

PREHABILITATION IN CANCER SURGERY: READY FOR PRIME TIME?

PRÉ-HABILITAÇÃO EM CIRURGIA ONCOLÓGICA: PREPARADOS PARA COMEÇAR?

 MARÍLIA CRAVO

Hospital da Luz Lisboa
Faculdade de Medicina, Universidade de Lisboa, Lisboa, Portugal

Cancer is the 2nd cause of mortality in the Western World and, in most instances, surgery remains the only potential curative therapy. Moreover, population is ageing which results in an elderly population being submitted to combined and aggressive therapies namely neo-adjuvant chemoradiotherapy followed by surgery with curative intent. This is associated with an increased risk of morbimortality of treated patients and represents a challenge for the peri-operative team.

Malnutrition namely cachexia and wasting, are characteristic of cancer patients namely in advanced stages of disease¹. The pathophysiology of cancer cachexia is not fully understood but certainly involves depletion of skeletal muscle due to proteolytic factors produced by the tumour itself or by immune system of the host in response to tumour antigens¹. In this issue, Moreira-Pais et al² review mechanisms whereby a cytostatic agent, doxorubicin (DOX), may trigger or potentiate the muscle wasting observed in cancer patients. In fact, DOX seems to induce the activation of the proteolytic ubiquitin proteasome pathway (UPP), which in turn can also be enhanced by DOX-induced increase in myostatin and tumour necrosis

factor (TNF)- α signalling pathways, as well as insulin resistance. This pro-inflammatory scenario is already present in most cancer cachetic patients but may be further worsened by chemotherapy. Furthermore, DOX-induced oxidative stress and mitochondrial dysfunction may also be critical contributors for muscle wasting. All these mechanisms contribute to the loss of skeletal muscle mass and function observed after DOX exposure, which may worsen cancer-cachexia². As neo-adjuvant therapies are increasingly used, this needs to be taken into account when treating and operating cancer patients. Ideally, cancer patients should be referred to a nutritionist shortly after cancer diagnosis with the aim of avoiding further deterioration of nutritional status associated to anti-cancer therapies namely chemotherapy.

Further supporting this observation, Ruivo et al³ observed that malnutrition was highly prevalent in patients operated for digestive and head and neck malignancies and this was associated with increased risk of post-operative complications and increased length of hospital stay. The authors used both NRI and PG-SGA with the former showing increased sensitivity. These results are in agreement with



previous publications and strongly reinforce the concept that pre-operative identification of at risk patients for malnutrition should be mandatory as well early nutritional intervention and follow-up.

In order to provide an overview of what type of post operative complications are present, L Lara Santos et al⁴ reviewed 2017 charts of patients admitted and treated in the years 2017 and 2018 in the surgical intermediate care unit (SICU) at IPO Porto. They observed that 832 postoperative complications occurred, most were grade I and II according to the Clavien-Dindo classification and a full descriptive analysis of all patients included was performed. No associations with nutritional status or type of intervention were sought but these data are certainly important to design future pre habilitation programs, proficient intraoperative care and a multidisciplinary post operative care aiming at improving final outcome.

To date the most robust program for perioperative care is certainly the Enhanced Recovery after Surgery (ERAS) program. The concept of ERAS was first described by Henrik Kehlet in 1997⁵, where this surgeon questioned traditional perioperative care including prolonged fasting, mobility limitations, mechanical bowel preparation and systematic use of abdominal drains. Kehlet postulated that the avoidance of such practices could shorten the length of hospitalization by reducing the metabolic stress, fluid overload, and insulin resistance. ERAS care has evolved over the years into a multidisciplinary team approach involving surgeons, anaesthesiologists, critical care physicians, physiotherapists, nutritionists and nurses, where the intervention of each player is vital for the success of the whole program^{6,7}. The implementation of ERAS protocols is well-established all over the world and has resulted in improvements of short- and long-term outcomes, namely survival, with simultaneous reduction in total costs. So far, in Portugal there are only a few Centres which adhered to ERAS, probably because of financial constraints but this number will certainly increase in the coming years.

