

# NUTRITIONAL STATUS AND FITNESS IN NEOADJUVANT CHEMORADIATION FOR OESOPHAGOGASTRIC CANCER

**Bernhard Riedel,<sup>1</sup> Hilmy Ismail,<sup>1</sup> Merran Findlay<sup>2</sup> and Rachelle Ryan<sup>2</sup>**

1. Department of Anaesthetics and Pain Management, Peter MacCallum Cancer Centre, University of Melbourne, Victoria.

2. Department of Nutrition and Dietetics, Royal Prince Alfred Hospital, New South Wales.

Email: Bernhard.Riedel@petermac.org

## Abstract

Resectable oesophagogastric cancer typically requires neoadjuvant chemoradiation therapy followed by surgical resection of the primary tumour. Consideration for surgery is on the basis of the risk–benefit profile of the expected surgical and cancer survival outcomes. Major surgery such as oesophagectomy is associated with a high incidence of postoperative complications, which in turn impacts long-term survival and healthcare expenditure. A clear need exists for an objective and reliable preoperative risk assessment and perioperative optimisation strategies to improve surgical outcomes. We discuss two key preoperative risk factors – nutritional status and fitness (physiologic capacity) – that may be optimised to improve the surgical outcome in this cancer population.

Resectable oesophagogastric cancer typically requires preoperative chemotherapy or chemoradiotherapy followed by surgical resection of the primary tumour four to eight weeks later. Consideration for surgery is based on the risk-benefit profile of the expected surgical and cancer survival outcomes. The greatest surgical risk is associated with major intra-abdominal and thoracic procedures, with an estimated 10-40% of the patients experiencing major postoperative complications after major abdominal surgery.<sup>1</sup> This impacts long-term survival and healthcare expenditure. A United States Department of Veterans Affairs study reported that postoperative complications independently reduced the 30-day and long-term survival by 69% and increased cost five-fold.<sup>2</sup> A clear need exists for an objective and reliable preoperative risk assessment and optimisation strategies. This paper discusses two important risk factors: nutritional status and fitness (physiologic capacity) that may be optimised to improve the surgical outcome in this cancer population.

The prevalence of malnutrition in patients with cancer varies according to the tumour type but is generally reported to be as high as 20-80%.<sup>3</sup> It has a negative impact on immunocompetence, treatment tolerance and wound healing, and as such is associated with increased adverse clinical outcomes, hospital length of stay and healthcare costs.<sup>4</sup> Patients with tumours of the upper gastrointestinal tract are at particularly high risk and are frequently malnourished on presentation.<sup>5</sup> Poor baseline diet, obesity and high alcohol intake are known nutritional risk factors for developing cancers of the gastrointestinal tract.<sup>6</sup>

Nutritional status can be further significantly compromised due to the dysphagia arising from mechanical obstruction, metabolic sequelae of the disease burden itself and severe nutrition-impact symptoms associated with multi-modal treatment regimens such as neoadjuvant chemoradiotherapy. Likewise, physical conditioning (fitness) correlates with physiological capacity and is associated with improved longevity in both the surgical

and non-surgical populations.<sup>7-10</sup> Lifestyle behaviours (dietary intake and physical activity), co-morbid conditions, disease state and associated multi-modal treatment regimens (eg. neoadjuvant chemoradiotherapy) can significantly impair the functional capacity (deconditioning) and have a negative physiological impact, leading to an inability to meet the metabolic demands of surgical stress.

