How can we minimize the risks by optimizing patient's condition shortly before thoracic surgery?

ABSTRACT

The "moderate-to-high-risk" surgical patient is typically older, frail, malnourished, suffering from multiple comorbidities and presenting with unhealthy life style such as smoking, hazardous drinking and sedentarity. Poor aerobic fitness, sarcopenia and "toxic" behaviors are modifiable risk factors for major postoperative complications. The physiological challenge of lung cancer surgery has been likened to running a marathon. Therefore, preoperative patient optimization or " prehabilitation " should become a key component of improved recovery pathways to enhance general health and physiological reserve prior to surgery. During the short preoperative period, the patients are more receptive and motivated to adhere to behavioral interventions (e.g., smoking cessation, weaning from alcohol, balanced food intake and active mobilization) and to follow a structured exercise training program. Sufficient protein intake should be ensured (1.5–2 g/kg/day) and nutritional defects should be corrected to restore muscle mass and strength. Currently, there is strong evidence supporting the effectiveness of various modalities of physical training (endurance training and/or respiratory muscle training) to enhance aerobic fitness and to mitigate the risk of pulmonary complications while reducing the hospital length of stay. Multimodal interventions should be individualized to the patient's condition. These bundle of care are more effective than single or sequential intervention owing to synergistic benefits of education, nutritional support and physical training. An effective prehabilitation program is necessarily patient-centred and coordinated among health care professionals (nurses, primary care physician, physiotherapists, nutritionists) to help the patient regain some control over the disease process and improve the physiological reserve to sustain surgical stress.

Key words: Aerobic capacity; exercise training; nutrition

Introduction

In thoracic cancer surgery, treatment modalities are usually discussed at Tumor Board meetings where information regarding patient history, comorbidities and quality of life, as well as tumor extent, pulmonary function and laboratory results are presented and shared between oncologists, surgeons, anesthesiologists, pneumologists and radiologists.

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In the early cancer stages, surgical resection remains the best therapeutic option as approximately 60% of patients are expected to survive at least 5-year after surgery compared with less than 15% under medical management.[1] Non-surgical treatments (e.g., chemo-immuno- and radiotherapy) can be proposed to patients unable to sustain surgical stress given preexisting severe organic dysfunction or poor health condition.[2]

Based on medical history, clinical examination and functional investigations, the anesthesiologist assesses and stratifies patient's perioperative risks.[3] The use of simple questionnaires that address exercise tolerance (Metabolic Equivalent Task, MET) and daily life activities (Duke Activity Status Index [DASI]) or simple dynamic tests (e.g., time up to go, gait speed) enables the perioperative physicians to estimate the patient's aerobic fitness and functional capacity. [Table 1][4] In thoracic surgery patients, cardiopulmonary exercise testing (CPET) on a cycloergometer or a treadmill represents the reference tool to quantitate aerobic fitness by measuring peak oxygen consumption (peakVO_2), anaerobic threshold, peak workload and ventilatory efficiency (slope or ratio of ventilation to carbon dioxide production). These CPET-derived parameters reflect the integrative response of the respiratory, circulatory and muscular systems during maximal exercise.[5] Alternatively, low technology exercise tests (e.g., shuttle, stair climbing, six-minute walk distance) can be used as a screening tool in preoperative evaluation and when CPET is not readily available.[6]

Historically, research efforts were initially focused on cardiovascular assessment since myocardial infarcts, arrhythmia, heart failure and stroke were the leading causes of operative mortality. Since 1990, the Goldman risk index and later the Revised Cardiac Risk Index (RCRI) coupled with the evaluation of aerobic fitness have been largely adopted to stratify cardiovascular risks and guide further investigations and treatments before surgery.[7] Better management of coronary artery disease, arrythmias and heart failure with myocardial revascularization, resynchronization/ablation techniques as well as pharmacological treatments have contributed to improve patient's cardiovascular condition and in turn, to minimize the perioperative risk of major cardiovascular events.[7]

