Assessing the role of physical activity in patients with oesophageal cancer-should we be prescribing exercise?!

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A 60 year old gentlemen presents to the Upper GI clinic following a series of investigations:

Doctor, " So can you tell me how you've been recently?"

Patient, "Well Doctor, I'm suffering with severe indigestion, I'm off my food, I've lost all this weight, I feel tired all the time and I've only just retired. I just don't know what's wrong with me, I'm only 60 years of age. I told my GP and he made my referral urgent. I'm just worried it may be cancer".

Doctor, "I'm afraid I do have some bad news to tell you. You see, this is the scan you had which shows cancer of the oesophagus, here. There is a 3cm cancer. I'm sorry to tell you this".

Patient, "Oh. So how long have I got? I've only just retired."

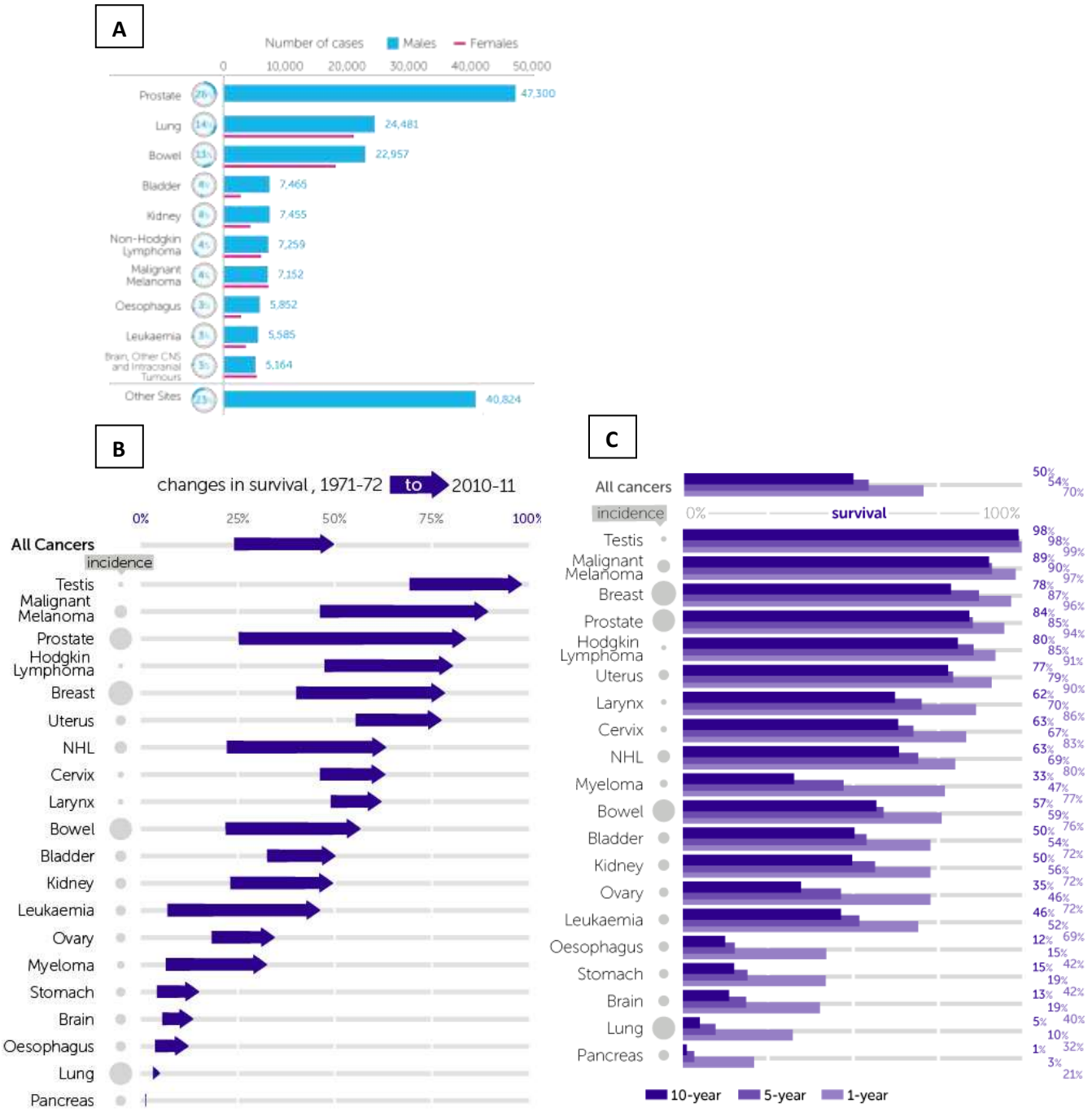
Doctor, "We would recommend a course of chemotherapy to shrink the cancer initially. Then we can perform an operation to remove your oesophagus to try and eradicate the cancer."

