



The effects of exercise prehabilitation in upper gastrointestinal oncology patients undergoing surgical resection: a systematic review

Emma M. Tyson¹, Muzaffar Malik², Chris Jones³

¹Peter MacCallum Cancer Centre, Melbourne, Australia; ²Brighton and Sussex Medical School, University of Brighton, Brighton, UK; ³Anaesthetic Department, Royal Surrey County Hospital, Guildford, UK

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Correspondence to: Emma M. Tyson. Anaesthetic Fellow, Peter MacCallum Cancer Centre, Melbourne 3000, Australia. Email: ems.tyson@gmail.com.

Background: Prehabilitation (PH) programs are being increasingly recognised as a tool for enhancing patient postoperative outcomes following major surgery. This systematic review aims to look specifically at the feasibility of exercise PH in patients undergoing upper gastrointestinal (UGI) cancer surgery and to evaluate the effectiveness of these PH programs on post-operative outcomes.

Methods: A systematic literature search was completed in May 2021 of the following databases: Medline, Embase, PubMed and CINAHL as well as a grey literature search. The search was conducted for trials evaluating the effects of exercise PH in UGI patients using an objective functional capacity measurement pre- and post-program prior to surgery. Both randomised controlled trials (RCTs) and high-quality non-randomised studies were included and assessed using the Risk of Bias-2 (ROB-2) and the Risk of Bias in Non-randomised Studies-1 (ROBINS-1) assessment tools respectively. The feasibility of exercise PH was assessed objectively by evaluating changes in functional capacity assessments. Postoperative outcomes were evaluated as secondary outcomes.

Results: Eight studies were included in this review: 2 RCTs and 6 observational prospective cohort studies. Risk of bias was low for the RCTs but moderate across the other six studies. A total of 402 patients were in the exercise PH groups across the studies, 208 of which underwent neoadjuvant chemotherapy (NAC). A significant improvement in functional capacity was seen in 6 of the studies. Postoperatively, one study observed a significant improvement in length of stay (median 23 *vs.* 30 days, $P=0.045$), but no change in overall incidence of postoperative complications.

Discussion: This review shows that it is feasible to conduct preoperative exercise-based PH programs in UGI cancer patients and that they can significantly improve functional capacity prior to surgery. Whether this improvement leads to superior postoperative outcomes is yet to be established as none of the studies included were adequately powered to assess this.

Keywords: Prehabilitation (PH); preoperative exercise; onco-anaesthesia

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Introduction

Upper gastrointestinal (UGI) cancers; including oesophageal, gastric, hepatic, pancreatic and biliary, were responsible for >25% of all cancer associated deaths worldwide in 2020 (1). Despite recent advances in patient perioperative care, the 5-year survival rates in this group are consistently amongst the worst of all tumour types: oesophageal is 20%, gastric is 32%, pancreatic is 10%, liver is 20% and biliary is 10% (2). The stubbornly low 5-year survival rate is mainly attributable to the advanced stages of the disease at diagnosis, as these cancers are often aggressive with symptoms occurring late and in a more elderly population (3). The consequence of which is that by diagnosis <50% of all patients in this group will have resectable disease, this drops to as low as 15% in pancreatic cancer patients (3). To date, systematic reviews and meta-analyses investigating the impact of prehabilitation (PH) on patient outcomes in GI cancer have always included colorectal carcinoma as a sub-group. This group generally gets diagnosed earlier through surveillance screening resulting in a lower disease burden at time of surgery with a significantly improved prognosis (63% 5-year-survival) compared to the UGI cohort. This systematic review was therefore designed to exclude this group of patients to generate a better understanding on how feasible it is to conduct exercise PH programs within the more functionally frail UGI cohort.

For UGI patients that do have a resectable disease, a combined surgical and oncological approach including neoadjuvant chemotherapy (NAC) and adjuvant chemo(radio)therapies is essential for treatment with curative intent (4). However, even with recent surgical advancements, these operations are highly complex and are associated with a significant degree of postoperative morbidity (5). neoadjuvant therapies are often poorly tolerated and can result in reduced patient functional capacity leading up to their procedure (6). This coupled with an elderly cohort and the inevitable disease-related decline in physiological status including sarcopenia, malnourishment and frailty (7), mean this group has a significantly higher rate of postoperative complications when compared to the rest of the surgical population (8).

This is of particular concern in this cohort as the best chance of overall and disease-free survival occurs when patients can complete their whole postoperative course of chemo(radio)therapy (9). Unfortunately, recent studies have shown that only 50–55% of gastric cancer patients will

successfully return to their intended oncological treatment (RIOT) (10,11). The inability to RIOT has also been linked to a reduced disease-free survival in liver (9) and pancreatic (12) cancer patients. The most common reasons for failure to RIOT are poor preoperative patient functional status and a high incidence of major postoperative complications (9,10). This has prompted a growing body of research to investigate whether taking measures to improve a patients' preoperative functional capacity can lead to a reduction their postoperative morbidity, allowing for a higher RIOT rate and ultimately prolonged disease-free survival (13).

PH is “the practice of enhancing a patient's functional capacity before surgery with the aim of improving post-operative outcomes” (14). PH programs are a relatively new concept in perioperative care, they aim to tap into the unique window of opportunity that arises in the preoperative period to encourage patients to make long-lasting changes to their health and lifestyle. Initially PH programs were predominantly exercise focused (15), but more recently they have started to evolve into multimodal interventions including respiratory, nutritional and psychological components (16,17). Whilst there is now evidence that some of these programs can improve preoperative functional capacity, the optimal strategy is still unknown (17,18). Should programs include aerobic or resistance muscle training, should they be multimodal or unimodal, should exercise be home or hospital based? Different disease processes are likely to benefit from different types of intervention depending on the length of time to surgery, preoperative morbidity and baseline function (14,16,19).