Nowadays, postoperative pulmonary complications (PPCs), namely atelectasis, pneumonia, acute respiratory distress syndrome, broncho-pulmonary fistula, pleural effusions-,

Table 1: Preoperative risk assessment

Score	Characteristics
ASA-PS score	Normal healthy patient Mild systemic disease Severe systemic disease Severe systemic disease, threat to life Moribund
Metabolic Equivalent Task (MET)	Light intensity: <3 MET (40-55% HR_{Max}, 20-40% VO_{2Max}), writing, desk work (1.8 MET), walking 4.0 km/h (2.5 MET) Moderate intensity: 3-6 MET (55-75% HR_{Max}, 40-60% VO_{2Max}), climbing 3-4 flights of stairs or bicycling 50-100 watts (3-5.5 MET) Vigorous intensity 6-9 MET (70-90% HR_{Max}, >60% VO_{2Max}), running, 8.0 km/h (8.1 MET), rope jumping (10 MET) High intensity >9 MET (>90% HR_{2Max}, >85% VO_{2Max})
Revised Cardiac Risk Index	Coronary artery disease Renal insufficiency (serum creatinin >2 mg/dl) Cerebrovascular disease Pneumonectomy (Diabetes mellitus requiring insulin)*
ARISCAT score	Age (<60, 51-80, 80) Preop SpO_2 (≥96, 91-95, ≤90%) Respiratory infection <1 month (yes/no) Preop Hb ≤10 g/dl Surgical incision site (peripheral, upper abdominal, intra-thoracic Duration of surgery (<2, 2-3, >3 h) Emergency procedure (yes/no)
Clinical Frailty Scale	Very fit: Robust, energetic, regular exercise Well: No active disease, occasional exercise Medical problem well controlled, routine walking Vulnerable: Symptoms limit activities (slowing) Mildly frail: Need help in high order IADL (finance, transportation, medications) Moderately frail: Need help for outside activities, keeping house, bathing Severely frail: Completely dependent for personal care (physical, cognitive) Severely frail: Dependent, approaching end of life (could not recover from minor illness) Terminally ill: Life expectancy <6 month

ASA-PS, American Society of Anesthesiology- Physical status; Hb, hemoglobin; HR_{Max}, maximal heart rate; SpO_2, pulsed oxygen saturation; VO_{2Max}, maximal oxygen consumption. *Not included in the Thoracic Revised Cardiac Risk Index are the most common adverse events after thoracic surgery, exceeding by far the incidence of cardiovascular complications. These PPCs pose major healthcare challenges by increasing hospital length of stay and medical costs while decreasing long term patient's quality of life and survival.[8]

Risk Factors and Mechanisms of Postoperative Complications

Surgical trauma induces neurohumoral and inflammatory responses that parallel the extent of tissue injury.[9] The resulting transient hypermetabolic status is manifested by a moderate elevation of body temperature, increased oxygen consumption and cardiac output, fluid retention, hyperglycemia due to central and peripheral insulin resistance as well as by mobilization of energy reserve to ensure tissue repair. Importantly, the catabolic processes that exceed anabolic activities on the days following surgery result in muscle wasting with the release of amino acids into the circulation and their preferential uptake by the liver to synthesize acute phase proteins and glucose (neoglucogenesis).

Sufficient preoperative physiological reserves are required to meet the postoperative energy demand and to sustain the surgical stress-induced mobilization of muscular protein while preserving patient functional capacity to breathe and move adequately.

