Changes in motor function and quality of life after surgery in patients with pancreatic cancer

Yuki Nakashima,[1,5)] Toshihiro Kawae,[2)] Daisuke Iwaki,[1)] Kenichi Fudeyasu,[1)] Hiroaki Kimura,[3)] Kenichiro Uemura,[4)] Hitoshi Okamura[5)]

[1]Division of Rehabilitation, Department of Clinical Support, Hiroshima University Hospital, Japan

[2]Department of Physical Therapy, Faculty of Makuhari Human Care, Tohato University, Japan

[3]Department of Rehabilitation Medicine, Hiroshima University Hospital, Japan

[4]Department of Surgery, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

[5]Department of Psychosocial Rehabilitation, Graduate School of Biomedical and Health Sciences, Hiroshima University, Japan

Abstract

Objective: To determine the changes in motor function and health-related quality of life after pancreatectomy and identify factors influencing postoperative quality of life.

Methods: This study was a single-center prospective observational study. The 6-min walking distance, grip strength, knee extension strength, and health-related quality of life variables were measured in patients with pancreatic cancer before and after surgery. The paired t-test and the Wilcoxon signed-rank test were used to compare the pre-and postoperative motor function and health-related quality of life variables. Factors associated with postoperative health-related quality of life were assessed using multiple regression analysis.

Results: Fifty-nine individuals were enrolled. Motor function values decreased significantly postoperatively compared with preoperatively, including the 6-min walking distance (mean ± standard deviation: 402.5 ± 95.4 vs. 497.7 ± 80.4 m, $P < 0.001$), knee-extensor strength (0.42 ± 0.10 vs. 0.47 ± 0.10 kgf/kg, $P < 0.001$), and grip strength (22.0 ± 8.9 vs. 24.5 ± 9.2 kg, $p < 0.001$). Multiple regression analysis showed significant association between 6-min walking distance change and postoperative physical functioning scores of health-related quality of life ($p = 0.036$).

Conclusion: Motor function decreased postoperatively. Our findings suggest that a decrease in 6-min walking distance after surgery may be associated with postoperative physical functioning scores of EORTC QLQ-C30 in pancreatic cancer patients.

Key words: Pancreatectomy, cancer, muscle strength, surgery, quality of life, walking

Introduction

Pancreatic cancer is one of the leading causes of cancer-related mortality in developed countries (Ferlay et al, 2013). Actually, more than 331,000 deaths per year - accounting for 4.0% of all cancer-related deaths - are attributed to this disease, making it the seventh leading cause of such deaths in men and women combined (Ferlay et al, 2013). In recent years, the death rate from pancreatic cancer has been increasing, and it is anticipated that this rate will continue to increase in the future (Rahib et al, 2014; Katanoda et al, 2015).

Surgical resection is the only curative treatment for pancreatic cancer (Tempero et al, 2017), and postoperative adjuvant chemotherapy has been shown to improve life expectancy in randomized controlled trials (Oettle et al, 2007; Oettle et al, 2013). Adjuvant chemotherapy is initiated approximately 2–10 weeks after the surgery, although the Karnofsky performance status score is required to be >50 for its administration (Ueno et al, 2009; Oettle et al, 2007; Oettle et al, 2013). Early postoperative mobilization is strongly recommended to prevent postoperative complications; however, there have been no studies on the influence of perioperative exercise therapy and motor function on the postoperative courses of patients who underwent pancreatic cancer surgery. Therefore, there exists a lack of established exercise therapy programs for such patients (Lassen et al, 2013).

In recent years, the importance of health-related quality of life (QOL) has been emphasized in patients with cancer (Esbensen et al, 2004; Morishita et al, 2018; Hawthorn, 1993). It has been shown that pancreatectomy reduces the health-related QOL in patients with pancreatic cancer (Lounis et al, 2019; Halloran et al, 2011); these studies also found that pancreatectomy has a major impact on motor and psychological functions.

Previous studies revealed that surgery is associated with decreased motor function in patients with esophageal and colorectal cancers (Tatematsu et al, 2013; Inoue et al, 2016; Olsén et al, 2005; Sánchez-Jiménez et al, 2015). Therefore, given that surgery for pancreatic cancer is more

invasive than that for colorectal cancer, motor function is also expected to decrease after pancreatectomy. However, very few studies have objectively investigated motor function in patients with pancreatic cancer(Hayashi et al, 2017), and there are no longitudinal studies that have compared motor function before and after surgery despite their potential importance in establishing perioperative rehabilitation programs. Additionally, health-related QOL is also expected to decrease after surgery; however, the effect of motor function on the postoperative health-related QOL is also unclear.

Therefore, we aimed to determine the effect of surgery on the motor function and health-related QOL in patients with pancreatic cancer, and to identify factors that influence the postoperative health-related QOL.