This systematic review has been designed to look particularly at the exercise component of PH programs in UGI cancer patients with the aim of ascertaining what the best and most pragmatic approach for this cohort is. Intuitively the optimal PH program is likely to be multimodal (20), but given the many unanswered questions still surrounding the various exercise interventions that have been trialled, it is important to gain a better understanding of this particular aspect of PH so we can better analyse the other components in due course.

Aims

- ❖ Primary outcome: to assess the feasibility of conducting an exercise based PH program in UGI oncology patients prior to undergoing surgical resection by evaluating patient compliance alongside improvements in overall

functional capacity.

- ❖ Secondary outcome: to evaluate the effectiveness of these PH programs on post-operative outcomes, including length of stay, complications, and patient quality of life (QoL) assessments.

This systematic review was reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA) reporting checklist (21) (available at <https://dmr.amegroups.com/article/view/10.21037/dmr-21-84/rc>).

Methods

The study protocol was submitted to the Brighton and Sussex Medical School Dissertation Committee for review on 8th June 2020 with full approval granted with no amendments required on the 2nd of July 2020. The review protocol can be made available on request.

A systematic literature search was carried out using the following databases: Medline, Embase, PubMed and CINAHL utilising the NICE Healthcare Databases Advanced Search (HDAS) tool (22). The first search was carried out on the 21st June 2020 with a second on 10th May 2021. There were no date restrictions for the included publications and results were limited to English language publications.

Six different search terms were used separately across the four databases aiming to capture PH studies across the UGI cancer spectrum: “(upper abdominal surgery OR upper gastrointestinal surgery) OR (oesophagectomy OR oesophageal cancer) OR (gastrectomy OR gastric cancer) OR (liver resection OR liver cancer) OR (pancreatectomy OR pancreaticoduodenectomy OR pancreatic cancer) OR (hepatobiliary cancer) AND (prehabilitation OR exercise)”. Following the database search, a further search of the grey literature was also conducted. This search primarily utilised the “google scholar” global search engine along with a review of citations found in editorials, other systematic reviews, guidelines and protocols. Once through the eligibility screening process, these results were then added to the final included studies from the database search.

All abstracts were screened for eligibility by EMT. Inclusion criteria included patients >18 years undergoing UGI cancer surgery following an exercise based PH program. Multi-modal PH programs were included, but they had to have an exercise component. All studies had to include an objective measure of functional capacity pre- and post-exercise PH to assess adherence and efficacy of

the exercise program. This was the main marker used to assess feasibility of the individual programs. If there was any ambiguity about including a particular study then this would be discussed with MM and CJ for a consensus opinion. No extra information was required of the authors from any of the full text articles reviewed.

The following data was manually extracted from each eligible article by EMT; patient demographics, study characteristics including the number of patients involved, study design, duration and cancer diagnosis, composition of the PH programs (exercise ± nutrition ± psychological), method of delivery, compliance and supervision of the PH programs, any preoperative changes in functional capacity following the introduction of these programs and any effects these PH programs had on post-operative outcomes and patient perceived QoL scores.

To ensure the conclusions drawn from this systematic review were robust and accurate, it was important that each study used within the review was assessed for quality and the potential risk of bias. One way to significantly reduce the risk of bias would be to only use randomised controlled trials (RCTs), however, due to the paucity of data currently available for PH programs in UGI cancer patients, non-randomised trials were also included provide a more complete understanding of what research has been conducted so far. To ensure the quality of these non-randomised trials, the Cochrane Risk of Bias in Non-randomised Studies-1 (ROBINS-1) tool was used (23). The risk of bias in the RCTs was assessed using the Risk of Bias-2 (ROB-2) tool from the Cochrane group (24). The risk of bias assessment was conducted by EMT and CJ, no studies were excluded due to an unacceptably high risk of bias.

On careful consideration of the studies eligible for inclusion in this review it was not considered appropriate to conduct a meta-analysis. The clinical variability within the studies in terms of program duration, design and functional capacity assessments did not easily lend themselves to whole group or sub-group statistical analysis. A meta-analysis in this case would at best be meaningless and at worst obscure genuine results/outcomes.

Results

Following the initial database search, 1,191 publications were identified, duplicates were manually removed and screened for inclusion, 36 articles were left for eligibility screening. From the grey literature search, 22 articles were identified for eligibility screening. The full text articles

