exercise Improves Patient Outcomes in Advanced Pancreatic Cancer Patient during Medical Treatment

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Abstract

Introduction: Advanced pancreatic cancer is still a major challenge in patients' treatment and is associated with poor prognoses and quality of life. Exercise seems to be a feasible and efficient approach to support the medical therapy in many cancer patients. This case study reports about the impacts of high intensity exercise in an advanced pancreatic cancer patient.

Method: The 46y-old male patient was diagnosed with a stage IV pancreatic cancer and received a palliative chemotherapy for two months, a neoadjuvant chemotherapy for three months (both FOLFIRINOX), a surgery and an adjuvant chemotherapy (Gemcitabine) for another two months. During the whole medical treatment, the patient performed a high intensity resistance and endurance exercise program twice a week. Data regarding body weight, physical performance, physical activity, fatigue, depression and anxiety and quality of life were measured at baseline, three and seven months after the exercise program started.

Results: The exercise program was well tolerated and feasible. The patient mostly maintained his body weight (-2,3%) and improved his physical performance despite chemotherapy and surgery. The patient's medical treatment protocol was changed from palliative to neoadjuvant during the exercise period. Additionally, self-reported quality of life and depression and anxiety values improved during the exercise program. Declines were noticed in the patient's regular physical activity, but still exceeded the international recommendations.

Conclusion: This first case study suggests the feasibility and efficacy of high intensity exercise in an advanced pancreatic cancer patient during medical treatment. Moreover, the exercise program led to clinically relevant improvements in physical and psychological patient outcomes, which may benefit the patient's tolerance to the medical treatment. Further research should verify these results in randomized-controlled trials and focus on the dose-response relation of exercise.

Keywords: PancreasCa; Exercise; Treatment; Cachexia

Introduction

About 14.1 million new cases of cancer were diagnosed worldwide in 2012 and 8.2 million died from it. Pancreatic cancer is relatively uncommon; 338.000 new cases were reported and 330.000 deaths were estimated worldwide [1]. But with its 5-year survival rate of approximately 5% it is considered as one of the most fatal diagnosis and most dangerous and aggressive cancer disease [2]. Improvement of treatment opportunities only led to a minimal effect on the 5-year-survival rate in the last 20 years. Treatment modalities are basically surgery, chemotherapy and radiation. Unfortunately, only 10% of pancreatic cancer patients have an operable tumor, leading to many palliative first-line treatments and patient's burden of an ongoing medical therapy [3].

Additionally, cancer and related medical treatments are associated with several impairing side effects. Fatigue, psychological distress and cachexia with weight loss of up to 30% of the originally pre-cancer weight are common side effects in pancreatic cancer with a profound

impact on a patient's quality of life (QoL) [4-6]. Furthermore, cachexia is associated with increased morbidity and mortality rates, reduced tolerance to anti-cancer therapies and complications in the patient's management [7].

Therefore, it is of great importance to address the patient's QoL by therapeutic interventions to manage and compensate the impacts of the cancer diagnose, the medical treatment and the previously mentioned adverse effects.

Based on scientific evidence throughout many high-quality studies, exercise seems to be an efficient and inexpensive approach to counteract many of these side effects. It has been shown, that physical activity can positively influence cancer related fatigue (CRF), symptoms of depression, the QoL and physical fitness [8-13]. Moreover, physical activity and exercise are feasible and even recommended in complex and strenuously treatments, as it comes with pancreatic cancer [14].

Cormie et al. showed in a first case study, that a pancreatic cancer patient (T2 N1 M0 stage 2b) under adjuvant chemotherapy and three

months after surgery was able to perform an intense exercise program for seven months. Additionally to the feasibility, the program had a positive impact on the patient's QoL, the cancer-related fatigue and depression and anxiety symptoms [15].

Despite the case report of Cormie et al., there is insufficient evidence and experience regarding exercise interventions in pancreatic cancer patients, especially in advanced stages of disease. That is why this case report examined the feasibility and effects of an intensive exercise program with a pancreatic cancer patient diagnosed with a peritoneal metastasising pancreatic cancer.