Methods

We conducted a single-center prospective study to investigate the effect of pancreatic resection on the motor function and health-related QOL in patients with pancreatic cancer. This study was approved by the redacted Epidemiological Ethics Review Board (approval number: E-656), and the patients provided written and verbal informed consent. All persons gave their informed consent prior to their inclusion in the study. The survey period spanned from June 2017 to June 2019.

The inclusion criteria were: 1) pancreatectomy performed for suspected invasive ductal carcinoma of the pancreas at our hospital during the aforementioned period; and 2) immediate referral to the rehabilitation department. Patients who required assistance while walking owing to motor organ and/or central nervous system disease, and those for whom the evaluation of motor function was difficult, were excluded from the study.

As 6-min walking distance was primary endpoint. The 6-min walking distance was measured as an index of exercise tolerance. Secondary endpoint as hand grip, knee extension strengths,

Health-related QOL. Hand grip and knee extension strengths were measured as indices of upper and lower extremity muscle strength, respectively. Health-related QOL measures were assessed by the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) version 3.0. The investigations were conducted by physical therapists. Patient information including age, sex, body weight, body mass index (BMI), diagnosis, chemotherapy regimens received before surgery, preoperative blood levels of C-reactive protein and albumin, surgical method, operation time, amount of blood loss, and postoperative hospitalization duration were obtained from medical records.

Details of the administered evaluation tests are as follows:

1) In the 6-min walking test, 30-m walking courses were created in an indoor corridor according to the guidelines of the American Thoracic Society statement (2002), with a cone installed to indicate the turnaround point. Patients were instructed to walk the longest distance they could cover during the 6-min period. Walking for 6 min is reportedly associated with peak oxygen uptake in patients with cancer, and is, therefore, a valuable indicator (Schmidt et al, 2013).

2) Knee extensor muscle strength, which is considered an index of lower limb muscle strength, was measured using an isometric muscle strength measuring device (μTas M-1, Anima Inc., Tokyo, Japan), while the isometric knee extensor strength was measured with a sensor pad immobilized on a belt at the distal lower leg (Nomura et al, 2018). The measurement posture was sitting at the edge of a chair, with both hands paired in front of the chest while the trunk was kept in an upright position. The sensor pad was placed distal to the participant's lower leg; the height of the sitting surface and length of the fixation belt were adjusted to place the knee joint at a 90° flexion, whereupon the belt was secured to the examination table. Isometric knee extension exercises with maximum effort were performed for approximately 5 s twice on each side, and the maximum value was adopted as the recorded knee extension strength. To eliminate the effect of body weight, the knee extension strength-to-weight ratio divided by the maximum isometric knee extension strength was calculated for normalization.

3) Grip strength measurement was performed using Smedley-type grip dynamometer while being in the standing position with the upper extremity in a drooping stance. The grip size of a dynamometer was adjusted until the second joint of the participant's index finger was at a 90° angle on the handle by examiner. The participants were instructed to grasp the device with their maximum strength; the right and left hand strength was each tested twice, and the maximum value was considered the grip strength.

4) The EORTC QLQ-C30 version 3.0, which comprises 30 questions for patients with cancer, was used to investigate the health-related QOL. The scores were classified according to the guidelines into five functional scales (physical, roles, cognitive, emotional, and social functioning), three symptom scales (fatigue, pain, nausea/vomiting), and six single items (constipation, diarrhea, insomnia, dyspnea, anorexia, and economic difficulties) and were converted to an overall score ranging from 0 to 100 (Fayers et al, 2001).

Motor function and EORTC QLQ-C30 were evaluation at two points before and after surgery. All participants in this study received the same physical therapy regimen during the perioperative period. Preoperative guidance included respiratory training, postoperative physical therapy orientation, and preoperative evaluation between 7 and 1 day(s) before surgery. Postoperative rehabilitation was performed starting on postoperative day 1 and continued until discharge. From the first postoperative day, the participants performed sputum drainage exercises and rose from their beds. Resistance and aerobic exercises were performed starting on postoperative day 4. Each patient performed a combination of resistance and aerobic exercise for 20 to 40 minutes. The focus was on lower extremity resistance exercises such as leg presses, leg extensions, hip adductions, hip abductions, and heel raises. Aerobic exercise included bicycle ergometer and walking for 10 to 20 minutes. Postoperative evaluation was performed 14 days after surgery.

The sample sizes were calculated using a standard deviation of 88 m based on a previous study, which examined the changes in 6-min walking times before and after gastrointestinal

surgery (Inoue et al, 2016). A decrease of 80 m during the 6-min walking test was considered clinically meaningful (Wise and Brown, 2005). The required sample size for an α error of 0.05 and a β error of 0.2 was calculated to be 41 participants.