The risk factors leading to poor postoperative outcomes have been identified by analyzing large databases. Advanced age, cardiopulmonary disease severity, complex and prolonged surgical time, smoking and alcohol consumption, mechanical ventilation using large tidal volume and driving pressure, poor nutritional status as well as low aerobic capacity (<5 MET or <16 ml/kg/min peakVO_2) are all strongly predictive factors of PPCs.[10-12] Low aerobic fitness is reported in up to 20–30% patients scheduled for lung cancer surgery and is predictive of poor survival. Likewise, sedentary individuals and patients with chronic inflammatory diseases, coronary artery disease (CAD), heart failure (HF), chronic obstructive pulmonary disease (COPD) and neurological disorders are all characterized by an impaired cardiopulmonary exercise tolerance and a reduction in lean body mass that both represent risk factor for diminished long term survival.[13]

In the early postoperative period, lung volumes (end-expiratory and end-inspiratory) become smaller compared with the preoperative phase, for two main reasons: (1) the lungs are *stiffer*, the reduced *pulmonary* compliance results from inflammation and ventilation-induced lung injuries with surfactant dysfunction/depletion consequent to the effects of anesthesia and overdistension and/or collapse of different parts of the lung (bio- volo- baro- and atelect-trauma), 2) the respiratory muscles are *weaker* with impaired contractile performance of inspiratory muscles resulting from residual depressive effects of anesthetic agents, surgery-induced systemic inflammation, ventilator-associated respiratory muscle disuse and incisional pain associated to inhibition of phrenic nerve activity.[14] Accordingly, weaker respiratory muscles are less "fatigue resistant", particularly when faced with the increased inspiratory loading conditions of stiffer lungs which require higher transpulmonary pressure to mobilize air and open alveolae, particularly in dependent lung areas. Consequently, the inefficient respiratory pumping capacity results in lower functional residual volumes, promoting ventilation–perfusion mismatch and atelectasis that paves the way for bacterial translocation and later onset of pneumonia.

Preoperative Patient Assessment and Implementation of improved recovery after surgery pathways

During the preoperative visit, the anesthesiologist plays a crucial role acting as a "gatekeeper" by judging the patient's ability to sustain the surgical procedure, mitigating the stress response with an individualized anesthesia/analgesia plan and, in selected patients, by prescribing optimization therapies through nutritional support and exercise training to enhance physiologic reserves before surgery.[15]

Regarding risk stratification, professional guidelines recommend using the American Society of Anesthesiology Physical Status (ASA-PS) score, the MET (or DASI, CPET-derived parameters), the Revised Cardiac Risk Index (or the dedicated Thoracic RCRI), the Assess Respiratory Risk in Surgical Patients in Catalonia (ARISCAT) score and the Clinical Frailty Scale [Table 1].[3,16-18] These scoring systems are also helpful to predict major postoperative complications, to identify "unfit" patients and to guide optimal curative or palliative treatments.[19]

In very high-risk patients, alternative non-surgical treatments, a less invasive approach or palliative care should be considered and agreed upon by the thoracic team. In moderate-to-high risk patients, "modifiable" risk factors should be the focus of interest and a treatment strategy should be designed to solve potential problems and mitigate the risk. Whenever possible, sufficient time should be allowed to correct nutritional deficits, increase muscle mass and aerobic fitness as well to inform, educate and empower the patient about the risks induced by sedentarity, smoking and alcohol consumption.

The anesthesiologist's assessment and proposals are incorporated into the Fast Track Clinical pathways or improved recovery after surgery pathways programs that have been adopted in many hospitals. These evidence-based protocols are aimed at standardizing the processes of perioperative care and at improving clinical and functional outcome while minimizing variability, errors and costs. For instance, health care professionals should adhere to specific recommendations, namely: Carbohydrate drinks up to 2 hours before surgery, skin preparation and antibiotic prophylaxis, minimally invasive surgery, lung protective ventilatory strategies, restrictive or goal-directed intravenous fluids management, prevention of nausea and vomiting, avoidance of/or early removal of drains and tubes as well as early mobilization and resumption of oral feeding after surgery.[20]

General recommendations are issued to optimize patient preoperative condition by stabilizing active illnesses (e.g., CAD, HF, COPD, asthma, infection), adjusting drug therapy (e.g., anticoagulants, anti-platelets, antihypertensive medications), correcting anemia and malnutrition as well as by encouraging patients to adopt a healthier lifestyle (physical activity, dental care and mouth disinfection, smoking cessation and limitation of alcohol consumption).[20-22]