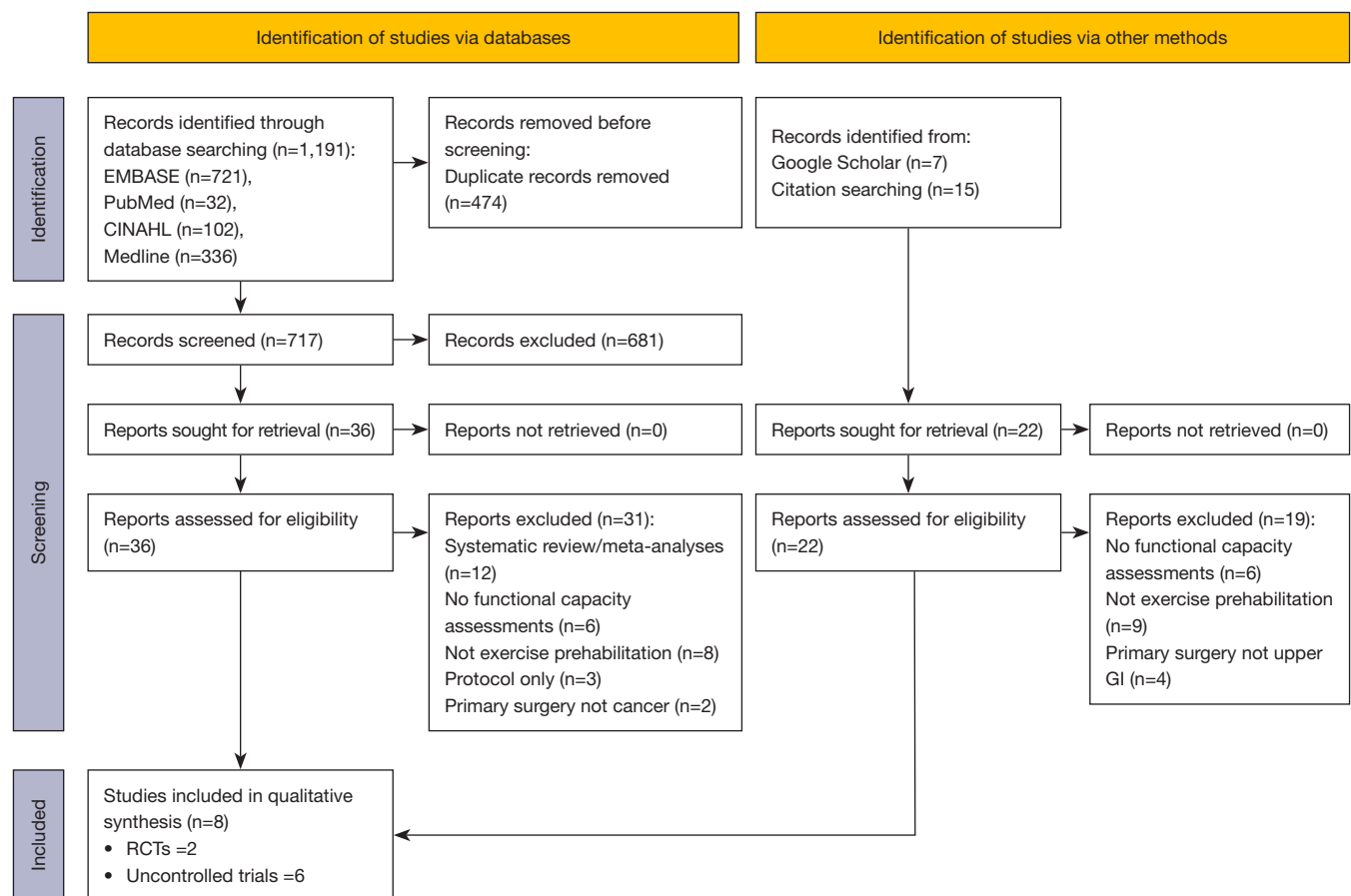


Figure 1 PRISMA 2020 flow diagram of the database search used for this systematic review. RCTs, randomised controlled trials; GI, gastrointestinal; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

were then obtained for all 58 articles, with 8 studies left completing the eligibility criteria. *Figure 1* outlines the flow diagram of the complete study identification process for this review.

Of the 8 studies included within this review, 2 were RCTs and 6 were observational prospective cohort studies, one of which contained matched pair analysis.

Risk of bias

The overall risk of bias for both RCTs was low risk, see *Figure 2*.

The risk of bias for the cohort studies was assessed using the ROBINS-1 assessment tool, see *Figure 3*. As expected, there were areas in all the studies that were at a moderate risk of bias, the most common being the risk of confounding bias or bias in the measurement of outcomes.

Bias due to confounding was more prevalent in Mikami

et al. (25), Ngo-Huang *et al.* (26) and Valkenet *et al.* (27). One reason for confounding bias is the self-selecting nature of patients for the PH programs, generally patients who are more motivated, live closer to the hospital or less frail will be more inclined to sign up to such programs. Valkenet *et al.* (27) looked at the baseline characteristics of those choosing not to participate found participants had significantly less severe disease than non-participants ($P=0.04$). The self-selecting process has a lower bias risk in Nakajima *et al.* (28) as they used matched pair analysis, Halliday *et al.* (29) as only one patient in 67 opted out and Yamamoto *et al.* (30), as all those deemed eligible were enrolled.

Bias in the measurement of outcomes was moderate across 4 of the studies (26,28-30). This was predominantly due to the self-reporting nature of the home-based programs which could be significantly over-estimated by some patients resulting in a falsely elevated level of adherence and compliance.

	Dunne et al.	Minnella et al.
Domain 1: Risk of bias arising from the randomization process	+	+
Domain 2: Risk of bias due to deviations from the intended interventions	+	+
Domain 3: Risk of bias due to missing outcome data	+	+
Domain 4: Risk of bias in measurement of the outcome	+	+
Domain 5: Risk of bias in selection of the reported result	+	+
Overall risk of bias	+	+

Figure 2 The Cochrane ROB-2 tool assessment of the quality of RCTs included in this review. +, low risk of bias. ROB-2, Risk of Bias-2; RCTs, randomised controlled trials.

	Mikami et al.	Ngo-Huang et al.	Nakajima et al.	Haliday et al.	Yamamoto et al.	Valkonen et al.
Domain 1: Bias due to confounding	?	?	+	+	+	?
Domain 2: Bias in selection of participants into the study	+	+	+	+	+	+
Domain 3: Bias in classification of interventions	+	+	+	+	+	+
Domain 4: Bias due to deviations from intended interventions	+	+	+	+	+	+
Domain 5: Bias due to missing data	+	+	+	+	?	?
Domain 6: Bias in measurement of outcomes	+	?	?	?	?	+
Domain 7: Bias in selection of the reported result	+	+	+	+	+	+
Overall risk of bias	+	+	+	+	+	+

Figure 3 The ROBINS-1 assessment of the quality of the cohort studies included in this review. +, low risk of bias; ?, moderate risk of bias. ROBINS-1, Risk of Bias in Non-randomised Studies-1.