Statistical Analysis

Continuous variables were checked for normality using the Shapiro–Wilk test. Comparisons between the two matched groups were performed using the paired t-tests for the 6-min walking distance, grip strength, and knee-extension strength based on a normal distribution, and using the Wilcoxon signed-rank tests for the EORTC QLQ-C30 without a normal distribution. Pearson correlation coefficients were then calculated to assess relations among preoperative motor function parameters and physical functioning scores of EORTC QLQ-C30, and the relation between the delta change in physical functioning scores and motor function parameters. Single regression analysis was followed by multiple regression analysis to investigate factors associated with physical function scores, as determined by the postoperative QLQ-C30. We chose physical functioning scores because physical functioning scores have been reported as an independent prognostic factor in patients with pancreatic cancer (Gupta et al, 2006). In addition, the 6 minutes walking distance for in patients with cancer correlates with the EORTC physical functioning scores (K Schmidt et al, 2013, Morishita et al, 2018).

The JMP® 14 software (SAS Institute Inc., Cary, NC, USA) was used for all statistical processing and analyses. All hypothesis tests were two-tailed. Single regression analysis was performed to select explanatory variables for multiple regression analysis; variables with P-values <0.20 were used as explanatory variables for multiple regression analysis. P-values <0.05 were considered statistically significant.

Results

The patients' selection process is presented in Figure 1. The patients' characteristics and surgical information are presented in Table 1. The median age was 66.5 years and the median BMI was 21.5 kg/m^2; 25(42%) and 34 (58%) participants were men and women, respectively. Seventeen patients (29%) underwent preoperative chemotherapy. The median postoperative hospital stay was 19 days and the median postoperative assessment time was at 14 days postoperatively.

Table 2 shows the preoperative and postoperative 6-min walking distances, grip strength, and knee-extensor strength test results; all variables significantly decreased after surgery. The postoperative 6-min walking distance, grip strength, and knee extension strength were at 81%, 90%, and 89% of their presurgical values, respectively. In the EORTC QLQC-30, significant decreases in physical, role, cognitive, social, and global functioning, fatigue, nausea and vomiting, pain, insomnia, appetite loss, and diarrhea scores were observed after surgery compared with their preoperative values (Table 3).

Regarding relations among preoperative motor function parameters and physical functioning scores of EORTC QLQ-C30, except for the relationship between hand grip strength and physical functioning scores, there was a significant relationship between each score (Table 4). The delta change in physical functioning of EORTC QLQC30 was significant correlated with the delta change in 6-min walk distance ($r = 0.257$; $p = 0.0495$), but not with the delta change in % knee extension force ($r = 0.048$; $p = 0.718$) and hand grip strength ($r = 0.075$; $p = 0.575$).

To investigate the factors associated with the physical function scores, as derived from the postoperative QLQ-C30, we performed a single-regression analysis using age, preoperative serum albumin, preoperative C-reactive protein, surgical duration, blood loss, preoperative and postoperative body weights, grip strength changes, knee-extension muscle strength changes, and 6-min walking distance changes as explanatory factors (Table 5). Subsequently, multiple

regression analyses were performed using blood loss, body weight change, and 6-min walking distance change (i.e., factors with P-values < 0.20 on single-regression analyses) as explanatory variables. Only the 6-min walking distance was found to be related to postoperative physical function on multiple regression analysis (Table 4).

Discussion

This was the first prospective study to investigate motor function before and after surgery in patients with pancreatic cancer. Our key finding was that motor functions, such as 6-min walking distance, grip strength, and knee extension strength, decreased after pancreatectomy, affecting the health-related QOL.

A previous study in patients with esophageal cancer revealed a decrease in the 6-min walking length, grip strength, and knee-extensor strength following surgical treatment (Tatematsu et al, 2013). Moreover, another work showed that grip strength and lower extremity muscle strength decreased in patients with colorectal carcinoma after surgery (Jensen et al, 2011). Furthermore, in a cross-sectional study of patients with pancreatic cancer performed 107.9 ± 53.6 days after pancreatectomy, muscle weakness of the upper and lower limbs was reported (Clauss et al, 2017). In our study, postoperative evaluation was performed after a median of 14 days postoperatively, indicating that motor functions, such as muscle strength and exercise tolerance, decline at an earlier stage.

Preventing such functional declines is important; despite receiving interventions, such as, preoperative instruction included respiratory training and postoperative physical therapy orientation. Postoperatively, patients were given walking from day 1 and resistance and aerobic exercises from day 4. Each patient performed a combination of resistance and aerobic exercises for 20 to 40 minutes. In spite of our participants experienced lower motor function, as evidenced by decreases to 81%, 90%, and 89% of their 6-min walking distance, grasping power,

and knee extension muscle force, respectively, when compared to their preoperative values. This was similar to previous studies in patients with other types of cancer (Tatematsu et al, 2013; Inoue et al, 2016), suggesting that the currently used in-hospital rehabilitation interventions may not be sufficient to fully restore motor function after surgery. Additionally, we found that many health-related QOL variables decreased postoperatively; this was consistent with data from previous studies that found a significant reduction in the QOL immediately after surgery (Schniewind et al, 2006; Heerkens et al, 2016). Moreover, our data also showed that the change in 6-min walking distance was significantly associated with the postoperative physical function scores as determined via the QLQ-C30. We hypothesized that the amount of change in motor function after surgery compared to the amount of change in preoperative physical function in the EORTC QLQ-C30 would affect postoperative physical function, and the amount of change in motor function was used as an explanatory factor. This suggests that some rehabilitation for preventing a decrease in the 6-min walking distance is needed to avert a decline in the postoperative QOL.