Increasing evidence supports the role of a screening tool that identifies patients at high risk of nutritional and functional deficits who may benefit from interventional strategies for optimisation. For example, nutritional intervention may improve the recovery of functional capacity after radiotherapy,<sup>11</sup> and improve postoperative outcome after surgery,<sup>12,13</sup> while acute exercise therapy may also improve surgical outcome.<sup>14-16</sup>

## Nutritional status: malnutrition screening and nutrition assessment

Malnutrition screening is a simple process used to identify patients at nutritional risk who require a more detailed nutrition assessment and is considered an important adjunct in modern surgical care. Current dietetic best practice guidelines recommend that all oncology patients be screened for malnutrition and that nutrition assessment is performed on high risk patients using tools validated in the oncology population.<sup>4,11,17</sup> One such tool is the Malnutrition Screening Tool that can be easily implemented to identify patients at nutritional risk.<sup>18</sup> Subsequent detailed assessment of nutritional status is important because malnutrition is not always obvious in this patient group; for example, an obese patient may have severely depleted lean-tissue stores and poor micronutrient status. It has become more widely appreciated that in isolation, proxy measures or biochemical indices are inadequate to accurately determine nutritional status.<sup>19</sup> A more comprehensive approach, including the scored Patient-Generated Subjective Global Assessment<sup>20</sup> or Subjective Global Assessment,<sup>21</sup> both validated for oncology patient populations, is recommended

by the current guidelines. These tools are used to categorise nutritional status as either well-nourished (Subjective Global Assessment A), moderate or suspected malnutrition (Subjective Global Assessment B), or severely malnourished (Subjective Global Assessment C). Importantly, nutritional status should be differentiated from nutritional risk, as even individuals who are assessed as well-nourished at diagnosis are at high risk of decline in nutritional status during the course of treatment.

### **Fitness: screening and physiologic capacity assessment**

Consensus is lacking as to the credibility of the traditional static (performed at rest) preoperative diagnostic pulmonary or cardiac function tests as risk predictors in patients undergoing major abdominal surgery. Dynamic testing to assess functional capacity is increasingly recognised as an important adjunct in modern surgical care. Cardiopulmonary exercise testing (CPET) is a dynamic test and provides the gold standard for evaluating an individual's functional/physiologic capacity (fitness level).<sup>22</sup> CPET-derived respiratory gas exchange analysis provides a uniquely individual and objective phenotypic assessment of the metabolic response to the stress of exercise by evaluating the coupling, by the cardiovascular system, of pulmonary respiration to the end-organ cellular (mitochondrial) respiration.<sup>22</sup> Whether a patient is deconditioned due to behavioural choice, organ disease, or associated therapy eg. chemoradiotherapy, such a reduction in physiologic capacity is increasingly recognised to represent the inability to physiologically meet the metabolic demands of perioperative stress with increased risk of postoperative morbidity and mortality.<sup>23-30</sup>

### **Physiologic capacity and preoperative risk stratification**

A number of CPET-derived variables allow the objective grading of physiologic dysfunction.<sup>23,31</sup> Of these, anaerobic threshold (AT) and peak oxygen uptake have been studied as markers of physiologic capacity and as risk predictors for adverse postoperative outcomes, and are used to guide perioperative decision-making. Such decision-making includes determining suitability and timing for major surgeries, postponement of surgery for optimisation strategies, and for triage of the postoperative destination e.g. postoperative care in the ICU, for high-risk patients.

Investigators identified risk prediction value in CPET-derived anaerobic threshold, with an AT value less than 11 mL/min/kg as a critical level of physiologic capacity that predisposed elderly patients undergoing major abdominal surgeries to be at an increased risk for postoperative cardiac mortality.<sup>24,25</sup> Patients with an AT less than 11 mL/kg/min had an 18% in-hospital cardiac mortality rate, whereas patients with a higher AT value had 0.8% mortality rate. The value of AT as an objective assessment of physiologic capacity in improved risk prediction of adverse surgical outcomes has been confirmed by additional studies: Snowden et al reported that AT values  $\leq 10$  mL/kg/min were associated with increased postoperative complications and length of hospital stay;<sup>26</sup> Smith et al confirmed that peak oxygen uptake and possibly AT, were valid predictors of postoperative morbidity and

mortality after thoraco-abdominal surgery;<sup>27</sup> and Hightower et al reported an improved risk prediction using a composite measure of heart rate variability and AT (area under curve = 0.826, sensitivity = 81%, and specificity = 69%,  $p = 0.023$ ) for adverse surgical outcome after major abdominal cancer surgeries.<sup>28</sup> More specific to patients requiring oesophagectomy, investigators reported the usefulness of CPET-derived peak oxygen uptake as a predictor of postoperative morbidity,<sup>29</sup> including cardiorespiratory complications.<sup>30</sup>