Besides ERAS program, multimodal pre habilitation programs, which focus on optimizing physiological and psychological well-being of surgical patients during the pre-operative period, have been proposed in order to face the increased burden of surgical aggression, aiming at decreasing post-operative morbidity and mortality⁸. The rationale for such intervention is related to the recognition that the prevalence of frailty increases with aging and older cancer patients undergoing surgery may face more post-operative complications as compared to younger ones⁹. Frailty is defined as a clinically recognisable state of increased vulnerability, more prevalent in older adults, resulting from age-associated decline in physiological reserve and function across multiple organ systems¹⁰. This concept somehow overlaps with the concept of sarcopenia, first coined by Rosenberg¹¹ and which refers to the loss of skeletal muscle mass and strength, also part of natural aging¹². There are now numerous studies demonstrating that body composition phenotypes may influence postoperative and long-term clinical outcomes. Most studies focus primarily on the impact of sarcopenia (low skeletal muscle) on major postoperative complications and overall survival and secondarily on visceral adipose tissue and low muscle radiation attenuation, a marker of fat infiltration of skeletal muscle, which reflects more muscle quality instead of muscle quantity^{13,14}. Most of these studies analyse one sole compartment and the influence of skeletal muscle infiltration by adipose tissue, as well as the proportion of visceral adipose tissue in regard to skeletal muscle tissue which has been strikingly less studied.

In this special issue of *Revista Portuguesa de Cirurgia* there are several well planned and written studies conducted mostly in Portuguese Centres which focus on the problematic of body composition changes, increased surgical risk and combined strategies to improve final outcomes. There is an urgent need to implement a pre-operative assessment of patients' risks in order to



programme a rehabilitation plan aiming at reducing post-operative complications and improving patient recovery.

This might be specific to type of intervention as showed by Kendall et al¹⁵ who evaluated risk of postoperative pulmonary complications (PPC) in patients submitted to lung resection. The authors observed that, besides smoking, preoperative maximal expiratory pressure (MEP) was the strongest predictor of PPC and should be considered for risk assessment in surgical candidates. It remains to be demonstrated that pre-operative intervention aiming at improving MEP can result in a decrease of PPC. This strategy of surgical risk assessment in order to mitigate POC, is also discussed in the review paper by Martins et al¹⁶. These risk factors involve individual factors where age is certainly one of the most important ones, type of disease/tumour, planned procedure, type of surgery and other social variables equally relevant. All these variables should be taken into account when deciding and proposing to the patient a certain type of intervention/ treatment. There are instances where the disease is surgical but the patient is not fit for surgery and other options should be considered. Different and numerous tools are available but, as stated by the authors (16), the decision on which is most appropriate is not easy. This is certainly not an argument and it is highly recommended that each Centre assesses surgical risk of all operated patients on a routine basis.

Regarding body composition which is now considered to be far more informative than BMI, Ferreira et al.¹⁷ found a prevalence of sarcopenia of 40.7% among gastric cancer patients undergoing gastrectomy and a positive association was found between sarcopenia and higher overall mortality. Interestingly and in accordance with a previous study by our group¹⁸, nutritional risk and percentage of body weight loss did not identify sarcopenic patients as 51.4% of sarcopenic patients were overweight and 2.9% were even obese. These observations highlight the fact that evaluation of body composition using

CT scans performed for cancer staging might be very helpful as, with the growing epidemics of obesity observed in the Western World, sarcopenia goes very often unrecognized.

In another study, Valentim et al¹⁹, analyzed the association between the presence of preoperative visceral obesity and an increased risk of postoperative morbimortality in patients with periampullary cancers. Although the authors did not find that preoperative visceral obesity was a risk factor for greater postoperative morbidity and mortality, there are some limitations recognized by the authors namely the reduced sample size and the inclusion of four types of tumors with distinct biologic behavior, which may explain the lack of association with visceral obesity .

One major issue of these two studies^{17,19} is the fact that both of them analyze muscle and fat mass/ area separately thereby missing important interplays between these two body compartments. In the study by Palmela et al¹⁸, performed in patients with locally advanced gastric cancer submitted to neo-adjuvant chemotherapy, the authors observed an association between need of termination of chemotherapy and both sarcopenia (P=0.069) and sarcopenic obesity (P=0.004). Also, the simultaneous presence of sarcopenia and obesity (sarcopenic obesity) was the worst case scenario associated with lower overall survival (6 vs. 25 months, P=0.000).