As aforementioned, our results suggest that commonly-used exercise therapies during hospitalization, may not be sufficient to prevent the postoperative deterioration of motor function. Recent studies have demonstrated the effectiveness of preoperative exercise therapy in preventing postoperative motor dysfunction. In patients with colorectal carcinoma, undergoing preoperative exercise therapy for approximately 1 month has been reported to improve the postoperative 6-min walking distance (Li et al, 2013, Minnella, E. M et al, 2013). Preoperative exercise has also been shown to be feasible in pancreatic cancer (Ngo-Huang, A et al, 2017), and increasing physical activity has been shown to increase preoperative 6-minute walking distance (Ngo-Huang, A et al, 2019).

In addition, significant weight loss was observed in the subjects of this study after surgery. This was similar to previous studies in patients with pancreatic cancer after surgery (Hashimoto, D et al, 2015). As weight has been used as one of the indicators of nutritional status in cancer patients (Bauer, J et al, 2002), it can be inferred that the subjects in this study are in worse

nutritional status after surgery. Deterioration in nutritional status may affect motor function. Such data suggest that preoperative exercise therapy and nutrition management may be necessary for the early improvement of motor function in patients with pancreatic cancer.

There were some limitations in this study. First, it was a single-center investigation and, therefore, did not necessarily reflect the general population. Second, although all participants in this study received rehabilitation interventions during their hospitalization, the Enhanced recovery after surgery(ERAS) protocol was not implemented at the hospital, as the ERAS protocol facilitates recovery and reduces postoperative hospital stay (Ji, H. B et al, 2018), which may help patients recover motor function and quality of life. Third, the duration of this study encompassed only a short period of time before and after surgery. However, it would be more informative to investigate the factors that impede motor function and QOL in a longitudinal study spanning a longer period of time before and after surgery.

In conclusion, we found that the motor functions of patients with pancreatic cancer decreased after surgery, and that the decrease in the 6-min walking distance was significantly associated with a lower health-related QOL. Our data suggest that additional perioperative rehabilitation should be considered to maintain postoperative motor function and health-related QOL in such patients.

References

ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. (2002) ATS statement: Guidelines for the six-minute walk test. American Journal of Respiratory and Critical Care Medicine, 166, 111–117. doi: 10.1164/ajrccm.166.1.at1102

Bauer, J., Capra, S., & Ferguson, M. (2002). Use of the scored Patient-Generated Subjective Global Assessment (PG-SGA) as a nutrition assessment tool in patients with cancer. European journal of clinical nutrition, 56(8), 779–785. https://doi.org/10.1038/sj.ejcn.1601412

Clauss, D., Tjaden, C., Hackert, T., Schneider, L., Ulrich, C.M., Wiskemann, J. and Steindorf, K. (2017) Cardiorespiratory fitness and muscle strength in pancreatic cancer patients. Supportive Care in Cancer, 25, 2797–2807. doi: 10.1007/s00520-017-3694-8

Esbensen, B.A., Østerlind, K., Roer, O. and Hallberg, I.R. (2004) Quality of life of elderly persons with newly diagnosed cancer. European Journal of Cancer Care, 13, 443–453. doi: 10.1111/j.1365-2354.2004.00546.x

Fagevik Olsén, M., Larsson, M., Hammerlid, E. and Lundell, L. (2005) Physical function and quality of life after thoracoabdominal oesophageal resection: Results of a longitudinal follow-up study. Digestive Surgery, 22, 63–68. doi: 10.1159/000085348

Fayers, P.M., Aaronson, N.K., Bjordal, K., Groenvold, M., Curran, D., Bottomley, A., on behalf of the EORTC Quality of Life Group. (2001) EORTC QLQ-C30 Scoring Manual (3rd ed.). Brussels: European Organisation for Research and Treatment of Cancer; 1–67.