Preoperative Patient Nutritional Condition

The term malnutrition defines "unbalanced" nutritional states that encompass either over- or undernutrition, which are responsible for abnormalities in body compartments, immune defense and organ function.[23] In Western countries, undernutrition in surgical patients (referred as malnutrition) results from insufficient nutrient intake owing to socio-economic factors, chronic/acute inflammation, malabsorption or bowel obstruction, cardio-pulmonary insufficiency as well as drug-induced adverse effects.

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Malnutrition is reported in up to 10 to 50% of patients admitted to the hospital, particularly among those with catabolic derangements and insufficient energy balance.[23] In more than 50% of community-dwelling older subjects, the minimal dietary protein requirements are not met and contributes to muscle wasting, reduced walking capacity, risk of falls and loss of physiological reserve.[24] Therefore, nutrition screening tools such as the MUST (Malnutrition Universal Screening Tool), the MNA (Mini-Nutrition Assessment, Table 2) or the PONS (Preoperative Nutrition Score) should be routinely used to identify undernourished patients before major cancer surgery.[25] In addition, computed tomographic thoracic scans that are performed preoperatively may precisely detect patients with low muscle mass and fatty muscle infiltration which are predictive of mortality, major complications and prolonged hospital stay after colorectal surgery and lung cancer resection.[26,27]

When severe malnutrition is identified (weight loss >10%, body mass index <18.5 kg/m^2, serum albumin <30 g/L), further investigations are required to estimate the energy needs (nitrogen balance, indirect calorimetry), to assess skeletal muscle mass and the fat compartment (mid-arm circumference, triceps skinfold, bioelectrical impedance analysis, dual-energy X-ray absorptiometry, computed tomography and magnetic resonance imaging) as well as the muscle strength (handgrip dynamometer, leg or chest press).[23] Dietary adjustments are made with high energy nutrients (~30-40 kcal/kg/day,

Table 2: Mini-Nutritional Assessment (MNA)*

A Decline in food intake over the past 3 months due to loss of appetite, digestive problems, chewing or swallowing difficulties?
0=severe decrease in food intake
1=moderate decrease in food intake
2=no decrease in food intake
B Weight loss during the last 3 months
0=weight loss >3 kg
1=does not know
2=1-3 kg weight loss
C Mobility
0=bed or chair bound
1=able to get out of bed/chair but does not go out
2=goes out
0=yes 2=no
E Neuropsychological problems
0=severe dementia or depression
1=mild dementia
2=no psychological problems
F1 Body Mass Index (BMI, kg/m2)
0=BMI <19
1=BMI 19 to less than 21
2=BMI 21 to less than 23
3=BMI 23 or greate
F2 (if BMI not available) Calf circumference (CC) in cm
0=CC <31
3=CC ≥31
Screening score
12-14 points → normal nutritional status
8-11 points → At risk of malnutrition
0-7 points → Malnourished

*Kaiser MJ, Bauer JM, Ramsch C, *et al*. Validation of the Mini Nutritional Assessment Short-Form: A practical tool for identification of nutritional status. J Nutr Health Aging 2009;13:782-788 carbohydrates, omega-3 fatty acids), high-quality source of proteins (~1.5-2 g/kg/day of protein spread over several meals; creatine monohydrate, essential aminoacids with arginine, glutamine and cysteine) and selective supplements (e.g., vitamin D, acid folic, cyanocobalamine, iron). For instance, consuming a multi-ingredient mixture composed of whey protein, creatine, calcium, vitamin D, and omega-3 polyunsaturated fatty acids has demonstrated favorable effects to improve lean body mass and muscular strength in the elderly, with further gains when nutrition support was combined with resistance exercise training.[28]

