Letter to the Editor

Multidisciplinary rehabilitation across the esophageal cancer journey

Linda O'Neill[1], Jenny Gannon[1], Emer Guinan[2], John V. Reynolds[3], Juliette Hussey[1]

[1]Discipline of Physiotherapy, [2]School of Medicine, Trinity College Dublin, Dublin, Ireland; [3]Trinity Translational Medicine Institute, Department of Surgery, Trinity College Dublin and St. James's Hospital, Dublin, Ireland

Correspondence to: Linda O'Neill. Discipline of Physiotherapy, School of Medicine, Trinity Centre for Health Sciences, St. James's Hospital, Dublin 8, Ireland. Email: oneilll8@tcd.ie.

Provenance: This is an invited article commissioned by Section Editor Dr. Di Lu (Department of Thoracic Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, China).

Response to: Gockel I, Pfirrmann D, Jansen-Winkeln B, *et al.* The dawning of perioperative care in esophageal cancer. J Thorac Dis 2017;9:3488-92.

Submitted Oct 07, 2017. Accepted for publication Nov 09, 2017.
doi: 10.21037/jtd.2017.11.72
View this article at: http://dx.doi.org/10.21037/jtd.2017.11.72

Weight loss, malnutrition, and sarcopenia are prevailing side effects of esophageal cancer and its treatments, resulting in significant deficits in quality of life (QOL) and physical functioning from diagnosis into survivorship. However, as survival rates start to improve, a growing emphasis has been placed on strategies to improve the QOL of survivors. Our research group strongly agree with the argument put forward in the editorial by Gockel *et al.* that there is a clear rationale for multidisciplinary rehabilitative measures, both in preparation for, and in recovery following esophagectomy.

Following diagnosis of locally advanced esophageal cancer, neoadjuvant chemotherapy (NAC)/chemoradiotherapy (NCRT) is now the standard of care. Notwithstanding the considerable survival advantages, neoadjuvant therapy is associated with significant reductions in exercise capacity (1), weight loss and sarcopenia (2), the consequences of which include increased treatment toxicity and greater postoperative complication risk. Akin to Gockel *et al.*, we recognise the importance of not only pre-habilitation in preparation for surgery but we also observe the necessity for pre-rehabilitative interventions designed to maintain physical function and body composition during neoadjuvant treatment to optimise treatment tolerance, and enhance readiness for surgery. To date, pre-habilitative interventions in esophageal cancer have focused either on maintaining physical function during neoadjuvant treatment or improving physical function in preparation for esophagectomy. A pilot study by Xu *et al.* (3) reported that compared to usual care (n=29), multidisciplinary rehabilitation (n=30) involving a walking and dietary intervention during NCRT, prevented decline in numerous endpoints including Six Minute Walk Test (6MWT) distance by 100 m (P=0.012), hand grip strength (HGS) by 3 kg (P=0.002), and weight loss by 2.7 kg (P<0.001). While these results are positive, Xu *et al.* (3) included male participants with squamous cell oesophageal carcinoma, the more common pathology observed in the Asian population, and further work is required, particularly in patients with adenocarcinoma.

There is clear justification for rehabilitation in advance of esophagectomy. Reduced pre-operative physical fitness is associated with increased risk of development of post-operative pulmonary complications (PPCs) following esophagectomy (4). Henceforth, pre-habilitative interventions which aim to improve pre-operative fitness over a short period of time in preparation for surgery require exploration. There is however a dearth of evidence in this area. One pilot study by Timmerman *et al.* (5), examined the impact of a pre-operative exercise programme only in 39 cancer patients scheduled for elective surgery, included five oesophageal cancer patients, and found significant improvements in exercise capacity could be achieved pre-operatively. Considerable work is required to identify suitable exercise modalities for this purpose.

Preoperative inspiratory muscle training (IMT) to prevent PPCs post-esophagectomy also seems to be a

promising area of exercise research. Recently our research centre at Trinity College Dublin and St. James's Hospital Dublin recruited to the international PREPARE trial which investigated the efficacy of IMT to prevent PPCs (6). The PREPARE trial aimed to recruit 248 patients from eight research centres across the Netherlands, Belgium and Ireland. Recruited patients were randomised to receive either a high intensity IMT (30 dynamic inspiratory efforts, twice daily, for a minimum of 2 weeks pre-operatively, at 60% maximum inspiratory effort), or usual care. We await publication of results. IMT has considerable potential as a pre-habilitative intervention and we look forward with anticipation for the results of the I-PEP study (7) which combines an IMT intervention with aerobic and resistance training from throughout neoadjuvant therapy until time of surgery, and includes a 3-month post-esophagectomy follow-up.