Case Presentation

History

This case study reports of a male patient, born in 1967, about 1.87m high and with a weight of 88 kg. He was a non-smoker, married and worked as a public administration specialist. He was 46 years old and in a good health condition with no known internistic maladies. Also, the patient was regularly physically active and walked 4-7 times a week a distance of 5 to 7 kilometres. Because of epigastric discomfort and difficulties in swallowing he underwent a gastroenterological check in February 2014. A high concentration of tumor markers CA 19-9 and CA 72-4 were noticed.

Diagnose

After an additional imaging-system check (MRI) of the abdomen and an explorative laparotomy in March 2014, he was diagnosed with peritoneal metastasising pancreatic carcinoma in the tail of the pancreas in pioneer stage IV (UICC - Union Internationale contre le Cancer) with following classification: cT4, cNx and pM1.

Medical treatment

In April 2014, the patient received his first palliative chemotherapy cycle following the FOLFIRINOX protocol, consisting of two hours of Oxaliplatin in 5% glucose solution, two hours of folinic acid in 0.9% Saline (After 30min 500ml Saline was given additionally over the time of 1.5 h) and 5min of Fluorouracil in 100ml 0.9% Saline. Additionally, Fluorouracil was given by an infusion for 46h starting the same day. That protocol was repeated on day 15. On day 7 Filgrastim was given additively to control the white blood cell count. This cycle was scheduled for four times. To prevent side effects the patient additionally took Ondansetron, Metoclopramide and Loperamide.

Physical examination findings

The patient made an appointment for anamnesis, physical examination and conception of the exercise program in the beginning of Mai 2014. At that time, the patient was in a good general condition. Regarding the primary endpoints of this case-report, the patient weighed 88 kg and had a BMI of 25.2. In the anamnesis the patient reported about symptoms of polyneuropathy in lower limbs, little cognitive impairments in concentration and memory performance and muscle ache in upper and lower limbs. He rated his physical capacity with 7 on a scale from 0 to 10 (very bad - very good) (Figure 1).

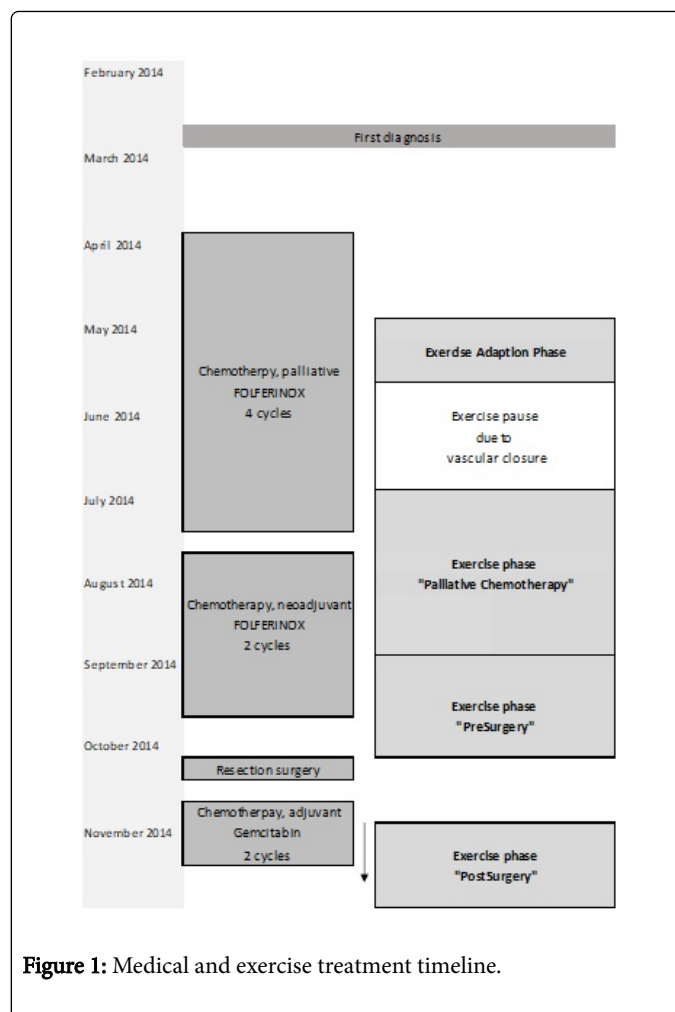


Figure 1: Medical and exercise treatment timeline.