Ferlay, J., Steliarova-Foucher, E., Lortet-Tieulent, J., Rosso, S., Coebergh, J.W.W., Comber, H., Forman, D. and Bray, F. (2013) Cancer incidence and mortality patterns in Europe: Estimates for 40 countries in 2012. European Journal of Cancer, 49, 1374–1403. doi: 10.1016/j.ejca.2012.12.027

Gupta, D., Lis, C. G., & Grutsch, J. F. (2006). The European organization for research and treatment of cancer quality of life questionnaire: implications for prognosis in pancreatic cancer. International journal of gastrointestinal cancer, 37, 65–73. https://doi.org/10.1007/s12029-007-0001-9

Halloran, C.M., Cox, T.F., Chauhan, S., Raraty, M.G., Sutton, R., Neoptolemos, J.P. and Ghaneh, P. (2011) Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. Pancreatology, 11, 535–545. doi: 10.1159/000333308

Hawthorn, J. (1993) Measuring quality of life. European Journal of Cancer Care, 2, 77–81. doi: 10.1111/j.1365-2354.1993.tb00167.x

Hashimoto, D., Chikamoto, A., Ohmuraya, M., Abe, S., Nakagawa, S., Beppu, T., Takamori, H., Hirota, M., & Baba, H. (2015). Impact of Postoperative Weight Loss on Survival After Resection for Pancreatic Cancer. JPEN. Journal of parenteral and enteral nutrition, 39, 598–603. https://doi.org/10.1177/0148607114520992

Hayashi, K., Yokoyama, Y., Nakajima, H., Nagino, M., Inoue, T., Nagaya, M., Hattori, K., Kadono, I., Ito, S., & Nishida, Y. (2017). Preoperative 6-minute walk distance accurately predicts postoperative complications after operations for hepato-pancreato-biliary cancer. Surgery, 161, 525–532. https://doi.org/10.1016/j.surg.2016.08.002

Heerkens, H.D., Tseng, D.S., Lips, I.M., Van Santvoort, H.C., Vriens, M.R., Hagendoorn, J., Meijer, G.J., Borel Rinkes, I.H., van Vulpen, M. and Molenaar, I.Q. (2016) Health-related quality of life after pancreatic resection for malignancy. British Journal of Surgery, 103, 257–266. doi: 10.1002/bjs.10032

Inoue, T., Ito, S., Ando, M., Nagaya, M., Aso, H., Mizuno, Y., Hattori, K., Nakajima, H., Nishida, Y., Niwa, Y., Kodera, Y., Koike, M. and Hasegawa, Y. (2016) Changes in exercise capacity, muscle strength, and health-related quality of life in esophageal cancer patients

undergoing esophagectomy. BMC Sports Science, Medicine & Rehabilitation, 8, 34. doi: 10.1186/s13102-016-0060-y

Jensen, M.B., Houborg, K.B., Nørager, C.B., Henriksen, M.G. and Laurberg, S. (2011) Postoperative changes in fatigue, physical function and body composition: An analysis of the amalgamated data from five randomized trials on patients undergoing colorectal surgery. Colorectal Disease, 13, 588–593. doi: 10.1111/j.1463-1318.2010.02232.x

Ji, H. B., Zhu, W. T., Wei, Q., Wang, X. X., Wang, H. B., & Chen, Q. P. (2018). Impact of enhanced recovery after surgery programs on pancreatic surgery: A meta-analysis. World journal of gastroenterology, 24, 1666–1678. https://doi.org/10.3748/wjg.v24.i15.1666

Katanoda, K., Hori, M., Matsuda, T., Shibata, A., Nishino, Y., Hattori, M., Soda, M., Ioka, A., Sodue, T. and Nishimoto, H. (2015) An updated report on the trends in cancer incidence and mortality in Japan, 1958-2013. Japanese Journal of Clinical Oncology, 45, 390–401. doi: 10.1093/jjco/hyv002

Lassen, K., Coolsen, M.M., Slim, K., Carli, F., De Aguilar-Nascimento, J.E., Schäfer, M., Parks, R.W., Fearon, K.C., Lobo, D.N., Demartines, N., Braga, M., Ljunggvist, O. and Dejong, C.H. (2013) Guidelines for perioperative care for pancreaticoduodenectomy: Enhanced recovery after surgery (ERAS®) society recommendations. World Journal of Surgery, 37, 240–258. doi: 10.1007/s00268-012-1771-1

Li, C., Carli, F., Lee, L., Charlebois, P., Stein, B., Liberman, A.S., Kaneva, P., Augustin, B., Wongyingsinn, M., Gamsa, A., Kim, D.J., Vassiliou, M.C. and Feldman, L. S. (2013) Impact of a trimodal prehabilitation program on functional recovery after colorectal cancer surgery: a pilot study. Surgical Endoscopy, 27, 1072–1082. doi: 10.1007/s00464-012-2560-5

Lounis, L., Aurran-Schleinitz, T., Turrini, O., Delpero, J.R. and Bréjard, V. (2019) Psychological outcomes and quality of life in relation to pancreatectomy. Pancreas, 48, 471–479. doi: 10.1097/MPA.0000000000001279

Minnella, E. M., Awasthi, R., Loiselle, S. E., Agnihotram, R. V., Ferri, L. E., & Carli, F. (2018). Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial. JAMA surgery, 153, 1081–1089. https://doi.org/10.1001/jamasurg.2018.1645