These data strongly suggest the following: (1) Cancer patients can complete a maximal effort, symptom-limited cardiopulmonary exercise test prior to undergoing major cancer surgery; and (2) preoperative parameters of physiologic capacity (AT, peak oxygen uptake and heart rate parameters during exercise) associate with postoperative complications.

### **Declining physiologic capacity after neoadjuvant chemoradiotherapy**

For oesophagogastric cancer patients having neoadjuvant chemoradiotherapy, a finite window of time exists wherein surgery should be performed so that physiologic recovery from neoadjuvant chemoradiotherapy occurs without the unfavourable radiation-induced tissue changes seen if surgery is performed too early or too late. The timing of the surgery is largely empirical and not based on an objective assessment of recovery of physical function after neoadjuvant chemoradiotherapy. Accurate determination of the time to return to optimal baseline fitness would potentially have a major impact on the timing of surgery, postoperative outcome and timing of adjuvant chemoradiotherapy. This could have potentially wider implications for any cancer surgery that follow neoadjuvant chemoradiotherapy. The ability to utilise CPET to objectively evaluate recovery and interventional strategies (eg. nutrition) to expedite recovery such that physiologic function after neoadjuvant chemoradiotherapy is optimal would ensure that definitive cancer resection occurs within the most optimal timeframe.

Preliminary data demonstrate that physiologic capacity may deteriorate by as much as 20-30% following neoadjuvant chemoradiotherapy.<sup>32,33</sup> Given the increased risk of adverse postoperative outcome with poor physiologic capacity (eg. AT < 11 mL/kg/min), such a decline in physiologic capacity after neoadjuvant chemoradiotherapy suggests that the previously "fit" patients may now fall below this threshold and potentially are at an increased risk of adverse postoperative outcomes. Presently, the ability to credibly identify adequate recovery from deconditioning that follows neoadjuvant chemoradiotherapy is lacking, and further studies are needed to determine if patients would benefit from postponement of surgery until they have recovered such that they are above the threshold of physiologic capacity. Whether such a waiting period would adversely impact long-term cancer outcomes and whether acute preoperative optimisation (eg. nutritional or exercise intervention) will accelerate recovery such that patients cross this threshold and thereby show lower postoperative risk is unknown.

## Nutrition intervention – the evidence

There is a paucity of high-quality nutrition intervention studies specific to the upper gastrointestinal cancer population having neoadjuvant chemoradiotherapy. A prospective randomised control trial in 60 patients with gastrointestinal or head and neck cancers undergoing radiation therapy, demonstrated the benefits of early and intensive nutritional intervention in minimising weight loss and deterioration in nutritional status, with improved measures of physical function and global quality of life.<sup>34</sup> A study of 24 patients who underwent definitive chemoradiotherapy for oesophageal cancer and received nutrition intervention, demonstrated improved weight maintenance and treatment tolerance, reduced unplanned hospital admissions and better radiation-dose completion rates than historical controls.<sup>35</sup>

The timeframe between completing neoadjuvant chemoradiotherapy and undergoing surgery is a period when patients are at a significant risk of rapid nutritional decline. The inflammatory state, as well as the marked nutrition-impact symptoms, related to the accumulated acute toxicities of chemoradiotherapy, predisposes patients to severe catabolism, which is of particular clinical significance in the perioperative period. Preoperative malnutrition and weight loss is associated with an increased risk of complications following major abdominal surgeries.<sup>36,37</sup> Postoperative complications may consist of delayed wound healing, increased infection risk, wound dehiscence and development of fistulae.