Relevant investigations

Using self-reporting questionnaires, the patient's fatigue (Multidimensional Fatigue Inventory, MFI), depression and anxiety (Hospital Anxiety and Depression Scale, HADS), quality of life (EORTC-C30) and regular physical activity (Global Questionnaire of physical activity, GPAQ) were assessed at baseline-examination as well as three and seven month into the exercise protocol. At baseline, the patient showed low depression and anxiety scores, a mostly good quality of life and a very high regular physical activity of 6480 MET-min. Fatigue-scores weren't available at baseline (Table 1).

Additionally, the patient's physical performance was assessed at given measure-points. The dynamic muscular strength was assessed by the hypothetical one repetition maximum (h1RM). The patient had to perform 3-8 repetitions until exertion with a pre-defined weight, based on his physical appearance and his self-perception. With the used weight and performed repetitions the h1RM was calculated due to Gießing's formular [16]. This procedure is well validated to be used for large muscle groups [17]. Following exercise machines were included: Leg-extension, Leg-curl, chest press and seated row, back-extension and abdominal-crunch.

Endurance capacity was measured at baseline with the 30/15 bicycle-ergometer and crosstrainer-ergometer test, starting with 30W and increasing by 15W every minute until exertion [18]. Based on this

assessment, the exercise intensities were calculated and documented. During the exercise intervention, the endurance intensities were adjusted to the patient's intensity-perception rated by the rate-of-perceived-exertion scale (RPE). The defined endurance-intensity was RPE score 6-7, meaning "hard and very hard". Results are shown in Table 1.

Outcome and prognosis from subsequent follow up visits

Following the baseline-examination in May 2014, the patient performed an intense hypertrophy exercise protocol twice a week, including 8-12 repetitions and two sets with 70-80% of the h1RM as strength training with mentioned exercise machines and endurance training with 70-80% of his maximum of watt on a bicycle-ergometer and crosstrainer-ergometer for 8 minutes each, two sets (Table 2). Due to a deep vein thrombosis in the right leg, the patient had to pause the exercise protocol from the 28th of May to the 21st of July 2014.

Meanwhile, the palliative chemotherapy was continued until early July 2014 for a tumor staging. A PET scan presented a reduction of the primary tumor and the peritoneal metastases, leading to a laparoscopy on 3rd July in which adhesions in the abdomen were undone and a partial resection of the omentum was performed. A small-sized

peritoneal carcinomatosis was inoperable. The lower abdomen showed a few lumps. According to this progress, the patient received further two cycles with the same FOLIFIRINOX protocol, but this time as a neo-adjuvant chemotherapy, scheduled up until 15th Sept 2014.

During the chemotherapy, the patient was able to attend to exercise twice a week. On the 28th of August, three month past baseline, the second examination of physical performance and psychological values was conducted. At this point, the patient maintained his body weight of 88 kg and his BMI of 25.2. Furthermore, he improved his functional performance in every regard (Table 1). The increases of the h1RM ranged from 9% in the seated-row-machine to 79% in leg-extension or 105% in the abdominal-crunch machine as well as increases of the performed watt in training sessions by 39% in both endurance exercises. In addition, the patient's self-reported anxiety and depression scores declined compared to baseline, MFI-fatigue scores were low and the global quality of life increased by 16.6%. More specific, the physical and emotional functioning-subscale of the C30 improved and the fatigue-scale decreased, whereas the symptom-scales of Dyspnoea, Insomnia and Constipation increased, indicating higher symptom burden. The reported regular activity declined by 22.7%.