Table 1 Characteristics of studies included in this systematic review

Study	Design	Type of surgery	No. of patients in PH group	No. of patients in CN group	No. of patients having NAC
Dunne <i>et al.</i> (31)	RCT	Liver resection for colorectal metastasis	20	17	22 (12 in PH, 10 in CN)
Minnella <i>et al.</i> (32)	RCT	Oesophageal cancer	26	25	35 (20 in PH, 15 in CN)
Mikami <i>et al.</i> (25)	Cohort	Pancreatic cancer	26	0	22
Ngo-Huang <i>et al.</i> (26)	Cohort	Pancreatic cancer	50	0	50
Nakajima <i>et al.</i> (28)	Cohort	Open abdominal surgery for HPB cancers	76	76	0
Halliday <i>et al.</i> (29)	Cohort	Oesophageal cancer	67	0	60
Yamamoto <i>et al.</i> (30)	Cohort	Gastric cancer	22	0	0
Valkenet <i>et al.</i> (27)	Cohort	GI cancer (pancreatic, liver, intestinal, gastric or oesophageal)	115	0	44

PH, prehabilitation; CN, control group; NAC, neoadjuvant chemotherapy; RCT, randomised controlled trial; HPB, hepato-pancreato-biliary; GI, gastrointestinal.

Table 2 Overview of the PH programs

Study	Design	Components of the PH program			Mean duration (weeks)	Type of exercise
		Exercise	Nutrition	Psychological		
Dunne <i>et al.</i> (31)	RCT	×			4	HIIT on bike
Minnella <i>et al.</i> (32)	RCT	×	×		5	Mix aerobic and resistance
Mikami <i>et al.</i> (25)	Cohort	×			1–2	Mix aerobic and resistance
Ngo-Huang <i>et al.</i> (26)	Cohort	×	×		16	Mix aerobic and resistance
Nakajima <i>et al.</i> (28)	Cohort	×	×		4–5	Walking and resistance
Halliday <i>et al.</i> (29)	Cohort	×		×	16	Mix aerobic and resistance
Yamamoto <i>et al.</i> (30)	Feasibility	×	×		2	Walking and resistance
Valkenet <i>et al.</i> (27)	Feasibility	×			4–5	Mix aerobic and resistance

×, component was included in the program. PH, prehabilitation; RCT, randomised controlled trial; HIIT, high intensity interval training.

Study characteristics

Of the 8 studies included for review, 3 had a patient control group, the 2 RCTs (31,32) and the matched pair analysis from Nakajima *et al.* (28). The other 5 were observational studies (25-27,29,30). Two studies looked specifically at oesophageal cancer patients (29,32), two at pancreatic cancer patients (25,26), one at patients with liver metastatic disease (31), one at gastric cancers (30), one with hepato-pancreato-biliary (HPB) cancers (28) and one with a mix of all GI cancers (27). There was a total of 402 patients in the PH groups across the studies, 208 of which underwent NAC. *Table 1* further outlines the characteristics of the studies included in this review.

Composition of PH programs

Table 2 shows an overview of the PH programs in each of the studies. All of the studies were required to have an exercise component as part of the eligibility criteria, 3 studies had a nutritional element (28,30,32) and one a psychological element (29). The duration of the programs varied significantly with Ngo-Huang *et al.* (26) and Halliday *et al.* (29) choosing to start their programs at the time of diagnosis which enabled them to commence the program prior to patients undergoing NAC treatment resulting in 16-week duration. The shortest programs were 1–2 weeks, one of which was hospital based (25), the other home (30).

Table 3 Delivery, compliance, and supervision of the PH programs

Study	Design	Mean duration (weeks)	Method of delivery	Supervision	Compliance
Dunne <i>et al.</i> (31)	RCT	4	Hospital-based, 12× interval bike sessions	Y	95%
Minnella <i>et al.</i> (32)	RCT	5	Home-based with 3× week aerobic and 1× week resistance training + individualised nutritionist plan with supplements	N	63%
Mikami <i>et al.</i> (25)	Cohort	1–2	Hospital based, daily aerobic and resistance	Y	100%
Ngo-Huang <i>et al.</i> (26)	Cohort	16	Home-based, 60 mins/week aerobic and 60 mins/week resistance training	N	84%
Nakajima <i>et al.</i> (28)	Cohort	4–5	Home-based, 3× weekly walking and resistance training + leucine-rich amino acid daily supplementation	N	Unknown
Halliday <i>et al.</i> (29)	Cohort	16	Home-based, 150 mins/week aerobic + resistance training. Increasing intensity over time. Motivational sessions with nurse	N	56% during NAC; 65% after NAC; 85% no NAC
Yamamoto <i>et al.</i> (30)	Feasibility	2	Home-based, daily walking and resistance training + individualised dietician plan	N	50%
Valkenet <i>et al.</i> (27)	Feasibility	4–5	Mix home and hospital-based. Hospital: 2× weekly aerobic and resistance training. Home: inspiratory muscle training + 5× weekly aerobic	Partly	Hospital-based: 82%; home-based: unknown

Y, yes; N, no. PH, prehabilitation; RCT, randomised controlled trial; NAC, neoadjuvant chemotherapy.

Type of exercise intervention

There was a significant amount of heterogeneity between the type and intensity of exercise involved. All the studies except for Dunne *et al.* (31) incorporated an element of resistance training as well as aerobic.