In a meta-analysis of 56 trials including 6'370 patients undergoing gastrointestinal surgery for cancer, perioperative nutritional support was associated with fewer postoperative complications (risk ratio (RR) and 95% confidence interval (CI) of 0.78 (0.72–0.85), particularly infectious complications and, a shorter length of hospital stay (pooled mean difference of 1.6 days (95%CI -1.8 to -1.3).[27] Interestingly, implementation of a short-term nutrition support (probiotics, multi-vitamins, proteins, complex carbohydrates) among patients awaiting lung cancer resection has been associated with lesser costs and better postoperative outcome in terms of bowel recovery, major complications and hospital length of stay).[29,30]

Given the association between undernutrition, poor physical fitness, decreased immune defense and the risk of postoperative complications, personalized diets should be ideally prescribed over 4 to 12 weeks to replenish muscle mass, correct nutritional deficiencies and restore both muscular strength and aerobic fitness.[31] A greater total protein intake coupled with active mobilization is often necessary to match the elevated protein turnover and anabolic resistance induced by surgical trauma, ongoing inflammation and malignant disease.

Preoperative Patient Physical Condition

Impact of aging, sedentarity and chronic diseases on skeletal muscles

Skeletal muscles represent 30–40% of total body mass and 70-80% of the organism's protein reserves. Muscle function supports key activities such as any movement (including breathing), static contractions (posture), thermoregulation and metabolic homeostasis. Age-associated reduction in aerobic capacity (5 to 15% per decade), in muscle mass and strength (sarcopenia and dynapenia, respectively) begins as early as 25 years of age, accelerates after 60-70 years, and is associated with increased falls, fractures and mortality.[32] In surgical patients, preexisting poor muscle function and further muscle wasting due to ongoing inflammation and immobilization result in difficulties for patients to sustain increased respiratory loads, to stand up and walk in the early postoperative period.

The number and size of muscle fibers (type I, slow-twitch, oxidative and type II fast-twitch, glycolytic) decline with aging in parallel with the loss of motoneurons, the rarefaction of capillaries and replacement by fat and connective tissue.[32] Noteworthy, type I fibers, through down regulation of the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α), are more susceptible to inactivity, immobilization and denervation-induced atrophy while type II fibers, through modulation of the transforming growth factor beta (TGFβ) and the nuclear factor kappa B (NF-κB), are more affected by cancer, diabetes and heart failure. Importantly, type I fibers, through down regulation of the peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1α), are more susceptible to inactivity, immobilization and denervation-induced atrophy while type II fibers, through modulation of the transforming growth factor beta (TGFβ) and the nuclear factor kappa B (NF-κB), are more affected by cancer, diabetes and heart failure.[32] With aging, type I fibers are less affected than type II due to collateral re-innervation and fast-to-slow fiber shift. The mechanisms and implications of muscle wasting are summarized in Figure 1.

Compared with younger individuals, skeletal muscles in older persons exhibit reduced insulin-stimulated glucose uptake and oxidation due to decreased glycogen stores and transmembranar transporter (reduced GLUT4 protein in type II fibers). Moreover, the aging mitochondria display morphological abnormalities, a decline in mitochondrial DNA and mRNA capacity, slower trafficking through the respiratory chain, reduced oxidative phosphorylation, impaired adenosine triphosphate (ATP) synthesis and excessive generation of reactive oxygen species (ROS) that contribute to the breakdown of myofibrillar proteins and cellular autophagy/apoptosis.[33]

Genetic factors determine about 20% to 40% of the oxygen transport and utilization capacity by influencing cardio-pulmonary function, hemoglobin content, muscle blood flow and mitochondrial ATP production.[32] Besides concomitant cardiopulmonary diseases and inappropriate nutritional intake, a sedentary behavior commonly prevalent among elderly may well be the prime cause of the aging-related decrease in aerobic capacity associated with the loss of muscle mass and strength.[17]