Measures	Baseline May	3 Month August	7 Month December	Change Baseline to 3 Month (%)	Change Baseline to 7 Month (%)
Physical Performance					
Leg-Extension h1RM	33,8 kg	60,5 kg	60,5 kg	79%	79%
Leg-Curl h1RM	39,7 kg	47,6 kg	38,3 kg	19,9%	-3,6%
Chest Press h1RM	41 kg	56,6 kg	58,7 kg	38%	43,2%
Seated Row h1RM	55,1 kg	60 kg	56,8 kg	8,9%	3,1%
Back Extension h1RM	46,3 kg	64 kg	75,3 kg	38,2%	62,6%
Abdominal Crunch h1RM	21,1 kg	43,3 kg	11,2 kg	105,2%	-88,4%
Crosswalker (TrainW)	90W	125W	135W	38,9%	50%
Bicycle (TrainW)	90W	125W	135W	38,9%	50%
Body weight	88 kg	88 kg	86 kg	0%	-2,3%
BMI	25,2	25,2	24,6	0%	-2,4%
HADS					
Depression	4	1	0	-5,4%	-7,1%
Anxiety	4	3	3	-1,8%	-1,8%
Total	8	4	3	-7,1%	-8,9%
MFI					
General Fatigue	/	4	5	/	/
Physical Fatigue	/	4	5	/	/
Reduced Activity	/	4	4	/	/
Reduced Motivation	/	4	5	/	/
Mental Fatigue	/	6	6	/	/

EORTC-QLQ-C30					
Physical Functioning	73,3	100	100	27,7%	27,7%
Role Functioning	66,7	66,7	100	0%	33,3%
Emotional functioning	66,7	75	83,3	8,3%	16,6%
Cognitive functioning	83,3	83,3	83,3	0%	0%
Social functioning	66,7	66,7	100	0%	33,3%
Fatigue*	33,3	11,1	0	-22,2%	-33,3%
Nausea/Vomiting*	16,7	16,7	0	0%	-16,7%
Pain*	50	0	16,7	-50%	-33,3%
Dyspnoea*	0	33,3	0	33,3%	0%
Insomnia*	0	33,3	33,3	33,3%	33,3%
Appetite*	0	0	0	0%	0%
Constipation*	0	33,3	0	33,3%	0%
Diarrhoea*	0	0	33,3	0%	33,3%
Financial difficulties*	0	0	0	0%	0%
Global health status/ QoL	66,7	83,3	83,3	16,6%	16,6%
GPAQ	6480MET-Min	5280MET-Min	4450MET-Min	-22,7%	-45,6%

Table 1: Overview of outcome measures at baseline, 3 and 6 month into the exercise program.*Negative change displays an improvement. H1RM=Hypothetical One-repetition maximum. TrainW=Trainingsperformance in Watt, HADS=Hospital Anxiety and Depression Scale. MFI=Multidimensional Fatigue Inventory. GPAQ=Global Physical Activity Questionnaire. METmin=METMinute.

Since the patient's medical therapy changed from palliative to neoadjuvant chemotherapy, the exercise protocol was adjusted following the second examination. In preparation for surgery, the exercise regime was further intensified by addition of eccentric resistance with 30% of the concentric h1RM (Table 2).

Phase exercise	of Repetitions /sets	Resistance intensity	Endurance intensity
Palliative Chemotherapy	8-12/x2	70-80% of h1RM	70-80% of HRmax 4-10 min
PreSurgery	8-12/x2	70-80% of h1RM + 30% eccentric of h1RM	70-80% of HRmax 4-10 min
PostSurgery	8-12/x2	70-80% of h1RM	70-80% of HRmax 4-10 min

Table 2: Overview of exercise intensities. h1RM=hypothetical one repetition maximum.

That exercise protocol was continued until surgery on the 2nd Oct 2014. The tail of the pancreas and the spleen were resected as well as partial resection of the colon and a peritonectomy. Following surgery, the HIPEC (hyperthermia intraperitoneal chemoperfusion) procedure was used to kill remaining cancer cells. The patient developed a pleural effusion and a pneumothorax following surgery, but no additional adverse effects. The oncological checkup examination showed no signs

of a primary tumor and no malignant infestation of lymphatic glands. However, remote metastases were still present. On 23rd Oct 2014 the patient was discharged from hospital in a good general condition. He was treated as outpatient with adjuvant chemotherapy for two cycles of Gemcitabine.

After surgery, the patient had to pause the exercise protocol for nearly four weeks and returned to exercise on the 28th of October 2014. The intensities were similar to the exercise protocol during palliative chemotherapy (70-80% h1RM in resistance exercise, 70-80% of HRmax in endurance exercise, Table 2), except for the back-extension and abdominal-crunch machine due to previous surgery. The patient realized this exercise protocol twice a week until December 2014 for the third and last examination of physical performance and self-reported outcomes seven month past baseline. The patient's body weight declined by 2 kg and the BMI decreased from 25.2 to 24.6 (Table 1). Regarding physical performance, most of the improvements from the 28th of August were maintained or even further increased, such as the h1RM regarding chest press (5%) back extension (24%) or performed training watt in endurance exercises (11%). The results of leg-curl (-23.5%) the seated-row machine (5.8%) and abdominal crunches (-193.6%) decreased from August to December. However, except for the leg-curl and the abdominal crunches, every performance was still increased from baseline to December.