Patient, "Right, ok, but how long have I got"?

Doctor, "It varies from patient to patient. Some patients live for many years after treatment but it can be anything from months to years. I know this is hard."

The impact of diagnosing oesophageal cancer

This scenario is an all too common case seen by the Upper GI surgeons. During my time in the clinic at the Queen Elizabeth Hospital, I saw four patients diagnosed with oesophageal cancer, all of whom required oesophagectomy, making me realise the impact and stark reality of a diagnosis of oesophageal cancer. Patients often present late, with indigestion plus or minus difficulty swallowing, in pain, generally lethargic and having lost significant weight in the preceding months. And yet, patients are often relatively young, with median age of diagnosis being 50-60 years [1,2]. With an increasingly ageing population, the incidence of oesophageal cancer also continues to rise, although the twenty first century lifestyle is also a major contributor to rising incidence. Risk factors for oesophageal cancer may be non-modifiable such as age and male gender but many are modifiable by lifestyle changes such as stopping smoking, limiting alcohol consumption and losing weight. These modifiable risk factors often precipitate further pathology such as acid reflux, hiatus hernias and exacerbate pre-malignant dysplastic (abnormal cells at risk of becoming malignant) conditions such as Barretts Oesophagus, all of which further increases risk of oesophageal cancer [3]. The greatest burden of oesophageal cancer, aside from the significant symptomology, is the prognosis, with only 15-20% of patients surviving 5 years [4]. This is in stark contrast to the most common cancers such as of the breast, colon and prostate where 80% survive 10years [**Figure 1: A-C** [4]**]**. Moreover, 50% of patients who present have an unresectable tumour and distant metastases hence cannot be operated on [3].



Figures 1 A-C: Incidence and survival for patients diagnosed with oesophageal cancer

[A] Oesophageal cancer is the eight most common cancer. [B] Comparatively, survival from oesophageal cancer is poor but has increased in the last four decades. [C] 42%, 15% and 12% of patients with oesophageal cancer can expect to lie for 1, 5 and 10 years respectively.

Current optimal management of patients with oesophageal cancer

Patients aged over 55years presenting with indigestion (dyspepsia) should be urgently referred for further investigation on the assumption of cancer until proven otherwise [1, 5]. Patients will typically have an endoscopy, with biopsy samples taken, endoscopic ultrasound, CT and PET scans and finally a laparoscopy for oesophageal lymph node biopsy and washings of the abdominal wall to identify micro-metastasise (spread of cancer cells that can only be seen under the microscope) [6, 7]. These

investigations will outline the extent of invasiveness of the tumour into the oesophageal wall and or surrounding organs, the involvement of surrounding local or distant lymph nodes and spread of the cancer to distant organs such as to the lung or liver. Thereafter, the most appropriate treatment and management options can be decided upon, by a multidisciplinary team comprised of upper GI surgeons, radiologists, pathologists, anaesthetists and senior nurse specialists, in liaison with the patient and their family [8]. In brief, management options consist of neoadjuvant (pre-operative) chemotherapy to shrink the tumour, which may or may not be undertaken prior to an oesophagectomy (removal of the oesophagus) [9]. Following surgery, the resected cancer specimen undergoes extensive pathological analysis to accurately assess tumour type, grading (i.e. the clarity of the cells under the microscope and their resemblance to normal cells), responsiveness of the tumour to chemotherapy (graded using the Mandard score), dimensions, involvement of the surgical resection margin (i.e. on removal of the cancer, was a border of normal tissue also taken to help prevent further growth/spread of the cancer or how much, if any cancer is left behind). According to the pathology report findings, the patient may be offered additional chemotherapy post-oesophagectomy [8].