Further strengthening the importance of considering body composition as a whole, Velho et al recently published a paper on the prognostic value of body composition in pancreatic cancer patients submitted to pancreatectomy²⁰. Besides analysing the influence of skeletal muscle mass or visceral fat mass *per se* on post-operative complications, the authors also considered Visceral Fat Area/Skeletal Muscle Area (VFA:SMA) ratio and found it to be associated with increased risk of complications (OR=2.24, 95%CI=1.14-4.87, p=0.02) and 90-day survival (HR=2.13, 95%CI=1.13-4.01, p=0.014). For predicting survival, the discrimination achieved with a model that includes three body composition



parameters (skeletal mass, visceral fat and muscle attenuation which refers to the infiltration of skeletal mass by fat) was superior to a model with four conventional clinical variables such as age, ASA score, disease histology and postoperative complications. We believe that this holistic approach to body composition analysis might be more meaningful as all tissues are equally important and expected to interplay in the modulation of final response to inflammatory stress.

However, if alterations in body composition, namely sarcopenia and sarcopenic obesity, are widely recognized as having a negative impact on cancer patients' outcome²¹, the benefit of intervention strategies to tackle these alterations remains unclear. Exercise has been associated with improved functional status and patient reported outcomes in cancer patients^{22,23}, but optimal exercise frequency, intensity and duration is still open to debate. On the other hand, dietary intake is also relevant since it seems to have an important role in skeletal muscle maintenance. It has been suggested that cancer patients may experience an anabolic resistance to protein stimuli, but protein synthesis is not completely blunted and may respond to an elevated protein intake²⁴. In fact, protein supplementation has proven to improve protein synthesis²⁵, body composition, muscle strength²⁶ and walking capacity²⁷ in cancer patients. Besides the effect of single nutrients, dietary patterns namely a high fat and fish diet, is associated with a reduced odds of sarcopenia²⁸ and simultaneous energy and protein intake seem to result in a more robust effect on muscle mass and strength²⁹.

In this issue of the Journal, Teixeira-Oliveira et al³⁰ performed a systematic review and a meta-analysis examining the role of pre habilitation in postoperative burden of high-risk cancer patients. Reflecting the paucity of good quality work published in this area, the authors only found six eligible papers. Despite the low number of papers included, the authors concluded that pre habilitation reduced the length of hospital stay (mean difference of - 2.7,

95% CI: -5.37 to -0.17, $p = 0.04$) and improved functional recovery as assessed by the distance covered in the 6 MWT (mean difference 29.06 meters, 95% CI 26.55 to 31.57, $I^2 = 42\%$, $p < 0.001$).

Further supporting the benefits of a pre habilitation program which includes supervised physical activity (PA), Cardoso et al³¹ show us the results of a prospective and observational study including 81 patients with newly diagnosed gastric or head/neck cancer, recruited at IPO-Porto in whom PA was monitored through accelerometry. The authors compared postoperative burden among those "complying" or "not complying" with PA recommendations. Patients spent 54% of their wearing time in sedentary behavior, 42% in light PA, and 4% in moderate to vigorous PA, and only 46.9% of patients accomplished the minimum amount of MVPA/week recommendations. Postoperative mortality was superior among those patients "not complying" with international recommendations of PA.

In another paper, Lages et al³² discuss a very important aspect of this intervention strategy which refers to the difficulties of implementing such intervention programs on a sick and aged population, most of the times with associated co-morbidities and difficulties in reaching the Hospital on a daily or even weekly basis. The authors very nicely provide a narrative of the why and the how their team is setting a community and home-based personalized prehabilitation clinic, which can certainly increase the compliance of these patients to these intervention programs. Further strengthening the relevance of pre-habilitation programs Moreira Gonçalves et al³³ are now developing a home based prehabilitation program, delivered through an internet-based platform, aiming at preparing patients for surgery, without the need of patients going to the Hospital. We look forward to see the results of this intervention study.