Two looked specifically at home-based walking interventions alongside resistance training. Yamamoto *et al.* (30) aimed for a daily step count of >7,500 whereas Nakajima *et al.* (28) only required 30 minutes 3× per week. However, the mean duration of the program was 2× longer in the Nakajima *et al.* cohort (28).

Three of the other studies also used a home-based mixed exercise program of aerobic and resistance training but in these the aerobic exercises involved walking, cycling or jogging (26,29,32). Minnella *et al.* (32) and Ngo-Huang *et al.* (26) both required 60 minutes/week of aerobic exercise with 1 and 2 resistance training sessions/week respectively. Halliday *et al.* (29) aimed for 150 minutes of aerobic exercise/week with an individualised program for resistance training.

Mikami *et al.* (25), whose program had a significantly shorter mean duration than almost all the other studies, set up a hospital-based program involving daily 50-minute

aerobic sessions encompassing walking and cycling alongside added resistance training. Valkenet *et al.* (27) was the only study to use a mixture of home-based and hospital-based programs. This program consisted of 2× week aerobic and resistance training as part of a group session followed by a further 30 minutes 5× per week moderate-vigorous exercise at home.

Supervision and compliance

Method of exercise delivery, supervision and compliance can be seen in *Table 3*. The highest levels of compliance can be seen in the hospital-based supervised programs (25,31). Ngo-Huang *et al.* (26) also had relatively high compliance, especially considering the duration of this program was 16 weeks. This was the only study to use an objective measurement of physical activity for a home-based program, patients were encouraged to wear an accelerometer for 2 consecutive weeks at the mid-point of each phase of treatment. Yamamoto *et al.* (30) had the lowest compliance levels of all the studies, this may partly be due to their elderly sarcopenic cohort coupled with the daily exercise requirement.

Table 4 Postoperative outcomes of the PH programs

Study	Design	Functional capacity outcome measures	Preoperative changes in functional capacity	Post-operative complications	Health related QoL
Dunne <i>et al.</i> (31)	RCT	VO ₂ max + AT	SI in AT by 1.5 mL/kg/min, and VO ₂ max by 2 mL/kg/min	No difference	SI: in both physical and mental health
Minnella <i>et al.</i> (32)	RCT	6MWD	SI in 6MWD—improved in 62% in PH vs. 4% in CN	No difference	Not assessed
Mikami <i>et al.</i> (25)	Cohort	6MWD + VO ₂ max + AT	SI in VO ₂ max across all ages and sexes. SI in AT in males and <75 years old only. SI in 6MWD across all ages and sexes	No control	Not assessed
Ngo-Huang <i>et al.</i> (26)	Cohort	6MWD	SI in 6MWD	No control	Lower scores in patients with baseline frailty and reduced compliance with PH
Nakajima <i>et al.</i> (28)	Cohort	6MWD	SI in 6MWD in both males and females	SI in post-op length of stay (median 23 vs. 30 days, P=0.045)	Not assessed
Halliday <i>et al.</i> (29)	Cohort	VO ₂ max and O ₂ pulse	VO ₂ max and O ₂ pulse were maintained during NAC with then a SI in the period following NAC prior to surgery	Amount of weekly PA sig associated with the risk of pneumonia following NAC prior to surgery	Not assessed
Yamamoto <i>et al.</i> (30)	Feasibility	4-m gait speed	Not significant	No control	Not assessed
Valkenet <i>et al.</i> (27)	Feasibility	VO ₂ max	Not significant	No control	No improvement

PH, prehabilitation; QoL, quality of life; RCT, randomised controlled trial; VO₂ max, maximal oxygen consumption achieved during the test; AT, anaerobic threshold; SI, significant improvement; 6MWD, 6-minute walk distance; CN, control group; O₂ pulse, indirect measurement of stroke volume; PA, physical activity.

Halliday *et al.* (29) assessed compliance levels in patients who underwent NAC, both during and after their treatment, as well as those with no NAC. Unsurprisingly the level of compliance with their exercise program improved once NAC treatment had ended, but compliance levels never reached that of the no NAC sub-group.

Outcomes of the PH programs

Table 4 shows an overview of the outcomes from the studies PH programs, including changes in preoperative functional capacity, post-operative complications, and patient QoL surveys.

Changes in preoperative functional capacity

Three studies used the 6-minute walk distance (6MWD) as their functional capacity assessment (26,28,32), three used maximal oxygen consumption achieved during test

(VO₂ max) ± anaerobic threshold (AT) (27,29,31), one study used both of these functional measures (25) and one looked at 4-m gait speed (30).

All the studies looking at 6MWD showed significant improvements following their PH programs. Three of these were home-based programs of 5–16 weeks duration (26,28,32), one was hospital based with 1–2 weeks duration (25), indicating that even with limited time it is feasible to meaningfully improve preoperative functional capacity in this cohort.

Of the studies looking at VO₂ max, only one out of four did not show any significant improvement, Valkenet *et al.* (27). Yamamoto *et al.* (30) also showed no significant improvement in 4-m gait speed following their 2-week home-based program.

Postoperative complications

There was no difference in the incidence of post-operative complications in either of the RCTs. Nakajima *et al.* (28) used

matched pair analysis to compare their current PH cohort with historic data which showed a significant decrease in length of stay in the PH group by an average of 7 days.

Halliday *et al.* (29) collected data on the incidence of post-operative pneumonia in their patient cohort. The data showed that the average weekly physical activity over the whole 16-week program significantly associated with the risk of pneumonia. The higher the average weekly activity, the lower the incidence of post-operative pneumonia.

QoL outcomes

Most studies did not collect any patient centred outcome data. Three looked at patient QoL outcome data (26,27,31). Valkenet *et al.* (27) used the 36-item short form survey (SF-36) and the EORTC QLQ-30 (European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire), Dunne *et al.* (31) used the SF-36 survey and Ngo-Huang *et al.* (26) used the FACT-Hep (Functional Assessment of Cancer Therapy-Hepatobiliary) questionnaire. Only Dunne *et al.* (31) found a meaningful increase in patient QoL.