Morishita, S., Tsubaki, A., Fu, J.B., Mitobe, Y., Onishi, H. and Tsuji, T. (2018) Cancer survivors exhibit a different relationship between muscle strength and health-related quality of life/fatigue compared to healthy subjects. European Journal of Cancer Care, 27, e12856. doi: 10.1111/ecc.12856

Ngo-Huang, A., Parker, N. H., Wang, X., Petzel, M., Fogelman, D., Schadler, K. L., Bruera, E., Fleming, J. B., Lee, J. E., & Katz, M. (2017). Home-based exercise during preoperative therapy for pancreatic cancer. Langenbeck's archives of surgery, 402(8), 1175–1185. https://doi.org/10.1007/s00423-017-1599-0

Ngo-Huang, A., Parker, N. H., Bruera, E., Lee, R. E., Simpson, R., O'Connor, D. P., Petzel, M., Fontillas, R. C., Schadler, K., Xiao, L., Wang, X., Fogelman, D., Sahai, S. K., Lee, J. E., Basen-Engquist, K., & Katz, M. (2019). Home-Based Exercise Prehabilitation During Preoperative Treatment for Pancreatic Cancer Is Associated With Improvement in Physical Function and Quality of Life. Integrative cancer therapies, 18, 1534735419894061. https://doi.org/10.1177/1534735419894061

Nomura, T., Ishiguro, T., Ohira, M. and Ikeda, Y. (2018) Diabetic polyneuropathy is a risk factor for decline of lower extremity strength in patients with type 2 diabetes. Journal of Diabetes Investigation, 9, 186–192. doi: 10.1111/jdi.12658

Oettle, H., Neuhaus, P., Hochhaus, A., Hartmann, J.T., Gellert, K., Ridwelski, K., Niedergethmann, M., Zulke, C., Fahlke, J., Arning, M.B., Sinn, M., Hinke, A. and Riess, H. (2013) Adjuvant chemotherapy with gemcitabine and long-term outcomes among patients with resected pancreatic cancer: the CONKO-001 randomized trial. JAMA, 310, 1473–1481. doi: 10.1001/jama.2013.279201

Oettle, H., Post, S., Neuhaus, P., Gellert, K., Langrehr, J., Ridwelski, K., Schramm, H., Fahlke, J., Zuelke, C., Burkart, C., Gutberlet, K., Kettmer, E., Schmalenberg, H., Weigang-Koehler, K., Bechstein W.O., Niedergethmann, M., Schmidt-Wolf, I., Roll, L., Doerken, B. and Riess, H. (2007) Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: A randomized controlled trial. JAMA, 297, 267–277. doi: 10.1001/jama.297.3.267

Rahib, L., Smith, B.D., Aizenberg, R., Rosenzweig, A.B., Fleshman, J.M. and Matrisian, L.M. (2014) Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Research, 74, 2913–2921. doi: 10.1158/0008-5472.CAN-14-0155

Sánchez-Jiménez, A., Cantarero-Villanueva, I., Delgado-García, G., Molina-Barea, R., Fernández-Lao, C., Galiano-Castillo, N. and Arroyo-Morales, M. (2015) Physical impairments and quality of life of colorectal cancer survivors: a case-control study. European Journal of Cancer Care, 24, 642–649. doi: 10.1111/ecc.12218

Schmidt, K., Vogt, L., Thiel, C., Jäger, E. and Banzer, W. (2013) Validity of the six-minute walk test in cancer patients. International Journal of Sports Medicine, 34, 631–636. doi: 10.1055/s-0032-1323746

Schniewind, B., Bestmann, B., Henne-Bruns, D., Faendrich, F., Kremer, B. and Kuechler, T. (2006) Quality of life after pancreaticoduodenectomy for ductal adenocarcinoma of the pancreatic head. British Journal of Surgery, 93, 1099–1107. doi: 10.1002/bjs.5371

Tatematsu, N., Hasegawa, S., Tanaka, E., Sakai, Y. and Tsuboyama, T. (2013) Impact of oesophagectomy on physical fitness and health-related quality of life in patients with oesophageal cancer. European Journal of Cancer Care, 22, 308–313. doi: 10.1111/ecc.12030

Tempero, M.A., Malafa, M.P., Al-Hawary, M., Asbun, H., Bain, A., Behrman, S.W., Benson, A.B. 3rd, Binder, E., Cardin, D.B., Cha, C., Chiorean, E.G., Chung, V., Czito, B., Dillhoff,

M., Dotan, E., Ferrone, C.R., Hardacre, J., Hawkins, W.G., Herman, J., Ko, A.H. and Darlow, S. (2017) Pancreatic adenocarcinoma, version 2.2017: NCCN clinical practice guidelines in oncology. Journal of the National Comprehensive Cancer Network, 15, 1028–1061. doi: 10.6004/jnccn.2017.0131