Finally, we wish to highlight the huge potential of multidisciplinary rehabilitative interventions in esophageal cancer survivorship. In survivorship, deficits in physical function are common. Gannon *et al.* (8) reported that exercise capacity, and time spent in moderate and vigorous physical activity were significantly lower in 25 patients >6 months post-esophagectomy compared to health age matched controls (P<0.001). Furthermore, with regard to QOL, this cohort reported reduced physical and role functioning (P<0.001). Weight loss and sarcopenia are also ongoing issues in esophageal cancer survivorship. At 1-year post-esophagectomy, Elliott *et al.* (2) reported a sarcopenia rate of 35% in a cohort of 72 patients who had undergone neoadjuvant chemotherapy in advance of esophagectomy. Given the long-term deficits in physical function, and ongoing issues with weight and muscle loss there is a clear rationale for investigation of multidisciplinary rehabilitative interventions combining exercise with dietary counselling to target these issues experienced by survivors.

Recently, our research group reported on the feasibility of a 12-week multidisciplinary rehabilitation programme consisting of supervised and unsupervised exercise sessions, dietary counselling, and group education sessions (9,10) in 12 survivors of esophageal cancer (>1 year post-esophagectomy). Feasibility was demonstrated through the recruitment rate (55%), adherence to the supervised sessions (82%±13%), and lack of adverse events. Moreover, significant improvements in physical fitness [VO_{2max} increased by 3.99±2.7 mL/min/kg, P=0.004); physical performance (6MWT distance) improved by 56.3±35.3 m, P=0.003], and global QOL (increased by 10.42±10.73, P=0.006) were observed following participation in the 12-week programme (10). Importantly, body composition remained stable throughout the programme. Furthermore, this feasibility study also explored the biochemical effects of physical activity, and found a significant reduction in interleukin (IL)-8 following participation in the programme [–11.25%, 95% confidence interval (CI): –20.98% to –1.51%, P=0.03] (9). Accordingly, the efficacy of this 12-week multidisciplinary rehabilitation programme has been investigated further by randomised control trial (RCT). The RCT was recently completed and data analysis is ongoing at present. Another trial by van Vulpen *et al.* (11) implementing an exercise intervention in 150 patients >4-week, and <1-year post-esophagectomy is ongoing in the Netherlands at present and will provide further evidence regarding exercise in esophageal cancer survivorship.

To conclude, given the physical function deficits, along with weight loss and sarcopenia, across the esophageal cancer journey there is clear rationale for multidisciplinary interventions to support patients throughout their treatment trajectories. However, the evidence for such programmes is limited at present and further high quality RCTs are required.

Acknowledgements

The authors would like to acknowledge the assistance and support of the Wellcome Trust/Health Research Board Clinical Research Facility at St. James's Hospital, Dublin, Ireland in providing a dedicated environment for the conduct of high-quality clinical research activities.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Jack S, West MA, Raw D, et al. The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery. Eur J Surg Oncol 2014;40:1313-20.
2. Elliott JA, Doyle SL, Murphy CF, et al. Sarcopenia: Prevalence, and Impact on Operative and Oncologic Outcomes in the Multimodal Management of Locally Advanced Esophageal Cancer. Ann Surg 2017;266:822-30.
3. Xu YJ, Cheng JC, Lee JM, et al. A Walk-and-Eat Intervention Improves Outcomes for Patients

With Esophageal Cancer Undergoing Neoadjuvant Chemoradiotherapy. Oncologist 2015;20:1216-22.
4. Moran J, Wilson F, Guinan E, et al. Role of cardiopulmonary exercise testing as a risk-assessment method in patients undergoing intra-abdominal surgery: a systematic review. Br J Anaesth 2016;116:177-91.
5. Timmerman H, de Groot JF, Hulzebos HJ, et al. Feasibility and preliminary effectiveness of preoperative therapeutic exercise in patients with cancer: a pragmatic study. Physiother Theory Pract 2011;27:117-24.
6. Valkenet K, Trappenburg JC, Gosselink R, et al. Preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophageal resection (PREPARE study): study protocol for a randomized controlled trial. Trials 2014;15:144.
7. Pfirrmann D, Tug S, Brosteanu O, et al. Internet-based perioperative exercise program in patients with Barrett's carcinoma scheduled for esophagectomy [iPEP - study] a prospective randomized-controlled trial. BMC Cancer 2017;17:413.
8. Gannon JA, Guinan EM, Doyle SL, et al. Reduced fitness and physical functioning are long-term sequelae after curative treatment for esophageal cancer: a matched control study. Dis Esophagus 2017;30:1-7.
9. Guinan EM, Doyle SL, O'Neill L, et al. Effects of a multimodal rehabilitation programme on inflammation and oxidative stress in oesophageal cancer survivors: the ReStOre feasibility study. Support Care Cancer 2017;25:749-56.
10. O'Neill L, Guinan E, Doyle SL, et al. Rehabilitation strategies following esophageal cancer (the ReStOre trial): a feasibility study. Dis Esophagus 2017;30:1-8.
11. van Vulpen JK, Siersema PD, van Hillegersberg R, et al. Physical ExeRcise Following Esophageal Cancer Treatment (PERFECT) study: design of a randomized controlled trial. BMC Cancer 2017;17:552.

Cite this article as: O'Neill L, Gannon J, Guinan E, Reynolds JV, Hussey J. Multidisciplinary rehabilitation across the esophageal cancer journey. J Thorac Dis 2017;9(12):E1140-E1142. doi: 10.21037/jtd.2017.11.72