Finally, Marta Ubre and Graciela Martínez-Pallí from Barcelona³⁴, report their experience in implementing a multimodal prehabilitation



programme as a mainstream service at the Hospital Clínic of Barcelona. The project started with a randomised clinical trial which showed the efficacy and cost-saving of pre-habilitation program in high risk surgical patients. This was followed by successive improvements and, as of today, high risk, less fit patients, receive at least 4 weeks of pre-habilitation programme which, besides a high protein diet, includes mainly home-based exercise training. Important to emphasize that in this Hospital all patients adhere to the Enhanced Recovery After Surgery standard of care recommendations.

Although it remains debatable the mechanism through which exercising might be beneficial in the pre-operative setting, most studies point out to a general sense of well-being related to the release of endogenous endorphins which counteracts the pro-inflammatory scenario characteristic of the surgical patient, and which is certainly harmful for a fast recovery. In addition, we might also expect that aerobic and resistance training over 4 to 6 weeks might contribute to increase skeletal muscle mass and/or decrease visceral fat which are detrimental and associated to an increase of post-operative complications. However, we may also speculate whether physical activity *per se* might also exert an anti-proliferative effect on the tumour itself. A number of previous studies showed that during exercise, contractile muscle fibers release proteins – the so called myokines, into the circulation. The first identified and most studied myokine is the gp130 receptor interleukin-6 (IL-6) which increases up to 100-fold during strenuous exercise. As opposed to IL-6 derived from fat which exerts a pro-inflammatory role through activation of

NF-Kb signaling pathway, IL-6 derived from muscle seems to mediate an anti-inflammatory effect. Both experimental and human studies have demonstrated that IL-6 infusion inhibits endotoxin-induced TNF production and stimulate the release of anti-inflammatory cytokines such as IL-1ra and IL-10. IL-15 is produced in muscle and has been thought to be involved in muscle-fat cross talk^{35,36}. It accumulates in the muscle as a result of regular training and elevated levels have been associated with significant reductions in body fat³⁵. In addition to IL-6 release from working muscles, there is also a coupled release of epinephrine from adrenal glands, which results in an epinephrine-dependent mobilization of IL-6 sensitive natural killer (NK) cells which have epinephrine receptors and thus migrate into tumors. NK cells are being evaluated as anti-tumor immune cell therapy in several clinical trials. These cells destroy proliferating tumor cells and prime the environment for adaptive immunity. Perderson et al³⁶ in an experimental study, found that exercise did not enhance NK cell cytotoxicity directly but instead increased the mobilization of tumor environment of NK and other T-cells which prime and destroy tumor cells. Another consequence of this mobilization of NK and other T cells into the tumor, is to eventually sensitize it to immunotherapy.

In conclusion, the benefit of pre habilitation programs in high risk surgical patients is largely demonstrated and accepted worldwide as a mean of decreasing post-operative complications and improving final outcome including overall survival. The major challenges for the next decade will be how to bring these intervention strategies into clinical practice.