Discussion

This systematic review shows it is feasible to conduct preoperative exercise-based PH programs in UGI cancer patients and that these programs can significantly improve their functional capacity prior to surgery.

Functional capacity outcome measurements

Despite a significant degree of heterogeneity across the studies in terms of duration, composition and mode of administration, six of the eight studies reviewed reported a significant improvement in functional capacity using either the 6MWD (25,26,28,32) or cardiopulmonary testing to ascertain $VO_2 \text{ max} \pm AT$ (25,29,31). Of the four studies using $VO_2 \text{ max} \pm AT$, two used a standard cardiopulmonary exercise testing (CPET) approach of maximal exercise testing on a cycle ergometer to provide direct measurements of CPET-derived variables including $VO_2 \text{ max}$ and AT (25,31). This technique is now well established as an objective measure of functional capacity and validated as a risk prediction tool for postoperative morbidity and mortality across a wide variety of major surgical procedures (33,34). The other two studies used submaximal exercise testing to provide indirect $VO_2 \text{ max}$ measurements, one

via the Chester Step Test (29) and the other utilising the Astrand nomogram (27). The ability of these studies to accurately predict $VO_2 \text{ max}$ has recently been evaluated via direct comparison to CPET (35). The Chester Step Test was found to be valid for predicting mean changes of $VO_2 \text{ max}$ in a group of patients, but that individual predictions were liable to considerable error (35). As this systematic review is focused on mean group improvements in $VO_2 \text{ max}$ following the implementation of a PH program, this method of functional capacity assessment is appropriate for use in this context. The validity of the Astrand test was less conclusive (35,36). The test requires patients to cycle for 5–6 minutes with heart rates of 120–170 bpm for the Astrand nomogram to predict a $VO_2 \text{ max}$ value. Patients with limited endurance or on beta blockers found it difficult to reach and maintain these heart rates, causing a high drop-out rate for this test in the evaluation study (35). Valkenet *et al.* (27) only have Astrand $VO_2 \text{ max}$ results for 38% of their PH patients, from which they were unable to observe any significant improvement following their PH program. The write up for this study was done a few years after it was conducted, and the authors are unable to account for the 62% of missing data. Steps have been taken to minimise the effects of this data gap by using a mixed-models analysis to try to provide an unbiased estimate of the missing data. Given the high volume of missing data and the potentially high drop-out rates using the Astrand method of testing, it would seem prudent to use alternative validated measurement methods for functional capacity testing in the future, such as CPET or the 6MWD.

The 6MWD was utilised by four studies (25,26,28,32) and is a validated measurement tool for functional capacity assessment (37). A significant change of 20m deviation from baseline was used across the studies in keeping with previous definitions (38). The 6MWD has been shown to correlate well to CPET-derived variables in both cardiac (39) and non-cardiac (40) surgery, there is also evidence that 6MWD may be useful in predicting postoperative outcomes including complications (41) and length of stay (42), but the distance thresholds required to define the higher-risk group are yet to be determined. All of the studies using the 6MWD as a measurement tool showed a significant improvement in their patient cohorts following their PH programs.

Yamamoto *et al.* (30) used 4-m gait speed as their measure of functional improvement. Attempts to validate this technique against the 6MWD have shown that whilst there is some correlation between the two, 4-m gait speed has a

reduced correlation in comparison to the 6MWD with age, lung capacity and muscle strength and therefore its ability to accurately assess functional performance is uncertain (43). Yamamoto *et al.* (30) found no significant difference in the 4-m gait speed following their PH program.

Feasibility of PH programs during NAC

The feasibility of PH programs in the UGI cancer cohort is highly dependent on these patients being able to adhere to exercise interventions whilst undergoing or having just completed a course of NAC. Six of the studies in this review had patients undergoing NAC (25-27,29,31,32), two of which conducted 16-week programs capturing data on patient adherence both during and after NAC treatment (26,29). Both these studies found a significant improvement in functional capacity tests by the end of their programs. Halliday *et al.* (29) also tested patients in the middle of their PH program following NAC completion, at this point they found no improvement in functional capacity but more significantly, no deterioration. The effects of chemotherapy on patient fitness have been well documented, there is often a substantial fall from baseline in these patients that struggles to improve back up to baseline prior to surgery (44,45). Therefore, the maintenance of functional capacity during NAC in Halliday *et al.* (29) followed by a significant improvement from baseline in the weeks prior to surgery is very encouraging. Compliance to the PH program in Halliday *et al.* (29) also differed significantly depending on where patients were in their treatment cycle. Compliance was at its lowest at 56% in patients undergoing NAC, rising to 65% when treatment was completed, those that never required NAC had a much higher compliance rate of 85%. The compliance rate in the other 16-week study, Ngo-Huang *et al.* (26), was up at 84% with every patient in this study undergoing NAC. Both of these PH programs were home-based and relied at least partly on patient self-reporting for compliance (Ngo-Huang also intermittently used accelerometers), and these results show that not only are patients undergoing NAC able to adhere to a PH program, but by attenuating the usual functional decline, they also stand to make significant improvements to their preoperative functional capacity (26,29).