### Nutrition support options

Early identification and management of patients demonstrating a compromised nutritional status is paramount for patients undergoing major upper gastrointestinal cancer surgeries. In recent years, there has been an increasing body of evidence suggesting that perioperative nutrition support improves the clinical outcomes for these patients. The European Society of Parenteral and Enteral Nutrition guidelines on enteral nutrition in surgery recommend nutritional support in patients with severe nutritional risk for 10-14 days prior to major surgery, even if surgery has to be delayed.<sup>38</sup> These guidelines define severe nutritional risk using parameters that are associated with increased complications: weight loss of more than 10-15% in the six months prior to surgery; body mass index of less than 18.5 kg/m<sup>2</sup>; and Subjective Global Assessment score C (severely malnourished). Similarly, the United Kingdom's National Institute for Clinical Excellence commissioned guidance document on nutrition support recommends preoperative enteral tube feeding in those patients scheduled for major abdominal procedures who are identified as malnourished and are unable to meet their nutritional requirements orally. The appropriate method of nutrition support may change according to where the patient is on the care pathway and is best determined on an individualised basis by a specialist dietitian in consultation with the patient, family and treating team. These options usually include food fortification, oral nutrition support with specialised medical nutrition therapy formula and/or initiating supplementary tube feeding when appropriate. Total parenteral nutrition is indicated only in rare cases.

Patients undergoing neoadjuvant chemoradiotherapy raise particular issues regarding supplemental tube feeding. In definitive chemoradiotherapy, the option of prophylactic gastrostomy placement in suitable patients allows the provision of supplemental enteral nutrition to be titrated according to the level of oral intake achieved as the patient progresses throughout treatment. In the case of neoadjuvant chemoradiotherapy, this option may not be compatible with the surgical plan due to the alteration in the gastric anatomy. In these circumstances, consideration should be given to alternative supplemental tube feeding methods eg. removable naso-enteric feeding tube or surgical jejunostomy. Compared to relying on oral intake alone, this will improve both preoperative and postoperative nutritional status of the patient.<sup>39-41</sup>

### Immunonutrition

More recently the benefits of oral and enteral nutritional formulae enriched with conditionally essential amino acids (arginine and/or glutamine), omega-3 fatty acids and ribonucleic acids have been investigated. These substrates are proposed to play a role in modulating the immune system, leading to improved clinical outcomes such as reduced rate of infection, wound complications and duration of hospital stay.

The impact of immunonutrition on postoperative morbidity and mortality has been evaluated in numerous studies with varying and sometimes contradictory results. Earlier meta-analyses of randomised control trials suggested that perioperative immunonutrition, used for patients undergoing major abdominal surgeries, significantly reduced postoperative hospital acquired infections, length of stay,<sup>42,43</sup> and wound healing.<sup>44</sup> The use of immunonutrition for all high-risk patients undergoing major abdominal surgeries was subsequently recommended. A more recent meta-analysis acknowledges that interpretation of these earlier reviews was confounded by factors such as variation in patient populations, diverse control groups and the differences in nutritional formulae and their administration protocols.<sup>45</sup> This meta-analysis was undertaken to specifically target the gastrointestinal surgical population and concluded, on the basis of data from 2730 patients, that the use of perioperative enteral immunonutrition decreases morbidity and length of hospital stay, but not mortality, in patients undergoing major gastrointestinal surgeries, and recommended its routine use. Of the 21 studies included, only 12 were considered to be of high quality, however, the beneficial effects remained with the exclusion of low-quality studies. The use of preoperative enteral nutrition, preferably with immune-modulating substrates, in patients undergoing major abdominal cancer surgeries, including oesophagectomy and gastrectomy, is likewise supported by the European Society of Parenteral and Enteral Nutrition guidelines on enteral nutrition.<sup>38</sup>