REFERENCES

- 1 Nishikawa H, Goto M, Fukunishi S, Asai A, Nishiguchi, Higuchi K. Cancer Cachexia: Its Mechanism and Clinical Significance. *Int. J. Mol. Sci.* 2021, 22, 8491-8505.
- 2 Moreira-Pais A, Ferreira R, Costa VM, Oliveira PA, Duarte JA. The molecular mechanisms involved in doxorubicin-induced skeletal muscle wasting. *Rev Port Cir.* 2021; (51): 13-22.
- 3 Ruivo I, Castro C, Gonçalves A, Alves P, Moreira-Gonçalves D, Santos LL. Pre-surgical nutritional status and surgical complications in patients with digestive and head and neck cancer. *Rev Port Cir.* 2021; (51): 35-44.
- 4 Santos LL, Castro C, Santos F, Santos CS, Reis J, Antunes P, Martins PC. Post-operative complications in risk surgical patients admitted to the Intermediate Care Unit of Portuguese Institute of Oncology, Porto: relevant information to plan a patient centered care. *Rev Port Cir.* 2021; (51): 137-142.
- 5 Kehlet H. Multimodal approach to control postoperative pathophysiology and rehabilitation. *Br J Anaesth.* 1997;78:606-617
- 6 Ljungqvist O. ERAS-enhanced recovery after surgery: moving evidence-based perioperative care to practice. *JPEN J Parenter Enteral Nutr.* 2014;38:559-566
- 7 Ljungqvist O, Scott M, Fearon KC Enhanced Recovery After Surgery: A Review. *JAMA Surg.* 2017 Mar 1;152(3):292-298.
- 8 Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation before major abdominal surgery: A systematic review and meta-analysis. *World J Surg.* 2019; 43(7):1661-1668.
- 9 Ethun CE, Bilen MA, Jani AB, Maithel SK, Ogan K, Master VA. Frailty and cancer: Implications for oncology surgery, medical oncology, and radiation oncology. *CA Cancer J Clin* 2017;67:362-377
- 10 Chen X, Mao G, Leng SX. Frailty syndrome: an overview. *Clin Interv Aging.* 2014;9:433-441.
- 11 Rosenberg IH. Summary comments. *The American Journal of Clinical Nutrition.* 1989 Nov 1;50(5):1231-1233.
- 12 Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: Report of the European Working Group on Sarcopenia in Older People. *Age and Ageing.* 2010 Jul 1;39(4): 412-423
- 13 Pamoukdjian F, Bouillet T, Lévy V, Soussan M, Zelek L, Paillaud E Prevalence and predictive value of pre-therapeutic sarcopenia in cancer patients: A systematic review. *Clin Nutr.* 2018 Aug;37(4):1101-1113.
- 14 van Dijk DP, Bakens MJ, Coolen MM, Rensen SS, van Dam RM, Bours MJ, Weijenberg MP, Dejong CH, Olde Damink SW Low skeletal muscle radiation attenuation and visceral adiposity are associated with overall survival and surgical site infections in patients with pancreatic cancer. *J Cachexia Sarcopenia Muscle.* 2017 Apr;8(2):317-326.
- 15 Kendall F, Silva G, Drummond M, Viana P, Pinho P, Oliveira J, Bastos PT. The predictive role of respiratory muscle function on postoperative pulmonary complications after lung resection. *Rev Port Cir.* 2021; (51): 63-73.
- 16 Martins PC, Santos F, Menezes AS, Fernandes A, Santos LL. Surgical risk assessment is crucial to mitigate postoperative complications. *Rev Port Cir.* 2021; (51): 75-88.
- 17 Ferreira M, Barreira AL, Sardinha F, Costa J, Rodrigues J, Gonçalves A, Costa PM. Sarcopenia in gastric cancer and body composition changes after gastrectomy. *Rev Port Cir.* 2021; (51): 23-34.
- 18 Palmela C, Velho S, Agostinho L, Branco F, Santos M, Santos MP, Oliveira MH, Strecht J, Maio R, Cravo M, Baracos VE. Body Composition as a Prognostic Factor of Neoadjuvant Chemotherapy Toxicity and Outcome in Patients with Locally Advanced Gastric Cancer. *J Gastric Cancer.* 2017 Mar;17(1):74-87
- 19 Valentim M, Silva P, Pereira A, Vilaça S, Costa C, Martins SF. Impact of visceral obesity on outcomes of periampullary cancer surgery. *Rev Port Cir.* 2021; (51): 45-52.
- 20 Velho S, Costa-Santos MP, Cunha C, Agostinho L, Cruz R, Costa F, Garcia M, Oliveira P, Maio R, Baracos VE, Cravo M Body Composition Influences Post-Operative Complications and 90-Day and Overall Survival in Pancreatic Surgery Patients. *GE Portuguese Journal of Gastroenterology.* DOI: 10.1159/000507206.
- 21 Joglekar S, N. NP, Mezhir JJ. The Impact of Sarcopenia on Survival and Complications in Surgical Oncology: A Review of the Current Literature. *J Surg Oncol.* 2015;112(5):503-509.
- 22 Jones LW, Alfano CM. Exercise-oncology research: Past, present, and future. *Acta Oncol (Madr).* 2013;52(2):195-215.
- 23 Cormie P, Zopf EM, Zhang X, Schmitz KH. The impact of exercise on cancer mortality, recurrence, and treatment-related adverse effects. *Epidemiol Rev.* 2017;39(1):71-92.
- 24 Antoun S, Raynard B. Muscle protein anabolism in advanced cancer patients: response to protein and amino acids support, and to physical activity. *Ann Oncol [Internet].* 2018;29(suppl_2):ii10-7. Available from: https://academic.oup.com/annonc/article/29/suppl_2/ii10/4913823
- 25 Deutz NEP, Safar A, Schutzler S, Memelink R, Ferrando A, Spencer H, et al. Muscle protein synthesis in cancer patients can be stimulated with a specially formulated medical food q. *Clin Nutr [Internet].* 2011;30(6):759-768.