Ueno, H., Kosuge, T., Matsuyama, Y., Yamamoto, J., Nakao, A., Egawa, S., Doi, R., Monden, M., Hatori, T., Tanaka, M., Shimada, M. and Kanemitsu, K. (2009) A randomised phase III trial comparing gemcitabine with surgery-only in patients with resected pancreatic cancer: Japanese Study Group of Adjuvant Therapy for Pancreatic Cancer. British Journal of Cancer, 101, 908–915. doi: 10.1038/sj.bjc.6605256

Wise, R.A. and Brown, C.D. (2005) Minimal clinically important differences in the six-minute walk test and the incremental shuttle walking test. COPD, 2, 125–129. doi: 10.1081/COPD-200050

Table 1. Patient baseline characteristics

	n=59
Age; years, mean (SD)	66.5 (11.6)
Body mass index; kg/m^2, mean (SD)	21.5 (2.7)
Sex; n (%)	
Male	25 (42)
Female	34 (58)
Hypertension; n (%)	18 (31)
Diabetes; n (%)	23 (39)
Hyperlipidemia; n (%)	16 (27)
Preoperative adjuvant therapy; n (%)	
Yes	17 (29)
No	42 (71)
Preoperative serum albumin; g/dL, median (IQR)	3.60 (3.30–3.90)
Preoperative C-reactive protein; mg/dL, median (IQR)	0.11 (0.04–0.29)
Surgical procedure; n (%)	
PPPD	34 (58)
DP	17 (29)
PD	4 (7)
DP-CAR	3 (5)
TP	1 (2)
Operative time; min, median (IQR)	304 (209–344)
Estimated blood loss; mL, median (IQR)	515 (277–795)
Postoperative hospital stays; days, median (IQR)	19 (17–25)
Postoperative evaluation day; days, median (IQR)	14 (12–17)

n: number, SD: standard deviation, IQR: interquartile range, PPPD: pylorus preserving pancreaticoduodenectomy, DP: distal pancreatectomy, PD: pancreatoduodenectomy, DP-CAR: distal pancreatectomy with celiac axis resection, TP: transduodenal papillectomy

Table 2. Differences in physical fitness and body weight before and after surgery

	Preoperative	Postoperative	95% CI	*P*-value†
6MWD; m, mean (SD)	497.7 (80.4)	402.5 (95.4)	-110.8 – -79.6	<0.001
HGS; kg, median (IQR)	24.5 (9.2)	22.0 (8.9)	-3.8 – -2.3	<0.001
%KEF; kgf/kg, mean (SD)	0.47 (0.10)	0.42 (0.10)	-0.06 – -0.03	<0.001
BW; kg, median (IQR)	53.2 (10.9)	52.2 (10.1)	-3.6 – -2.2	<0.001

6MWD: 6-min walk distance, HGS: hand grip strength, KEF: knee extension force, BW: body weight, SD: standard deviation, IQR: interquartile range, CI: confidence interval, †: paired t-test

Table 3. Postoperative changes as determined using the EORTC QLQ-C30

Condition	Preoperative	Postoperative	95% CI	*P*-value†
Physical functioning	93.3 (86.7–100)	80.0 (66.7–86.7)	-19.0 – -10.6	<0.001
Role functioning	100.0 (66.7–100)	66.7 (33.3–66.7)	-34.0 – -19.7	<0.001
Cognitive functioning	83.3 (66.7–100)	66.7 (66.7–83.3)	-15.6 – -5.3	0.002
Emotional functioning	83.3 (66.7–91.7)	83.3 (66.7–91.7)	-10.0 – 5.5	0.620
Social functioning	83.3 (66.7–100)	66.7 (50.0–100)	-21.5 – -6.7	<0.001
Global functioning	66.7 (41.7–83.3)	50.0 (33.3–58.3)	-21.4 – -7.4	<0.001
Fatigue	22.2 (11.1–33.3)	44.4 (33.3–55.6)	16.5–27.9	<0.001
Nausea and vomiting	0 (0–0)	16.7 (0–16.7)	-5.1–15.9	<0.001
Pain	0 (0–16.7)	33.3 (16.7–50)	16.2–29.0	<0.001
Dyspnea	0 (0–33.3)	33.3 (0–33.3)	3.1–16.1	0.007
Insomnia	0 (0–33.3)	33.3 (0–33.3)	8.5–23.1	<0.001
Appetite loss	0 (0–33.3)	33.3 (33.3–66.7)	26.7–45.6	<0.001
Constipation	33.3 (0–33.3)	33.3 (0–66.7)	-9.3–10.5	0.860
Diarrhea	0 (0–0)	33.3 (0–66.7)	23.0–43.6	<0.001
Financial difficulties	0 (0–33.3)	0 (0–33.3)	-0.02–13.6	0.020

Values are presented as the median (IQR). EORTC: European Organisation for Research and Treatment of Cancer; QLQ-30: quality of life questionnaire-C30, IQR: interquartile range, CI: confidence interval, †: Wilcoxon signed-rank test

Table 4. Relations among preoperative motor function parameters and physical functioning scores of EORTC QLQ-C30

	PF	6MWD	%KEF	HGS
PF	-	0.397 (P=0.002)	0.279 (P=0.033)	0.173 (P=0.189)
6MWD		-	0.323 (P=0.013)	0.374 (P=0.004)
%KEF			-	0.296 (P=0.023)
HGS				-

6MWD, 6-min walk distance; HGS, hand grip strength;KEF, knee extension force; PF, physical functioning scores of EORTC QLQ-C30.