Impact of preoperative exercise programs on postoperative outcome

Physical training programs mainly encompass *resistance* or strength type exercises and *endurance* or aerobic type exercises that are focused specifically on respiratory muscles (inspiratory muscle training, IMT), selected muscle groups (upper/lower body, trunk/abdomen) or whole body (e.g., running on a treadmill, cycling or rowing). Increasing the muscular mass is usually achieved by "resistive work" or static (isometric) contractions with little change in muscle fiber length.[32] In contrast, dynamic (isotonic) muscle actions entail concentric and eccentric contractions leading to muscle shortening and lengthening, respectively.[32]

Chronic endurance training (ET) in master endurance athletes (>60 yrs) is associated with preservation of the aerobic capacity (~43 ml/kg/min $VO_{2\ Max}$ vs 27 ml/kg/min in age-matched controls) and lesser decline in muscle strength.[34] Likewise, mitochondrial gene expression and protein content of the electron transport chain complexes and the PGC-1α are all substantially greater in the vastus lateralis muscle of older highly trained individuals compared with younger individuals and age-matched controls.[35] Because PGC-1α level is reduced in sedentary individuals and that physical training upregulates its expression, ET could represent a simple measure to counteract the effects of aging and chronic diseases on mitochondrial biogenesis, oxidative capacity and muscle mass development.[36] Likewise, resistance training at moderate loads has been shown to induce hypertrophic changes of type II fibers with increased muscle strength, these effects being augmented by the intake of dietary components (e.g., proteins, macronutrients) and nutritional supplements (e.g., creatine, vitamin-D, omega-3 polyunsaturated fatty acids).[37] In a meta-analysis of seven trials including 248 older individuals, inspiratory muscle performance was significantly improved after IMT

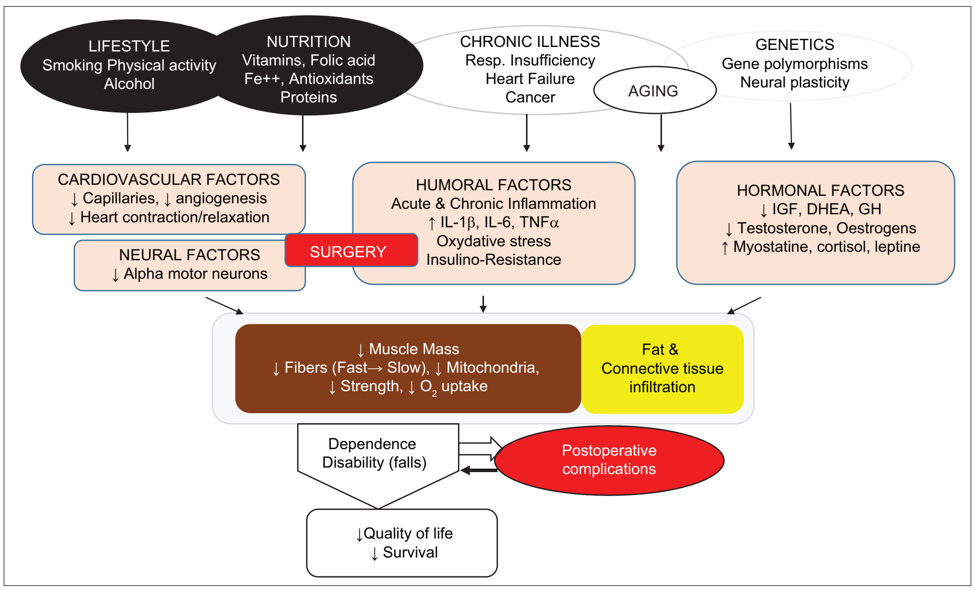

Figure 1: Mechanisms and clinical implications of muscle loss DHEA, dehydroepiandrosterone; GH, growth hormone; IL-1 and IL-6, interleukine-1 and interleukine-6; IGF, insulin growth factor; TNF-α, tumor necrosis factor-alpha