- 26 Cereda E, Turri A, Klersy C, Cappello S, Ferrari A, Filippi AR, et al. Whey protein isolate supplementation improves body composition, muscle strength, and treatment tolerance in malnourished advanced cancer patients undergoing chemotherapy. *Cancer Med.* 2019;8(16):6923–6932.
- 27 Gillis C, Loiselle SE, Fiore JF, Awasthi R, Wykes L, Liberman AS, et al. Prehabilitation with Whey Protein Supplementation on Perioperative Functional Exercise Capacity in Patients Undergoing Colorectal Resection for Cancer: A Pilot Double-Blinded Randomized Placebo-Controlled Trial. *J Acad Nutr Diet [Internet].* 2016;116(5):802–812.
- 28 Velho S, Moço S, Cruz R, Agostinho L, Lopes F, Strecht J, et al. Dietary patterns and its relationship to sarcopenia in Portuguese patients with gastrointestinal cancer: An exploratory study. *Clin Nutr.* 2018;37:S203–204.
- 29 Zanetti M, Cappellari GG, Barazzoni R, Sanson G. The impact of protein supplementation targeted at improving muscle mass on strength in cancer patients: A scoping review. *Nutrients.* 2020;12(7):1–16.
30. Teixeira-Oliveira F, Silva G, Santos F, Martins PC, Moreira-Gonçalves D. Prehabilitation and postoperative burden of high-risk cancer patients: a systematic review and meta-analysis. *Rev Port Cir.* 2021; (51): 99-114.
31. Cardoso R, Guedes M, Pauli N, Ehrenbrink G, Poças K, Castro C, Santos CS, Schmidt C, Moreira-Gonçalves D. Preoperative physical activity levels and postoperative burden in cancer patients: a prospective observational study. *Rev Port Cir.* 2021; (51): 53-61.
32. Lages P, Oliveira G, Simões J, Costa PM. The time has come for a community and home-based prehabilitation: narrative of an implementation process. *Rev Port Cir.* 2021; (51): 115-123.
33. Moreira-Gonçalves D, Fernandes A, Mota CD, Antunes J, Canappele C, Martins PC, Santos F, Cabral S, Castro C, Santos CM, Almeida S, Rodrigues J, Romano O, Fonseca AS, Lages P, Costa PM, Santos LL. A home-based prehabilitation program, delivered through an internet-based platform, in patients with locally advanced gastroesophageal junction and stomach adenocarcinoma, undergoing perioperative chemotherapy: protocol for a feasibility and acceptability study. *Rev Port Cir.* 2021; (51): 125-135.
34. Ubre M, Martínez-Pallí G. Evolutionary steps in the implementation of a prehabilitation service: from knowledge generation to clinical practice. *Rev Port Cir.* 2021; (51): 89-98
- 35 Pedersen BK. Exercise-induced myokines and their role in chronic diseases. *Brain Behav Immun [Internet].* 2011;25(5):811–816.
- 36 Pedersen L, Idorn M, Olofsson GH, Lauenborg B, Nookaew I, Hansen RH, et al. Voluntary running suppresses tumor growth through epinephrine- and IL-6-dependent NK cell mobilization and redistribution. *Cell Metab.* 2016;23(3):554–562.

Correspondência:

MARÍLIA CRAVO

e-mail: marilia.cravo@sapo.pt

Data de recepção do artigo:

23/02/2021

Data de aceitação do artigo:

13/04/2021