Table 5. Associations between indicators of relative decline in physical functioning score in the EORTC QLQ-C30

	Simple regression analysis			Multiple regression analysis		
	β	SE	*P*-value	β	SE	*P*-value
Age	-0.070	0.181	0.600			
Preoperative serum albumin	-0.161	4.619	0.223			
Preoperative C-reactive protein	0.120	5.576	0.366			
Operative time	-0.016	0.020	0.902			
Estimated blood loss	-0.222	0.002	0.091	-0.105	0.003	0.437
δBW	-0.185	0.793	0.160	-0.178	0.756	0.158
δHGS	0.107	0.760	0.419			
δKEF	0.018	29.342	0.895			
δ6MWD	0.332	0.033	0.010	0.289	0.036	0.036

BW: body weight, HGS: hand grip strength, KEF: knee extension force, 6MWD: 6-min walking distance, SE: standard error

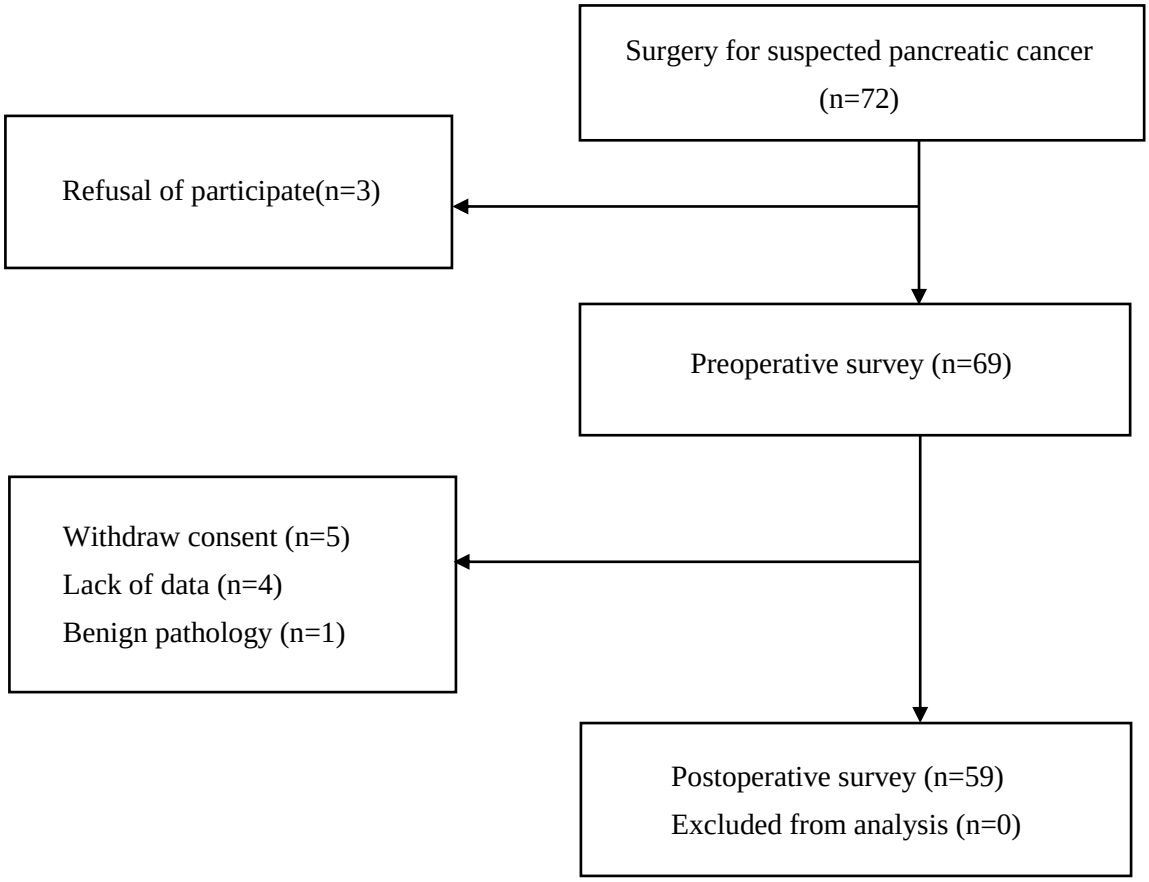

Figure 1. Flow diagram showing the selection of study participants