International disease management guidelines for oesophageal and gastric cancer recommend nutritional support for both radical and palliative management. Therefore, it is essential to ensure that patients have ready access to appropriate dietary advice.<sup>46</sup> The Australian best practice nutritional management guidelines

recommend early screening and referral to and monitoring by a dietitian for patients undergoing gastrointestinal chemoradiotherapy.<sup>11</sup>

### Exercise capacity intervention – the evidence

Feeney et al showed that patients who developed postoperative pulmonary complications following oesophagectomy engaged in less physical activity in the pre-operative period.<sup>47</sup> This suggests that there is a potential for pre-surgical exercise training to improve cardiorespiratory fitness and to potentially improve postsurgical recovery. Mechanisms whereby exercise training may yield benefit as an effective therapy include improved endothelial function and reduced inflammatory status – factors central to postoperative morbidity.<sup>48</sup>

Although exercise regimens may be logistically harder to administer, studies have shown improved functional capacity associates with improved surgical outcomes. In patients who attended more than 80% of the prescribed exercise sessions, the training increased preoperative peak oxygen uptake by 3.3mL/kg/min.<sup>49</sup> Similarly, in a small randomised study of 30 patients awaiting abdominal aortic surgery, AT increased by 2ml/kg/min after intervention with a six week, bi-weekly, 30 min aerobic exercise program.<sup>12</sup> Greatest increase in AT can be expected in patients with poor baseline AT.<sup>13</sup> In a prospective randomised trial, Arthur et al demonstrated that a CPET-based exercise intervention eight weeks prior to cardiac surgery resulted in significant reductions in postoperative intensive care unit and hospital length of stay.<sup>14</sup> In a meta-analysis of 12 studies, preoperative exercise therapy consisting of inspiratory muscle training or exercise training, reduced hospital length of stay and complication rates in patients undergoing cardiac or abdominal surgery, but not in patients undergoing joint replacement surgery.<sup>15</sup> Specific to the cancer surgery population, a pilot study of an individually designed preoperative therapeutic exercise program in patients awaiting elective abdominal/thoracic surgery showed 84% attendance of sessions, with significant increase in cardiorespiratory fitness and muscle strength despite a relatively short period (five weeks) of training.<sup>16</sup>

It is likely that home-based programs of moderate exercise may be safe, readily administered (eg. using the Borg scale 12-14; or keeping heart rate to that below AT) and that patients will be readily motivated to exercise when they understand it may reduce their perioperative risk. As such, larger studies are required to evaluate if preoperative (prehabilitation) with exercise therapy is a logistically feasible and cost-effective strategy to reduce postoperative morbidity and mortality.

### Summary

The link connecting poor nutritional status and poor functional capacity with adverse surgical outcome and a reduction in quality of life is well recognised for the surgical population. Adequate assessment of nutritional status and physiological capacity (fitness) with appropriate interventional strategies could modify this relationship. The

use of CPET as an adjunct to assessment before high-risk surgery is gaining increasing acceptance. Importantly, data indicates the greatest improvement in physical function occurs when nutrition intervention and exercise therapy are combined than through either intervention alone.<sup>50</sup> This may be equally applicable to the surgical population albeit more challenging. As such multidisciplinary care in surgical oncology should include specialist anaesthesia and dietetic services to promote the assessment of functional capacity and nutritional status. Implementation of interventional strategies during neoadjuvant therapy and during the perioperative period should be considered to ensure optimal postoperative outcomes for this patient population.