The impact of oesophagectomy

An oesophagectomy is a major operative procedure, taking a full days work for an Upper GI surgeon and is usually performed in two or three stages. Numerous techniques for oesophagectomy are validated including open, hybrid, transhiatal and the more recent minimally-invasive option; the procedure type used will depend on the cancer, the patient and the surgeon [5]. With the performance of major surgery, comes the heightened risk of morbidity and mortality postoperatively and particularly in an aged cohort with coexistent chronic disease [11, 12] [**Figure 2** [10]]. Although age per se is not an exclusion criterion for surgery, with advancing age comes accumulation of chronic disease, and physiological deterioration with organ dysfunction affecting the lungs, liver and kidneys, which will increase the risk of postoperative complications [12], as depicted in **Figure 2**. Mortality from oesophagectomy ranges from 2-9% but studies show that specialised and high-volume centres achieve lower mortality rates; therefore upper GI surgeons are expected to perform a set number of oesophagectomies a year to be deemed competent. Morbidity is also highly variable occurring in up to 80% of cases but of varying severity. Morbidities can be systemic in nature e.g. heart attack or chest infection, or can be related to the procedure itself e.g. an anastomotic leak (from the join made following resection of the tumour) or damage to the nerve responsible for voice (recurrent laryngeal nerve palsy). Chest infections are the most common followed by heart problems. With age comes increased susceptibility to infection, respiratory capacity declines, hence aeration of the lungs is reduced, which predisposes to chest infections. Moreover, raised blood pressure, often seen with advancing age and calcified arteries from a diet rich in cholesterol puts more strain on the heart so in an operative setting the heart is less able to cope with the additional strain of surgery, hence why patients are at risk of heart attacks or an aberrant hear rhythm such as atrial fibrillation post-operatively [12-14].

Although every surgeon would wish to offer their patient the potentially curative option of oesophagectomy, an unfit patient will not be able to cope with the major stress of surgery both during and after the procedure. Therefore, for these patients, the option of palliative chemoradiotherapy, although non-curative, will inevitably enable a more peaceful course for the patient and family alike [8].

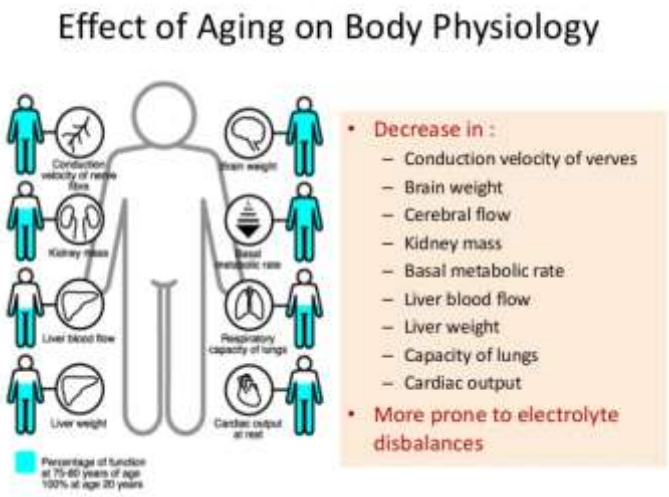


Figure 2: Effect of ageing of body physiology

Although ageing should not be considered a pathological process, physiological changes occur which confer risk and predispose to chronic disease and reduce ability to cope with stressors, such as surgery. The heart, lungs and liver deteriorate most rapidly with advancing age, alongside the kidneys and brain [10].

