Editorial

The dawning of perioperative care in esophageal cancer

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The currently published paper "*Reduced fitness and physical functioning are long-term sequelae after curative treatment for esophageal cancer*: *a matched control study*" by Gannon *et al.* (1) focuses on a highly relevant topic of esophageal surgery, which has been greatly under-addressed in the past. Objective data on physical performance outcomes and health-related quality of life (HRQOL) of disease-free survivors after esophagectomy for cancer compared with a noncancer control group are rare (1). Data by Gannon *et al.* clearly show that disease-free survivors of curative esophageal cancer treatment display a significant compromise in physical functioning as compared to the control group, highlighting the multiple, complex rehabilitative needs of this cohort (1).

In the recent years, new surgical techniques with reduced operative trauma, such as hybrid, minimally-invasive or robotic esophagectomy (2) and advanced possibilities of postoperative intensive care treatment, as well as measures with positive impact on enhanced recovery-rehabilitation (3) as optimized clinical pathways (4,5) have been introduced. In principal, these measures should prevent cardiorespiratory complications and restore patients' physical functioning and fitness more quickly and, thus, quality of life. Regardless of these improvements, persisting long-term dysfunctions and their respective consequences following esophagectomy for cancer still seem a largely underestimated feature in clinical practice. In this context, the enormous delay of recovery after surgery does not only influence patients' private life, life quality and physical, psychological and social re-integrity, but also health-economic and socio-medical aspects, considering additional costs associated with prolonged stationary or ambulatory medical treatments, as well as loss of working hours due to sick leave. Thus, the study of Gannon *et al.* (1) hints to two relevant approaches, which consequently have to be drawn from their data: the urgent need for (I) prevention, preconditioning and prehabilitation before surgery, and for (II) more comprehensive, complex and holistic rehabilitation measures after esophagectomy. Analysis of the current literature clearly concludes a paradigm shift emphasizing the high value of preconditioning and promoting a culture of prehabilitation for the surgical cancer patient (6). Multimodal prehabilitation has impressively been shown to improve patients' functional capacities in the long run (7). Preliminary findings indicate that a group of interventions, such as physical exercise, nutrition and anxiety reduction/coping in the preoperative period can improve functional restoration and complement the enhanced recovery program as facilitating the return to baseline activities of daily living (6). However, it is not clear at this stage, whether the preoperative increase in functional capacity mitigates the burden of postoperative morbidities and subsequent cancer therapies (6).

Oncologic esophagectomy for cancer is a demanding and sophisticated two-hole (abdomino-thoracic) procedure accompanied by significant surgical trauma, thus relevantly interfering with patients' physiologic state and physical integrity. Initially reduced physical well-being, due to

malnutrition caused by dysphagia (8), or even due to sarcopenia (9) at first presentation may further compromise clinical outcome. Additionally, neoadjuvant therapy alone or in combination with (radio-) chemotherapy at the time of surgery may each for itself decrease the cardiorespiratory and muscular reserves (10) and deteriorate the postoperative course, with the possibility that in some patients the harms of neoadjuvant therapy may outweigh its benefits (11).

Esophagectomy entails the risk of relevant morbidity and mortality (12). Perioperative complications influence short- and long-term outcomes after esophagectomy. Patients undergoing surgery for esophageal cancer have a high risk for postoperative deterioration of lung function and consequently for pulmonary complications. This is partly due to one-lung ventilation during thoracotomy/thoracoscopy. It often accounts for prolonged stay on the intensive care unit, delayed postoperative reconvalescence, and reduced quality of life. Potential surgical complications in the postoperative phase contain—on top of medical and general events, such as the above mentioned pulmonary, as well as cardiovascular, thromboembolic and infectious events—the risk of anastomotic leak, tracheobronchial fistula, arrosion bleeding, conduit necrosis, chyle leak, vocal cord injury/palsy, which can be life-threatening (12,13). If severe post-esophagectomy complications occur and patients survive, they might exert a persisting negative effect on HRQOL in the long run (14). Specific restrictions and aspects of quality of life do even deteriorate throughout the follow-up in patients with major postoperative complications, as compared to patients without major complications (14). With regard to surgical factors associated with HRQOL outcomes after esophagectomy for cancer, Rutegård *et al.* in a population-based study clearly showed, that there is no evidence to suggest that less extensive surgery for esophageal cancer should be recommended from the perspective of HRQOL (15). Thus, extensive surgery, as indicated by a transthoracic approach, more extensive lymphadenectomy, wider resection margins and a longer duration of surgery, was not associated with worse HRQOL measures than less extensive operations, and dysphagia was similar in patients who had handsewn and stapled anastomoses (15). However, technical surgical complications had significant deleterious effects on several aspects of HRQOL (15). In analogy to the study of Gannon *et al.* (1), HRQOL items were assessed 6 months after esophagectomy (15). Interestingly, the same study group reported, that HRQOL in long-term survivors after esophagectomy does not improve between 6 months and 3 years after surgery, and is worse than in a comparable age- and sex-adjusted reference population (16). Much longer intervals after esophagectomy for cancer, in turn, seem to improve and restore quality of life and functioning scores significantly, as shown by own data, assessing quality of life, as well as secondary cancers/diseases and esophagectomy-related, or unrelated interventions in the long-term course of surgery (17). Patients defined as long-term survivors (≥5 years after esophagectomy) displayed a good quality of life alongside with physical, emotional and cognitive functioning (17). The esophagus-specific quality of life (EORTC QLQ-OES 18) revealed a median value (scale, 0–100) of 0 each for dysphagia and difficulties with swallowing saliva, whilst reflux was a major problem with a score of 50.0 (17).