### References

1. Arozullah AM, Daley J, Henderson WG, Khuri SF. Multifactorial risk index for predicting postoperative respiratory failure in men after major noncardiac surgery. The National Veterans Administration Surgical Quality Improvement Program. *Ann Surg.* 2000 Aug; 232(2):242-53.
2. Khuri SF, Henderson WG, DePalma RG, Mosca C, Healey NA, Kumbhani DJ, et al. Determinants of long-term survival after major surgery and the adverse effect of postoperative complications. *Ann Surg.* 2005 Sep;242(3):326-41.
3. Kubrak C, Jensen L. Critical evaluation of nutrition screening tools recommended for oncology patients. *Cancer Nurs.* 2007 Sep-Oct;30(5):E1-6.
4. Watterson C, Fraser A, Banks M, Isenring E, Miller M, Silvester C, et al. Evidence based practice guidelines for the nutritional management of malnutrition in adult patients across the continuum of care. *Nutrition and Dietetics.* 2009;66:1-34.
5. Garth AK, Newsome CM, Simmance N, Crowe TC. Nutritional status, nutrition practices and post-operative complications in patients with gastrointestinal cancer. *J Hum Nutr Diet.* 2010 Aug;23(4):393-401.
6. World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity And The Prevention Of Cancer: A Global Perspective.* Washington, DC: AICR, 2007.
7. Goffaux J, Friesinger GC, Lambert W, Shroyer LW, Moritz TE, McCarthy M Jr, et al. Biological age – a concept whose time has come: a preliminary study. *South Med J.* 2005 Oct;98(10):985-93.
8. Gulati M, Pandey DK, Arnsdorf MF, Lauderdale DS, Thisted RA, Wicklund RH, et al. Exercise capacity and the risk of death in women: the St James Women Take Heart Project. *Circulation.* 2003 Sept 30;108(13):1554-9.
9. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. *N Engl J Med.* 2002 Mar 14;346(11):793-801.
10. Carlisle J, Swart M. Mid-term survival after abdominal aortic aneurysm surgery predicted by cardiopulmonary exercise testing. *Br J Surg.* 2007 Aug;94(9):966-9.
11. Isenring E, Hill J, Davidson W, Brown T, Baumgartner L, Kaegi K, et al. Evidence based practice guidelines for the nutritional management of patients receiving radiation therapy. *Nutrition and Dietetics.* 2008;65:S1-S20.
12. Kothman E, Batterham AM, Owen SJ, Turley AJ, Cheesman M, Parry A, et al. Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms: a pilot study. *Br J Anaesth.* 2009 Oct;103(4):505-10.
13. Honnesh S, Goosen L, Adams N, Forni L, Lavies N, Venn R. Effect of short-term exercise training on aerobic fitness in patients with abdominal aortic aneurysms. *Br J Anaesth.* 2010 Feb;104(2):265-6.
14. Arthur HM, Daniels C, McKelvie R, Hirsh J, Rush B. Effect of a preoperative intervention on preoperative and postoperative outcomes in low-risk patients awaiting elective coronary artery bypass graft surgery. A randomized, controlled trial. *Ann Intern Med.* 2000 Aug 15;133(4):253-62.
15. Valkenet K, van de Port IG, Dronkers JJ, de Vries WR, Lindeman E, Backx FJ. The effects of preoperative exercise therapy on postoperative outcome: a systematic review. *Clin Rehabil.* 2011 Feb; 25(2):99-111.
16. Timmerman H, de Groot JF, Hulzebos HJ, de Knikker R, Kerckamp HE, van Meeteren NL. Feasibility and preliminary effectiveness of preoperative therapeutic exercise in patients with cancer: a pragmatic study. *Physiother Theory Pract.* 2011 Feb;27(2):117-24.
17. Bauer JD, Ash S, Davidson WL, Hill JM, Brown T, Isenring EA, et al. Evidence based practice guidelines for the nutritional management of cancer cachexia. *Nutrition and Dietetics.* 2006; 63: S3-S32.
18. Ferguson M, Capra S, Bauer J, Banks M. Development of a valid and reliable malnutrition screening tool for adult acute hospital patients. *Nutrition.* 1999;15:458-464.
19. Marshall WJ. Nutritional assessment; its role in the provision of nutritional support. *J Clin Pathol.* 2008 Oct;61(10):1083-8.
20. Ottery FD. Patient generated-subjective global assessment. In: McCallum PD, Polisena CG, ed. *The clinical guide to oncology nutrition.* Chicago: The