Assessing patient fitness for surgery

Given the aforementioned risks of oesophagectomy, an accurate assessment of fitness for surgery for each patient is imperative. A patient with greater physiological reserve will be far more likely to overcome the stresses of surgery, which are multi-fold and often unappreciated [12-14], see **Figure 2.** Often, a decision regarding fitness for surgery is made by an Upper GI multidisciplinary team based on patients' past medical history, current staging of the cancer, scan results etc [12]. However, several objective tools also exist such as the Age-related Charlson Comorbidity Index which gives an assessment of the presence or absence of organ dysfunction namely of the liver, kidneys, heart, lungs and brain and takes account of major comorbidities such as AIDS, diabetes and cancer; the higher the score, the greater the prediction of poorer outcome and reduction in survival [15]. Another generally used scoring system is the American Society of Anaesthesiologists grading (ASA) which makes a global assessment of patients' comorbidities and level of function i.e. mobility, activities of daily living etc [16]. The ACCI and the ASA scores both assess fitness for surgery, whereas other scoring systems predict post-operative morbidity and mortality. For example, the O-POSSUM, is the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity, specifically for oesophagogastric procedures. This tool requires physiological parameters such as blood pressure to assess fitness and giving a likelihood of mortality accordingly [17]. Moreover, the Preoperative Nutrition Index (PNI), which was originally validated for liver cancer assesses albumin levels and inflammation, plus immune cell counts, giving an assessment of malnutrition and fitness and can be used in oesophageal cancer [18]. **Figure 3** demonstrates the scoring systems used to assess fitness in patients with oesophageal cancer.

These three example scoring systems have their strengths whereby a study by Scarpa et al. 2015 [12], showed ACCI to be the best tool to assess fitness whereas PNI was the best discriminator of morbidity post-operatively. Nevertheless, the study was performed in a small subset of patients

(n=39). The weakness of these tools is that they all assess different aspects of fitness and risk in different ways, rather than providing a holistic assessment that takes into account combined patient physiology, comorbidity, function, pathology etc. Furthermore, differences in the predictive outcomes (morbidity/mortality) attained by these scoring systems are then difficult to interpret. In addition, these tools are often not validated in the elderly or the frail, hence bringing their validity into question although, on the contrary, the less fit the patient, the more accurate these models tend to be at predicting outcome. Finally, MDT discussion often comes to the same conclusion as these scoring systems, which further questions their utility. Given the disparities, this demonstrates the need for one robust global assessment to be constructed and validated. Moreover, in spite of performing assessments of patient fitness for surgery, complication rates post-oesophgaectomy remain high and mortality remains as high as 9%; we cannot assume that lack of patient fitness is the causative factor for death after surgery, but it is a worthy consideration [12, 13]. Could we have prolonged life by avoiding surgery? How can we get better at assessing patient fitness for surgery? And, is there any way to improve patient's fitness for surgery following a diagnosis of oesophageal cancer but prior to receiving oesophagectomy?!

A

Age-related Charlson Comorbidity Index (ACCI)

1.	50-59yrs=1, 60-69yrs=2, >70yrs	= 3
2.	AIDS	= 6
3.	Metastatic solid tumour	= 6
4.	Mod-Severe Liver disease	= 3
5.	Any non-metastatic tumour	= 2
6.	Malignant lymphoma	= 2
7.	Leukaemia	= 2
8.	Diabetes + end organ damage	= 2
9.	Mod-severe renal disease	= 2
10.	Diabetes -end organ damage	= 1
11.	Mild liver disease	= 1
12.	Ulcer disease	= 1
13.	Connective tissue disease	= 1
14.	Chronic pulmonary disease	= 1
15.	Dementia	= 1
16.	Cerebrovascular disease	= 1
17.	Peripheral vascular disease	= 1
18.	Congestive heart failure	= 1
19.	Myocardial infarction	= 1