The challenge in esophageal surgery, thus, consists of preoperatively elevating functional reserves and capacities to levels above baseline, as they are known to decline below baseline immediately after the operation. Using this measure of prehabilitation, functional recovery in the postoperative course is then much faster and on a higher level as compared to standard care (6). Physical preconditioning has become a crucial leverage to optimize fitness and lung function in patients scheduled for esophagectomy, in particular during the time period of neoadjuvant therapy, which should be utilized meaningfully for each patient, dependent on initial and developing individual capacities. Data derived from thoracic surgery strongly indicate, that preoperative exercise training (PET) in moderate to intense modalities exerts positive effects on aerobic capacity, physical fitness and quality of life (18). A reduction of postoperative complications and length of hospital stay was evident, whereas specific programs and intensities of training, especially the respiratory exercises, as well as outcome parameters were heterogeneous in the systematic review by Pouwels *et al.* (18). However, it was not stated, if smoking cessation was obligatory and successful in all studies (18). The feasibility and effectiveness even of a home-based exercise training program (HBETP) before lung resection surgery (LRS) has been demonstrated by Coats *et al.* in patients with lung cancer awaiting LRS (19). HBETP improved both exercise tolerance and muscle strength. The authors pointed out the clinical relevance, as poor exercise capacity and muscle weakness are known predictors of postoperative complications (19). Even patients with only low experience of physical activity and poor baseline walking capacity are most likely to improve their functional status preoperatively within a multimodal prehabilitation concept (20). Benefits have even been demonstrated for

"medium-risk" surgery, as colorectal resections, where even short-term programs (e.g., preoperative exercise for 4 weeks) with minimum effort [e.g., 6-minute walk distance (6MWD)] significantly increased the amount of moderate- and vigorous-intensity physical activities performed and where patients with prehabilitation also demonstrated a greater improvement in 6-minute walk test (6MWT) compared to controls (21). As patients undergoing 6MWD before colorectal surgery—in spite of greater improvement in walking capacity throughout the whole perioperative period, when compared to rehabilitation started after surgery—displayed no significant differences with respect to complications and the duration of hospital stay (7), such programs may be more clinically meaningful and cost-effective, if targeted to specific subgroups with high perioperative risks, such as patients undergoing esophagectomy.

However, structured supervision, monitoring and follow-up, ideally by a professional sport's therapist, patients' security, adherence and compliance are the main pillars of sustained and long-term success performing prehabilitation. Indisputable in the context of preconditioning prior to esophagectomy is the positive effect of inspiratory muscle training to prevent postoperative pulmonary complications (PPC), especially with the use of high-intensity inspiratory exercise, being significantly more effective than endurance training (22), and to improve respiratory function (23).

The ongoing PREPARE study (preoperative inspiratory muscle training to prevent postoperative pulmonary complications in patients undergoing esophageal resection) by Valkenet *et al.* (trial registration: NCT01893008) is the first multicenter randomized controlled trial to evaluate the hypothesis that preoperative inspiratory muscle training leads to decreased pulmonary complications in patients undergoing esophageal resection (24). Patients have to complete 30 dynamic inspiratory efforts twice daily for 7 days a week until surgery with a minimum of 2 weeks. Main study endpoint is the incidence of postoperative pneumonia. Secondary objectives are to evaluate the effect of preoperative inspiratory muscle training on length of hospital stay, duration of mechanical ventilation, incidence of other postoperative (pulmonary) complications, quality of life, and on postoperative respiratory muscle function and lung function (24). However, intervention in this study does not start before the recovery period after (radio-) chemotherapy, potentially losing a valuable time interval, and it focuses on inspiratory exercise only. Follow-up measurements, e.g., of lung function, will end before hospital discharge and long-term data are not intended in the current study protocol (24).

Thus, we initiated the iPEP-study (internet-based Perioperative Exercise Program) (trial registration: NCT02478996), a prospective multicenter randomized-controlled trial. The objective is to evaluate the impact of an internet-based exercise program on postoperative respiratory parameters and pneumonia rates in patients with Barrett's carcinoma scheduled for esophagectomy (25). Training consists of a combination of endurance, strength and intensive respiratory exercise. During the whole neoadjuvant therapy and recovery, patients in the intervention group receive an individually designed intensive exercise program based on functional measurements at baseline. Personal feedback of the supervisor with customized training programs is provided in weekly intervals. Primary endpoint is the change in peak oxygen uptake (VO_{2peak}), secondary endpoints are the changes in forced expiratory volume in 1 second (FEV_1) and in forced vital capacity (FVC) directly prior to surgery and at 12 weeks after surgery. Tertiary endpoints are pneumonia, surgical complications, length of postoperative stay, quality of life, and social support of disease coping (25). This study will evaluate, if an intensive individually adapted training program via online supervision during neoadjuvant therapy will improve cardiorespiratory fitness and reduce pulmonary complications following esophagectomy for cancer.

The above discussed programs and current studies will contribute to optimizing outcomes following esophagectomy for cancer and to counteracting postoperative reduced fitness, physical functioning and quality of life. Further research including large patient cohorts are warranted, in order to more comprehensively understand the ideal timing, intensity, duration, modalities and respective dynamics of perioperative prehabilitation and rehabilitation. In addition, detailed analyses of the simultaneous application of neoadjuvant (radio-) chemotherapy and physical exercise programs with regard to patients' immune function and tumor behavior will provide more insights into the wide range from possibilities of improvement to potential threats of tumor spread. Physical, psychological and social integrity after esophagectomy correlate with quality of live dimensions and, thus, sustainable good functional outcomes should be the highest goal of esophageal cancer treatment in addition to high-quality

oncologic results with favorable long-term prognosis.

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Footnote

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