- American Dietetic Association. 2011;11-23.
21. Detsky AS, McLaughlin JR, Baker JP, Johnston N, Whittaker S, Mendelson RA, et al. What is subjective global assessment of nutritional status? *JPEN J Parenter Enteral Nutr.* 1987 Jan-Feb;11(1):8-13.
  22. Wasserman K, Hansen JE, Sue DY, Stringer WW, Whipp BJ. Principles of Exercise Testing and Interpretation; Including Pathophysiology and Clinical Applications. 4 ed. 2005, Philadelphia: Lippincott Williams & Wilkins.
  23. Older P, Smith R, Courtney P, Hone R. Preoperative evaluation of cardiac failure and ischemia in elderly patients by cardiopulmonary exercise testing. *Chest.* 1993 Sep;104(3):701-4
  24. Older P, Hall A, Hader R. Cardiopulmonary exercise testing as a screening test for perioperative management of major surgery in the elderly. *Chest.* 1999 Aug;116(2):355-62.
  25. Older P, Hall A. Clinical review: how to identify high-risk surgical patients. *Crit Care.* 2004 Oct;8(5):369-72.
  26. Snowden CP, Prentis JM, Anderson HL, Roberts DR, Randles D, Renton M, et al. Submaximal cardiopulmonary exercise testing predicts complications and hospital length of stay in patients undergoing major elective surgery. *Ann Surg.* 2010 Mar;251(3):535-41.
  27. Smith TB, Stonell C, Purkayastha S, Paraskevas P. Cardiopulmonary exercise testing as a risk assessment method in non cardio-pulmonary surgery: a systematic review. *Anaesthesia.* 2009 Aug; 64(8): 883-93.
  28. Hightower CE, Riedel BJ, Feig BW, Morris GS, Jnr Ensor JE, Woodruff VD, et al. A pilot study evaluating predictors of postoperative outcomes after major abdominal surgery: Physiological capacity compared with the ASA physical status classification system. *Br J Anaesth.* 2010 Apr;104(4):465-71.
  29. Nagamatsu Y, Shima I, Yamana H, Fujita H, Shirouzu K, Ishitake T. Preoperative evaluation of cardiopulmonary reserve with the use of expired gas analysis during exercise testing in patients with squamous cell carcinoma of the thoracic esophagus. *J Thorac Cardiovasc Surg.* 2001 Jun;121(6):1064-8.
  30. Forshaw MJ, Strauss DC, Davies AR, Wilson D, Lams B, Pearce A, et al. Is cardiopulmonary exercise testing a useful test before esophagectomy. *Ann Thorac Surg.* 2008 Jan;85(1):294-9.
  31. Guazzi M, Myers J, Arena R. Cardiopulmonary exercise testing in the clinical and prognostic assessment of diastolic heart failure. *J Am Coll Cardiol.* 2005 Nov 15;46(10):1883-90.
  32. Dang A, Grosshans D, Schier R, Aguilar J, Hofstetter W, Mehran R, et al. Quantifying the Physiologic Effects of Neoadjuvant Chemoradiation on Patients with Carcinoma of the Esophagus by Integrative Cardiopulmonary Exercise Testing (CPET). Presented at The American Radium Annual Meeting, Amsterdam, Holland, 2007.
  33. Hofstetter WL, Hightower CE, Morris GS, Sun XG, Riedel BJ, Mehran RJ et al. Changes in cardiopulmonary reserves associated with neoadjuvant therapy in patients with esophageal cancer. Presented at The American Society of Clinical Oncology Annual Meeting, 2009.
  34. Isenring EA, Capra S, Bauer JD. Nutrition intervention is beneficial in oncology outpatients receiving radiotherapy to the gastrointestinal or head and neck area. *Br J Cancer.* 2004 Aug 2;91(3):447-52.