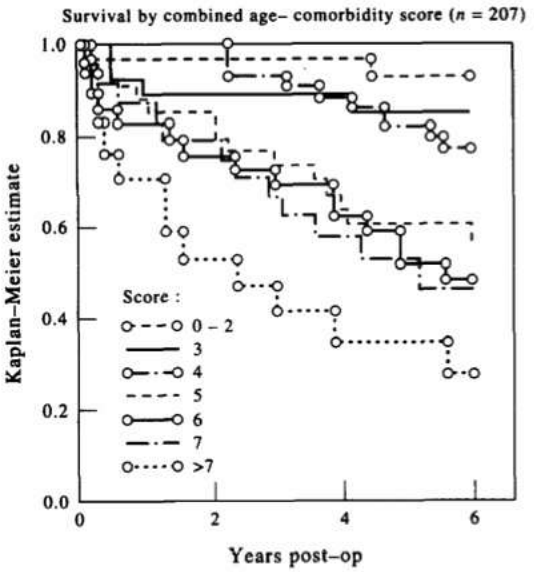


Fig. 3. Survival of patients according to combined age–comorbidity score.

B

Operative Parameters

Operation Type	Oesophagectomy
Malignancy Status	not malignant
CEPOD	elective

Physiology Score	Mortality (%)
11	0.3

C

ASA Classification

ASA Grade	Status	Absolute Mortality (%)
1	Normal healthy patient	0.1
2	Mild systemic disease, or patient over 80 years old	0.2
3	Systemic disease that causes definite functional limitation on life	1.8
4	Severe systemic disease that is a constant threat to life	7.8
5	Moribund patient unlikely to survive 24 hours without surgery	9.4

Figure 3: A-C: Scoring systems for assessing patient fitness for surgery

A number of objective scoring systems are available to assess fitness of a patient with oesophgaeal cancer for oesophgaectomy. A: The AACI score gives points for presence of cormbidites and advancing age and predicts survival [15]. B: The P-POSSUM predicts morbditiy and mortality taking into account physiological factors and the conditions of the operative prcoecure [18]. C: The ASA system is widely used measure of global function and health [16].

The role of physical activity in patients with oesophagaeal cancer

Literature examining the effectiveness of either higher baseline physical activity levels or physical activity interventions prior to oesophagectomy, albeit sparse, show promising results. The remainder of this essay will explore the benefits of physical activity, with a particular focus on patients planned for oesophagectomy for treatment of oesophageal cancer.

The World Health Organisation (WHO) guidelines recommend 150 minutes of moderate activity or 75 minutes of vigorous activity throughout the week for over 65 year olds, stipulating that this is dependent on functional status [19]. Yet, guidelines on sedentary time remain unavailable. MET (Metabolic equivalents-minutes) is defined as the ratio of the individuals metabolic rate during physical activity compared to at rest and is used to grade the intensity of physical activity undertaken [19]. Moderate activity is classed as 3-6 metabolic equivalents (METs) whereas vigorous physical activity is equivalent to ≥6 METs [19-20]. Examples of moderate physical activity include brisk walking, gardening and housework whereas vigorous activity would include carrying heavy loads, running and aerobics [20]. Physical activity is generally associated with lower all-cause mortality, cardiovascular disease and musculoskeletal health in over 65 year olds [19]. On the contrary, sedentary behaviour elicits the inverse of the aforementioned. Sedentary time is defined as ≤1.5 MET and is distinct from lack of physical activity, forming an independent negative predictor of health [21]. In spite of the benefits of physical activity, the older generation remain the most sedentary, with only a minority undertaking exercise [19, 21] The benefits of being physically active are multi-fold and include: reduction in blood pressure, insulin sensitivity, anti-inflammatory sequelae, cardiac conditioning, improved mood and enhanced quality of life [19]. Benefits from physical activity hold true in the aged for example, a study by Pollock et al showed that metabolic health, muscle mass and strength and thymic output are maintained in a cohort of 125 highly active older adults aged 55-79 years [22].

Thus far, studies have considered baseline physical activity levels and assessed exercise tolerance to determine whether this alters risk of cancer and/or postoperative complications, namely cardiopulmonary morbidity.