Table 3: Prehabilitation components and evidence-based efficacy

Interventions	Modality	Evidence
Education and Psychological support	Smoking arrest Alcohol arrest Physical activity	Low Low Moderate
	Relief anxiety by comprehensive information Behavioral or relaxation strategy for coping with stress	Low
Nutrition	Screening body mass index, weight loss >5% food intake (protein, calories, …) lean body mass (e.g., body electrical impedance, CT-scan)	Moderate Moderate
	Correct nutritional defects (vitamins, proteins, essential fat, …) Restore muscle mass	
Physical Fitness	Screen physical activity in daily life (MET, DASI) or perform CPET Prescribe exercise protocols (supervised or home-based), personalized according to patient's condition Endurance training (e.g., running, walking, climbing stairs/uphill, bicycling; continuous moderate intensity or interval high intensity) Resistance training (e.g., power lifting, isometric contractions with elastic bands) Inspiratory muscle training (e.g., volume incentive spirometry, resistive threshold loading device, deep breathing)	Moderate High

CPET, Cardio-Pulmonary Exercise Test; DASI, Duke Activity Score Index; MET, Metabolic Equivalent Task at moderate intensity levels (30-80% of maximal inspiratory pressure) over at least 4 weeks compared with sham treatment.[38]

Various physical training modalities have been applied within the limited time frame preceding thoracic surgery to enhance patients' physiological reserve and facilitate postoperative recovery.[39,40] In a meta-analysis of 29 RCTs including 2'070 patients scheduled for major surgery, preoperative exercise training resulted in enhanced aerobic fitness (∼+12%) and maximal inspiratory pressure (∼+15%), decreased occurrence of PPCs (OR of 0.43, 95% confidence interval 0.31 to 0.59) and shorter hospital length of stay (-2.4 days, 99% CI -4.1 to -0.8).[41] The exercise-induced beneficial effects were effective across various surgical procedures (cardiac, abdominal and thoracic), even within a short time delay (one week, 1 to 8 weeks) and using different exercise modalities (ET, IMT or a combination of both).

A strong body of scientific evidence lends support to the improved oxygen transport capacity and aerobic fitness following short-term ET through upregulation of PGC-1α within skeletal muscles (respiratory and locomotor) and cardiovascular adaptive changes manifested by an expansion of the circulatory volume, improved ventricular and vascular relaxation, greater capillary density and reduced sympathetic activity with vagal neural predominance. Likewise, short-term IMT using resistive threshold loading devices, volume incentive spirometry and/or breathing exercises has all been shown effective to strengthen inspiratory muscles and to increase diaphragm thickness owing to hypertrophic changes of fast-twitch fibres and a higher proportion of slow oxidative fibres. Finally, both ET and IMT result in structural and adaptive changes within the respiratory muscles that confer higher strength and resistance to fatigue and therefore enable patients to sustain the higher ventilatory workload while improving gas exchange and minimizing atelectasis formation. With improved metabolic capacity and more efficient contraction-relaxation cycling of the respiratory muscles there would be less muscle fatigue, which in turn would alleviate the sympathetically-mediated vasoconstriction and promote the redistribution of blood flow from the respiratory muscles towards the limb muscles (metaboreflex), thereby improving walking capacity.

Conclusions

Many patients scheduled to undergo curative lung cancer resection present with low physical fitness, poor muscle strength and mass as well as inappropriate food intake. There is sound physiological rationale and scientific evidence for training-induced improvement in aerobic capacity and for nutrition-induced increase in muscle mass within the short time frame before surgery with the aim to enhance the patient's ability to sustain surgical stress and facilitate early functional recovery [Table 3]. Continuation of the exercise training program and adhesion to healthier life style is necessary to consolidate functional gains and increase life expectancy.[42] Future studies will help to design an individualized optimization approach based on a greater understanding of the complex interplay between the patient's genetic background, pathophysiological responses to surgery and social environments.

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Conflicts of interest

There are no conflicts of interest.

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