Regarding the self-reported outcomes, the HADS-score remained low and further declined by one point compared to August. The fatigue-scores were mostly stable, except for slight increases in

dimensions such as general and physical fatigue and reduced motivation. The quality of life-values revealed some changes from August to December. The functioning scales such as role, emotional and social functioning improved, while some symptom-scales such as Dyspnoea and Diarrhoea also increased, meaning higher symptom burden (Table 1). However, symptom scales such as Fatigue, Pain or Nausea/Vomiting were simultaneously reported to be reduced. The overall quality of life maintained at the value from August. The self-reported physical activity declined further by 22.9%.

The adjuvant chemotherapy ended up in December 2014, leaving the patient without any know tumor burden in remission. The exercise protocol was finished after the last examination in the end of December 2014.

In February 2015 he went on rehabilitation for four weeks.

In April 2015, the patient reported about a recurrence of cancer. Despite therapy, the patient demised in July 2015.

Discussion

In this case study, we report about the feasibility and safety of an intense, supervised exercise program in an advanced pancreatic cancer patient during medical treatment. The patient was able to maintain his body weight and BMI for the most part and only lost 2 kg in seven month. In that context, the patient didn't fell into the classification of cachexia. These results are very interesting and of clinically importance since patients with pancreas cancer are highly vulnerable for cachexia and are known for suffering the highest weight loss up to 30% of the originally pre-cancer weight [4]. In addition to the stable weight, the patient's medical treatment protocol was changed from palliative to neoadjuvant, indicating a process of therapy that wasn't expected at first.

The exercise protocol was well tolerated and the patient managed to attend exercise on average of two times a week, which is the first major finding of this case report. The capability of a stage IV metastatic pancreatic cancer patient to perform high-intensity exercise during intense palliative and adjuvant chemotherapy is highly noteworthy. But even more, the patient was able to maintain or improve his physical performance, quality of life and psychological distress over the exercise period. These results should be paid attention, especially since these outcomes were expected to decline while chemotherapy, surgery and due to the development of cachexia, which is associated with loss of muscle mass and muscular strength [19,20].

Given that cachexia is associated with systemic inflammation and a disturbed metabolism, exercise interventions may counteract the progression of cachexia. Resistance exercise is known to be a potent stimulus of muscle synthesis even in catabolic situations like cachexia [21]. Also, endurance exercise is associated with an anti-inflammatory effect and probably able to attenuate the chronic expression of pro-inflammatory cytokines [22]. Since the exercise protocol combined intense resistance and endurance exercise and the patient additionally walked 5-7 km four to seven days a week, the anti-inflammatory effects and stimulated muscle synthesis may compensated the cachexia-induced weight and muscle mass loss. In regards of muscular strength, the patient improved his h1RM in leg- extension and -curl, chest press, seated-row, back extension, and abdominal crunch from baseline to month three by mostly more than 30%, indicating an increase of muscular strength. These improvements mostly maintained to month seven, except for declines in knee-curl and abdominal crunch due to

the proceeded surgery in October 2014. In that regard, the maintenance of the patient's weight and improvements in muscular strength are very favourable and clinically highly relevant, because cachexia is related to poor prognoses and reduced QoL [7]. Also, the endurance capacity improved from baseline to month three and seven, resulting in an increase up to 50%. The maintenance and improvements of physical performance and condition possibly even contributed to the patient's tolerance to chemotherapy or the surgery.

During the exercise program no adverse effects occurred, except for the deep vein thrombosis (DVT) in the right leg, causing an exercise-stop for nearly two months. Since DVT is a common side effect of advanced pancreatic cancer, this complication was seen as not exercise-induced and exercise was continued as soon as possible [23].