Review of studies assessing baseline physical activity levels

For example, a recent study by Moore et al, 2016 [23] identified that regular physical activity lowers the risk of developing 13 cancers. The greatest risk reduction was seen for oesophageal cancer whereby the risk was 42% lower in the physically active compared to their sedentary counterparts, regardless of obesity and/or smoking status. In this study, physical activity levels were assessed using the International physical activity questionnaire, a relatively subjective but well validated tool in the young and elderly alike. Likewise, Tatematsu in 2013 [24], showed in an observational (non-interventional) study that lower baseline physical activity levels (i.e. patient undertaking less than 30minutes of brisk walking or equivalent for 5 days a week) in patients planned for oesophagectomy was an independent predictor of postoperative complications in a cohort of 51 Japanese patients. A study by the same group, Nagamatsu et al, 2001 [25], assessed objective exercise tolerance (where patients use a treadmill or exercise bike and keep going until they can't do anymore, i.e. the point of exhaustion) in a cohort of 91 patients (97% male, all smokers) with oesophageal squamous cell cancer, using lung function (spirometry) testing to ascertain expired gas from incremental exercise testing. It was shown that a reduction in maximal oxygen intake or VO_2, (VO_2 is the best indicator of exercise tolerance following incremental exercise) correlated with an increased rate of cardiopulmonary complication post-oesophagectomy equivalent to 86% (VO_2<699ml/min/m^2) compared to those with better exercise tolerance and higher maximal oxygen uptake for whom the complication rate fell dose-dependently from 44% (VO_2=700-799ml/min/m^2) to 10% (VO_2=1100-1199ml/min/m^2). Further statistical testing demonstrated that VO_2 was considered to play a significant role ($p<0.0001$) in the observed increased rate of development cardiopulmonary disease. A retrospective study by Song et al, 2014 [26], took a cohort of patients who had received oesophgaectomy and looked back at their reported dinner-bedtime length and presence or absence of a post0dinner walk to elucidate correlates with risk and poorer patient outcomes in patients with oeosphageal squamous cell carcinoma demonstrating that shorter dinner-bedtime length is harmful whereas post-dinner walk is protective. There are inevitable limitations to this study design (case-control methodology) but the sample size was large with over 200 patients and similar numbers of matched healthy control subjects. Contrary to these aforementioned positive findings, two studies incorporating large patient numbers considered the importance of preoperative physical activity levels and its effect on mortality, although neither study identified a significant benefit of higher physical activity levels. Nevertheless, the documentation of exercise in both studies was somewhat incomplete [27-29].

VO_2 max testing is a sophisticated form of exercise tolerance testing which is usually only available in larger centres. Simpler tools to assess exercise tolerance exist such as shuttle testing, which correlate well with VO_2 max testing. Murray et al [30], showed in a cohort of 53 patients, that those who were more successful at the shuttle walk test (i.e. were more exercise tolerant) and achieved >340m (the shuttle walk test is measured in terms of distance achieved against a timer, much like a runner's bleep test), no deaths occurred whereas 5 of the 8 patients who died within 30 postoperative days scored <340m on the shuttle walk test, hence had reduced exercise tolerance.

Wang et al, 2016 [31], not only considered the role of baseline physical activity levels as a marker of risk for postoperative complication, but also correlated postoperative physical activity levels with survival and quality of life. They elicited in a cohort of 303 patients over a 3year period, that being physically activity post-operatively is likewise beneficial and can prolong overall survival and disability-free survival. Improvements in quality of life were also demonstrated **[Figure 4].**