Type and duration of exercise

There was a wide variety of exercise programs used across the studies, most used a mixture of aerobic and resistance

training with the exception of Dunne *et al.* (31), and the majority were able to show a significant increase in patient functional capacity following their interventions. The two studies that found no improvement in functional capacity were Yamamoto *et al.* (30) and Valkenet *et al.* (27). Yamamoto *et al.* (30) conducted a daily 2-week home-based program in sarcopenic elderly patients with the lowest reported compliance rate of 50%. It is likely that this particularly frail group of patients needed more hands-on involvement to enable them to complete the program as Mikami *et al.* (25) have shown that even with a 2-week program window, a meaningful improvement in patients can be attained. However, the Mikami *et al.* (25) program did require a 2-week hospital admission preoperatively, guaranteeing 100% compliance to daily exercise. Valkenet *et al.* (27) had a longer hospital-based program lasting up to 5 weeks, requiring two outpatient visits a week for a mix of aerobic and resistance training. On closer analysis, the average patient attendance was only 5.7 training sessions prior to having their operation. Given only half of these sessions were aerobic, it is not surprising they were unable to show any significant change in their cardiorespiratory functional assessments.

There is a growing body of evidence to show that the inclusion of aerobic exercise as part of a comprehensive PH program can result in significant improvements to patient functional capacity (26,29,46,47), but the type and duration of exercise is yet to be determined. From the six studies showing significant functional capacity improvement (25,26,28,29,31,32), the shortest time period required was 2 weeks as described above by Mikami *et al.* (25), but given that a 2-week hospital stint for all UGI cancer patients is not feasible, the next practical time period was 4–5 weeks conducted by Dunne *et al.* (31), Minnella *et al.* (32) and Nakajima *et al.* (28). The aerobic sessions required in each of these programs were all 3× weekly, using a mixture of high intensity interval training (HIIT), walking, cycling and jogging (28,31,32). These results appear to suggest that the type and intensity of aerobic exercise conducted is less important than the frequency of the sessions and the duration of the program. These studies in themselves are too small and heterogenous to definitively reach this conclusion and larger pragmatic multi-centred RCTs are needed, but this would open up the prospect of being able to design individualised PH programs utilising a variety of different exercise interventions to achieve maximum patient compliance.

The benefit of using resistance training, although

it seems intuitive, is less clear (48). Five of the studies reporting an increase in functional capacity used some form of resistance training (25,26,28,29,32), however functional strength was only directly tested in one of these. Ngo-Huang *et al.* (26) conducted two functional strength tests; speed taken to do 5× sit-to-stands and hand grip strength using a handheld dynamometry. Their program was conducted over 16 weeks and found a significant improvement in the sit-to-stand time, but not handgrip strength. The theory behind including resistance training techniques in these PH programs is the increased anabolic stimulus you get from this particular mode of exercise. This should work to counteract the effects of NAC-induced sarcopenia by helping to build and maintain muscle and also by aiding the recovery of muscle function postoperatively (48,49). A recent systematic review looking at a wide variety of resistance training methods in the general population advised a program length of >6 weeks was required before any appreciable results are demonstrated (50). This program duration would likely only be achievable in most UGI cancer settings if it was started at the time of diagnosis as in Ngo-Huang *et al.* (26) and Halliday *et al.* (29). Unfortunately, due to the lack of direct testing in the other studies, it is difficult to form any conclusions as to the effectiveness of including resistance training in these PH programs.

Supervision and compliance

The studies in this review conducted a mix of both hospital (25,27,31) and home-based (26,28-30,32) exercise programs. Attendance to the hospital-based programs was significantly higher than the self-reported compliance during the home-based programs, with an overall attendance rate between 82–100% (25,27,31), compared to 50–86% in the home-based studies. A recent study comparing the two modes of delivery concluded that supervised programs result in a higher patient compliance and will therefore have better outcomes (51). However, significant improvements in functional capacity were also elicited in the home-based programs of this review with compliance rates of >80% in two studies (26,29). Three of the home-based studies used regular weekly or fortnightly telephone follow-ups to improve patient adherence to the program (26,29,32). Ngo-Huang *et al.* (26) also used accelerometers for up to 6 weeks during their 16-week program. The use of technology to assist in improving home-based compliance is ever evolving. From the recent exponential rise in video calling

as a result of the COVID-19 pandemic, group sessions can now take place in the home more readily and apps/watches to track individual health data can provide real-time updates promoting increased activity and encouraging accountability (52,53). The home-based studies in this review have demonstrated that it is possible to improve functional capacity even with compliance rates as low as 63% (32), but more could be done to utilise the technology now widely available to try and increase compliance even further.

When analysing the compliance rates, it is important to note that almost all of the patients in these studies were self-selected. This is a study limitation as self-selected patients had a high level of motivation and wanted to participate in the exercise programs when they consented. Of all the patients eligible for inclusion in Valkenet *et al.* (27), 32% declined to take part. They analysed the baseline characteristics for the different groups and noted that those who refused lived further from the hospital (this was a hospital-based program) and had more severe systemic disease. Similarly high levels of patient refusal were seen in Dunne *et al.* of 57% and Minnella *et al.* of 40% (31,32), increasing the risk of confounding bias which could potentially skew the overall results. Dunne *et al.* (31) also noted that the patients starting their program with low functional capacity baselines had the most considerable gains in VO₂ max and AT, hypothesising that it may be these more systemically unwell patients that stand to benefit the most from PH. This further supports the need for individualised PH programs, to promote inclusivity and encourage patient involvement.

Postoperative outcomes

All the studies included in this review were primarily designed to establish the feasibility of a PH program and/or the effects on patient functional capacity following them. None of the studies were adequately powered to assess postoperative outcomes, as such any conclusions inferred from these studies will need to be verified in further adequately powered RCTs.