  35. Odelli C, Burgess D, Bateman L, Hughes A, Ackland S, Gillies J, et al. Nutrition support improves patient outcomes, treatment tolerance and admission characteristics in oesophageal cancer. *Clin Oncol (R Coll Radiol).* 2005 Dec;17(8):639-45.
  36. Sungurtekin H, Sungurtekin U, Balci C, Zencir, M, Erdem E. The influence of nutritional status on complications after major intraabdominal surgery. *J Am Coll Nutr.* 2004 Jun;23(3): 227-32.
  37. Bozetti F, Gianotti L, Braga, Di Carlo V, Mariani L. Postoperative complications in gastrointestinal cancer patients: the joint role of nutritional status and nutritional support. *Clin Nutr.* 2007 Dec;26(6):698-709.
  38. Weimann A, Braga M, Harsanyi L, Laviano A, Ljungqvist O, Soeters P, et al. European Society of Parenteral and Enteral Nutrition (ESPEN) Guidelines on Enteral Nutrition: Surgery including organ transplantation. *Clin Nutr.* 2006 Apr;25(2):224-44.
  39. Jenkinson AD, Lim J, Agrawal N, Menzies D. Laparoscopic feeding jejunostomy in esophagogastric cancer. *Surg Endosc.* 2007 Feb;21(2):299-302.
  40. Daly JM, Weintraub FN, Shou J, Rosato EF, Lucia M. Enteral nutrition during multimodality therapy in upper gastrointestinal cancer patients. *Ann Surg.* 1995 Apr;221(4):327-38.
  41. Martin L, Lagergren J, Jia C, Lindblad M, Rouvelas I, Viklund, P. The influence of needle catheter jejunostomy on weight development after oesophageal cancer surgery in a population-based study. *Eur J Surg Oncol.* 2007 Aug;33(6):713-7.
  42. Waitzberg D, Hideaki S, Plank L, Jamieson G, Jagannath P, Hwang T, et al. Postsurgical infections are reduced with specialized nutrition support. *World J Surg.* 2006 Aug;30(8):1592-604.
  43. Zheng Y, Li F, Qi B, Luo B, Sun H, Liu S, et al. Application of perioperative immunonutrition for gastrointestinal surgery: a meta-analysis of randomized controlled trials. *Asia Pac J Clin Nutr.* 2007;16 Suppl 1:253-7.
  44. Marik P, Zaloga G. Immunonutrition in high risk surgical patients: a systematic review and analysis of the literature. *JPEN J Parenter Enteral Nutr.* 2010 Jul-Aug;34(4):378-86.
  45. Cerantola M, Hubner F, Grass F, Demartines N, Schafer M. Immunonutrition in gastrointestinal surgery. *Br J Surg.* 2011 Jan;98(1):37-48.
  46. Allum WH, Griffin SM, Watson A, Colin-Jones D. Guidelines for the management of oesophageal and gastric cancer. *Gut.* 2002 Jun;50 Suppl 5:v1-23.
  47. Feeney C, Reynolds JV, Hussey J. Preoperative physical activity levels and postoperative pulmonary complications post-esophagectomy." *Dis Esophagus.* 2011 Sep;24(7):489-94.
  48. Ribeiro F, Alves AJ, Duarte JA, Oliveira J. Is exercise training an effective therapy targeting endothelial dysfunction and vascular wall inflammation? *Int J Cardiol.* 2010 Jun 11;141(3):214-21.
  49. Jones LW, Peddle CJ, Eves ND, Haykowsky MJ, Courneya KS, Mackey JR, et al. Effects of presurgical exercise training on cardiorespiratory fitness among patients undergoing thoracic surgery for malignant lung lesions. *Cancer.* 2007 Aug 1;110(3):590-8.
  50. Villareal DT, Chode S, Parimi N, Sinacore DR, Hilton T, Armamento-Villareal R, et al. Weight loss, exercise, or both and physical function in obese older adults. *N Engl J Med.* 2011 Mar 31;364(13):1218-29.