Considering the fact that the patient was classified as stage IV pancreatic cancer patient and under palliative chemotherapy, the QoL was expected to be impaired. However, the patient showed healthy scores in the QoL, fatigue as well as depression and anxiety questionnaires before and during the exercise period. For instance, the patient's global health status/QoL was 66,7 at baseline and 83,3 three and seven months into the exercise program. The scale is ranged from 0-100 and higher scores relate to higher QoL. In view of these scores, the patient's self-reported QoL is uncommonly high when compared to C-30 reference values of liver/bile/pancreas cancer patients (55,9) before their medical treatment [24]. Also, the symptom-related scales at baseline were mostly lower than the reference values, indicating less symptom burden as usual. Some symptoms such as pain, nausea/vomiting and fatigue declined after three and seven months, whereas some symptoms were reported only three or seven months after the exercise program started, such as dyspnoea, insomnia, constipation and diarrhoea. Given the previous month of chemotherapy or rather surgery, these developments seem regular.

The HADS questionnaire showed similar results with low values at baseline, month three month and seven, indicating low or no psychological distress. The HADS is a screening tool for psycho-oncological care and suggests psychological support by a score higher than 13 [25]. The patient's baseline score of 8 was reduced throughout the exercise program to a score of 4 and 3 after three and seven months. These findings are consistent with results from the study from Craft et al. 2012, which showed a modest anti-depressive effect of exercise, especially by exercise duration of more than 30 minutes [26].

Unfortunately, the baseline scores of the patient's self-reported fatigue were not available. The scores of three and seven months show very low fatigue values, which undercut reference values for both sick and healthy people [27]. These low fatigue values are conforming with the reported low fatigue-score within the C30-questionnaire, indicating little to no fatigue. These results may be related to the very high physical activity values of the patient. The patient's weekly activity scores were extremely high with 6480 METmin at baseline, 5280 METmin after three months and 4450 METmin after seven months. These values seem very high when compared to the recommendations of 500-1000 METmin a week by the American College of Sports Medicine [28]. Given the fact, that the patient performed the exercise protocol twice a week and additionally walked 4-7 days a week five to seven kilometres, these numbers seem achievable and imply very regular physical activity. One reason for the decline of METmin over the exercise period may be the extent and duration of chemotherapy and surgery, restricting his very high daily activity routine.

It should be noted, that some limitations may influence the meaningfulness of this case report: (1) The missing baseline MFI-questionnaire for fatigue inhibits differentiated statements to the influence of exercise regarding fatigue. (2) The endurance performance was only evaluated by the exercise intensity during regular training. Only a baseline-test was done measuring the maximum endurance capacity. (3) Unlikely for many cancer patients, the here described patient showed a very regular physical activity, a good physical condition and probably a better tolerance to such intense exercise intensities than most cancer patients. One reason may be the early inclusion of the patient into the exercise protocol at the beginning of his medical treatment without any developed adverse effects such as strong fatigue or cachexia. Eventually, that contributed to a better physical condition during medical treatment and prevented the development of adverse effects. (4) As it comes with case reports, the sample size is too little to distribute reliable information. Nevertheless, to our knowledge there are no high-quality investigations of intense exercise protocols in pancreatic cancer patients. Therefore, this case report provides relevant information of the feasibility and the benefits of a structured, intense exercise protocol in an advanced pancreatic cancer patient and supplies a basis to concept future randomized and controlled trials on.

Conclusion

In summary, the exercise program was feasible and had a positive impact on the patient's physical performance and quality of life. Moreover, the patient mostly maintained his body weight and BMI throughout the entire seven month of treatment. These beneficial impacts possibly contributed to the patient's tolerance to the medical therapy. Also, the results confirm the findings of the case study from Cormie et al. that showed positive effects of an exercise program to manage a stage II pancreatic cancer patient [15]. But in contrast to Cormie et al., this case study investigated intense exercise in an advanced, metastatic pancreatic cancer patient under palliative treatment, what provides additional and new data. These findings showed the safety and suggest the beneficial role of exercise as supportive therapy to manage pancreatic cancer and to improve the patients' quality of life. Further studies are necessary to confirm these findings in a greater sample size. Additionally, the exercise dose-response relation to counteract cachexia should be investigated future trials. For now, exercise should be an individualised recommendation for every pancreatic cancer patient as soon as possible in medical treatment and considered as component of complementary therapy.

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