Of the three studies that had a control group, the two RCTs (31,32) and the matched pair analysis (28), the two RCTs found no difference in postoperative outcomes whereas Nakajima *et al.* (28) observed a significant improvement in length of stay, but no difference in the incidence of major postoperative complications. This finding is interesting as it suggests that although some of

the key risk factors for developing major complications (e.g., cancer stage and surgical complexity) may not be modifiable by simply increasing patient fitness, PH may result in a faster recovery from these complications when they do arise.

Given the particularly high rate of postoperative pulmonary complications in oesophageal cancer patients (54,55), Halliday *et al.* (29) monitored the incidence in their PH cohort. A significant correlation was observed between the amount of patient reported weekly physical activity and the risk of developing postoperative pneumonia. This has the potential to be a very significant finding in this cohort where the overall incidence of postoperative complications is up at 59% (56), and it will be interesting to see if these results can be replicated in further studies.

Only three studies looked at patient-centred outcomes using QoL measurement tools (26,31). Traditionally, it has been biomedical outcomes rather than QoL assessments that have been the principal endpoints in medical research (57). However, there is now an increasing drive to put patient-centred care at the forefront of new health innovations, particularly in cancer patients, with the aim of reducing the psychological toll of treatment. Dunne *et al.* (31) found a significant improvement in their PH group using the SF-36, a widely adopted tool designed to measure health related QoL. Dunne *et al.* (31) also noted that QoL in their control group did not change even when their fitness levels dropped, leading them to hypothesise that some of the QoL improvements may not be solely related to an improvement in fitness, but possibly through doing the training as a group with other participants in similar situations. However, contrary to Dunne *et al.* (31), Ngo-Huang *et al.* (26) did find a link between those least compliant with the program, who were more sedentary on the accelerometer, with lower QoL scores suggesting there is some correlation with fitness levels. QoL is an important outcome measure that should be used as standard in future studies. The highlighted variability of the current published work means it is important to understand the impacts of new PH programs on patient QoL as this will enable patient-centred improvements in the design and implementation process leading to higher compliance rates and ultimately more successful programs.

Multi-modal components

Four of the studies reviewed had nutritional components (26,28,30,32) to their PH programs and one had a

psychological component (29). The nutritional components were all predominantly focused on high protein intake; two had leucine-rich amino acid supplements taken before and after exercise (28,30), one had a high protein meal post-exercise (26), and one had a high protein diet with additional whey protein supplements (32). Given the heterogeneity of the different methods used across the studies for monitoring their nutritional interventions, it is difficult to ascertain whether these supplements made any significant contribution to study outcomes. There is pre-existing evidence to suggest that protein supplementation could improve muscle strength and size during new exercise regimes (58,59), but these conclusions need to be more robustly investigated in the context of PH using validated nutritional assessment tools to accurately monitor the effects on this group of patients (60).

Halliday *et al.* (29) had an additional psychological component to their study. Patients were given sessions with a clinical nurse specialist where “*the rationale for prehabilitation was reinforced, potential barriers and facilitators to exercise were explored and motivational interviewing techniques were used to facilitate positive behavioural change*”. Unfortunately, there was no objective assessment carried out to determine how their patients reacted to this intervention or if it made any difference to overall patient compliance levels. This has again highlighted the need for valid outcome measurement tools to be incorporated into any study to enable accurate evaluations of each intervention implemented.

Limitations of this review

As a relatively new area of research, there is a paucity of large, pragmatic RCTs from which to extract data from and form conclusions. The studies reviewed in this paper were all small single centred studies with only two RCTs. The need for more robust RCTs is required to reduce the risk of selection bias, particularly in this self-selecting group of patients and to minimise the risk of confounding variables.

Although there are clear comparisons between the individual UGI sub-groups of low 5-year survival rates, high levels of sarcopenia and a growing use of neoadjuvant therapies which makes it useful for them to be reviewed together, there are also significant differences between these groups that would benefit from more detailed separate analysis. These include the degree of malnutrition on diagnosis, the types and treatment course of NAC,

additional use of radiotherapy and therefore window of opportunity for which exercise PH would be most useful.

The data from these studies suggests that functional capacity can be improved through exercise PH programs, but none of these studies were adequately powered to evaluate if these changes in functional capacity are enough to affect outcomes. A large multi-centred trial is currently underway across the UK which has been designed to establish whether a PH exercise program ± psychological support can reduce postoperative length of stay in intra-cavity major cancer surgery (61). This study is aiming to recruit >1,500 patients to be adequately powered for their primary outcome. The results for this study are due in March 2022 and will hopefully go some way to answering some of the questions posed in this review.

This study was conducted as part of a Master's dissertation and as such there was only one main reviewer in the study selection process. Although robust database searches were conducted at two different time intervals to reduce the risk of omitting eligible studies, two reviewers in the selection process would provide further assurance all studies were captured. The use of exclusion of non-English language studies is also a limitation.

Recommendations for future research

Larger multi-centred RCTs designed using a patient-centred pragmatic approach are required to fully evaluate some of the unanswered questions following this review, in particular:

- (I) Does a significant change in preoperative functional capacity result in improved postoperative outcomes; including complications, length of stay and/or QoL?
- (II) What is the optimal pragmatic duration and intensity of a PH exercise program?
- (III) Can we utilise health data tracking technology to make home-based programs just as accessible as hospital-based programs to improve compliance?
- (IV) What is the optimal nutritional component of PH and how does it affect postoperative outcomes?
- (V) What is the optimal psychological component of PH and how does it affect postoperative outcomes?

Conclusions

This systematic review has shown that it is feasible to conduct a PH program in UGI cancer patients which

results in a significant improvement in functional capacity. It has also shown them to be feasible whilst patients are actively undergoing NAC treatment where it is found to be particularly effective at attenuating the usual functional decline. Whether a significant improvement in a patients' preoperative functional capacity can enhance their postoperative outcomes is yet to be determined.

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