Response to the comment on "The impact of prehabilitation on patient outcomes in hepatobiliary, colorectal and Upper Gastro-intestinal cancer surgery: A PRISMA-Accordant Meta-Analysis" by Onerup et al.

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Dear Editor,

We commend Onerup et al. for their valuable contribution to this interesting and emerging field. We noted with interest that their randomised controlled trial in a cohort of colorectal cancer patients showed no difference in patient reported short-term outcomes with mild/moderate exercise prehabilitation strategies[1]. Indeed, the prehabilitation studies to date have shown mixed results both in-favour of exercise interventions[2,3] equivocal[4] and others have shown no effect[5]. In our opinion, 'prehabilitation' within the context of cancer surgery, may have several moving parts. These are likely related to (i) the type of cancer (ii) type of prehabilitation (uni, bi or multimodal) and (iii) type of outcomes measured (functional, clinical or other).

Different cancers may exert different physiological effects in the same way that jaundiced patients with malignant biliary obstruction[6] or anaemic patients[7] with colorectal cancer may perform poorly on cardiopulmonary exercise testing (CPET). This idea suggests that prehabilitation might not be a 'one size fits all' strategy and may have to be tailored to suit the cancer type. Prehabilitation is predicated on having sufficient time to implement an effective programme. The time-critical nature of cancer intervention often dictates the available time for prehabilitation. To that end, the EMPOWER Trial run by Loughney et al. demonstrated statistically significant improvements in quality of life and fitness as measured by CPET following a 9-week community-based exercise prehabilitation programme[8]. This was achieved in a cohort of patients undergoing long-course chemo/radiotherapy for locally advanced rectal cancer. This suggests that there may be some value in longer duration programmes.

With reference to the type of prehabilitation, overall, the literature suggests that low to moderate intensity exercise was less likely to significantly impact on fitness and recovery after major cancer surgery than high intensity exercise. We noted in our meta-analysis[9] that it is possible that volume, intensity, frequency and whether exercise is supervised or not, may influence the effectiveness of an exercise-based programme. We note that your study implemented a home-based unsupervised mild/moderate intensity programme. We think that this a practical and feasible strategy but has its limitations like all other programmes; including poor adherence and compliance with the most motivated patients tending to derive most benefit. There is also the issue of how best to monitor compliance. With this in mind, we support the standardisation of exercise interventions. Also, the role of a nutritional intervention within bi or multi-modal programmes to date has not been fully evaluated.

Considering outcomes, we found no difference in complication rates, mortality, or functional capacity[9]. We did find a reduction in hospital length of stay. The caveat with length of stay is the relationship with other factors such as discharge pathways, patient-related social issues, community provisions and other patient factors. It is also worth considering the contributory

effect of enhanced recovery strategies, which are now standard care in most NHS cancer units in the UK. There is considerable subjectivity in patient reported outcomes which may feed into the broader issue of the psychology of how patients perceive their illness and inherent patient differences. In our opinion this aspect also requires further evaluation.

Another aspect sometimes over-looked in the literature is the 'non-responder' effect[10]. There is evidence to suggest that some patients, particularly those with colorectal cancer, tend not to respond to exercise interventions. This may be multi-factorial and could involve factors related both to the disease itself and possibly to genetic factors. This suggests the need for a better understanding of the mechanisms by which prehabilitation might achieve the physiological change underpinning improvements in clinical outcomes. We are currently investigating this in the SPECS Trial (NCT04880772), which is currently recruiting.

While some patients derive no benefit from prehabilitation, we believe that there is insufficient evidence to declare its futility in all formats and patient groups. We suggest instead that further studies are required to understand the underlying physiological mechanisms that may lead to a more tailored approach to prehabilitation.

References

1. Onerup A, Andersson J, Angenete E, et al. Effect of Short-Term Homebased Pre- and Postoperative Exercise on Recovery after Colorectal Cancer Surgery (PHYSSURG-C). *Ann Surg*.;Publish Ah . Epub ahead of print April 9, 2021. DOI: 10.1097/SLA.0000000000004901.
2. Minnella EM, Awasthi R, Loiselle SE, et al. Effect of Exercise and Nutrition Prehabilitation on Functional Capacity in Esophagogastric Cancer Surgery: A Randomized Clinical Trial. *JAMA Surg*. 2018;153:1081–1089.
3. Nakajima H, Yokoyama Y, Inoue T, et al. Clinical Benefit of Preoperative Exercise and Nutritional Therapy for Patients Undergoing Hepato-Pancreato-Biliary Surgeries for Malignancy. *Ann Surg Oncol*. 2019;26:264–272.
4. Bousquet-Dion G, Awasthi R, Loiselle SÈ, et al. Evaluation of supervised multimodal prehabilitation programme in cancer patients undergoing colorectal resection: a randomized control trial. *Acta Oncol (Madr)*. 2018;57:849–859.
5. Ausania F, Senra P, Meléndez R, et al. Prehabilitation in patients undergoing pancreaticoduodenectomy: a randomized controlled trial. *Rev Esp Enferm Dig*. 2019;111:603–608.
6. Junejo MA, Siriwardena AK, Parker MJ. Peripheral oxygen extraction in patients with malignant obstructive jaundice. *Anaesthesia*. 2014;69:32–36.
7. Otto JM, O'Doherty AF, Hennis PJ, et al. Association between preoperative haemoglobin concentration and cardiopulmonary exercise variables: a multicentre study. *Perioper Med*.;2 . Epub ahead of print December 13, 2013. DOI: 10.1186/2047-0525-2-18.
8. Loughney L, West MA, Kemp GJ, et al. The effects of neoadjuvant chemoradiotherapy and an in-hospital exercise training programme on physical fitness and quality of life in locally advanced rectal cancer patients (The EMPOWER Trial): study protocol for a randomised controlled trial. *Trials*. 2016;17:24.
9. Lambert JE, Hayes LD, Keegan TJ, et al. The Impact of Prehabilitation on Patient Outcomes in Hepatobiliary, Colorectal, and Upper Gastrointestinal Cancer Surgery.

Ann Surg.;274 . Epub ahead of print July 2021. DOI: 10.1097/SLA.0000000000004527.
10. Timmons JA, Knudsen S, Rankinen T, et al. Using molecular classification to predict gains in maximal aerobic capacity following endurance exercise training in humans. *J Appl Physiol*. 2010;108:1487–1496.