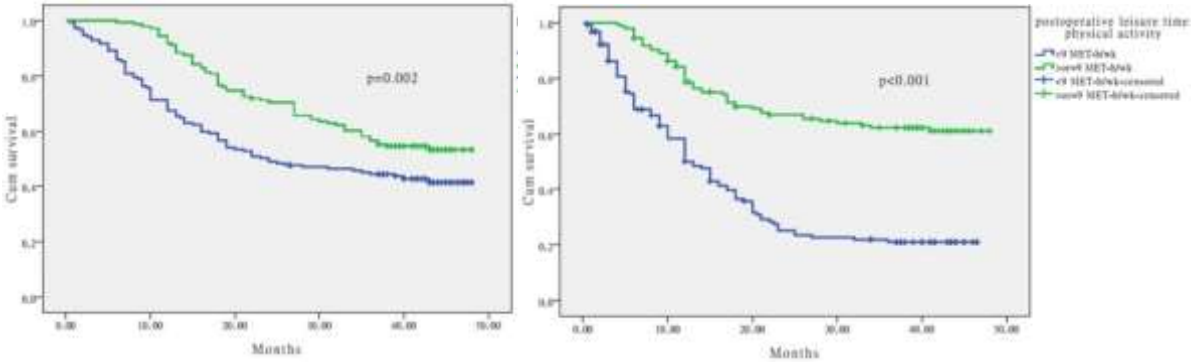


Figure 4: Overall and Disability Free Survival stratified according to levels of physical activity

Wang et al demonstrated that in patients with oesophageal cancer who undertook 9METs, equivalent to 30 minutes of brisk walking for 5 days a week, their overall and disability free survival following oesophagectomy was significantly improved [31].

Review of studies assessing an exercise intervention

It would appear that one published study to date has assessed the efficacy of a physical activity intervention in patients diagnosed with oesophageal cancer who were planned for oesophagectomy. An Australian Randomised Controlled Trial by Winzer et al [32], called the Exercise and Prevention Of Cancer study (EPOC) assessed the efficacy of a 24 week moderate-intensity exercise intervention programme in a population of 33 males (aged 18-70 years) with Barretts oesophagus (a pre-malignant condition) at lowering risk factors which predispose to adenocarcinoma of the oesophagus. The only significant reduction was seen in waist circumference with inflammatory markers and insulin resistance demonstrating no change following the exercise intervention. The study suffered from low sample size (low numbers of patients) and contamination of the intervention i.e. it is hard to prescribe exercise!

A further study by Van Adrichem et al, 2014 [33], assessed the efficacy of a preoperative inspiratory training intervention in patients planned for oesophagectomy for oesophageal cancer, using a randomised, single blind study design (i.e. only the patient did not know the therapy they were receiving; double blind where the healthcare professional and the patient do not know the intervention is optimal, as this eliminates this form of bias). Two forms of inspiratory muscle training were compared and contrasted, i.e. high intensity vs endurance methods, performed over three weeks prior to oesophgaecotmy. 20 and 19 patients were assigned to the comparative interventions but there were some patents who dropped out. For patients who achieved the high intensity training, higher a had lower rates of pulmonary complications compared to patients receiving endurance muscle training although no control comparisons group was present, hence severely limiting the conclusions that can be drawn from this study.

Concluding remarks

Evidently, the evidence base supporting the utility and efficacy of physical activity is lacking. Studies that have been performed lack patient numbers and their study design methodology is inferior. In spite of this, given the overwhelmingly positive findings reported in patients undertaking higher levels of physical activity from the aforementioned studies, this justifies and warrants the performance of higher quality research studies, ideally in the form of a randomised controlled trial implementing an exercise intervention prior to and/or post-operatively to ascertain its efficacy at improving outcomes for patients, i.e. lowering postoperative morbidity, prolonging survival and enhancing quality of life. Only then can we truly appreciate the value of physical activity. Imagine being diagnosed with oesophageal cancer and receiving a script for physical activity or gym membership! I predict that we have only just scratched the surface with regards to the benefits of physical activity in patients with oesophageal cancer.

In conclusion, the impact of diagnosing oesophageal cancer remains immense; incidence is increasing, mortality and morbidity remain high and survival is poor. Although much work has now well elucidated the optimal surgical techniques and chemotherapy regimens, there is still work to do in terms of improving outcomes for patients with oesophageal cancer. There are tools available to assess fitness of patients for curative oesophagectomy, but their utility is disputable. Every doctor dreams of a magic bullet cure for their patients, something cheap, effective, practical and useful; could this take on the form of physical activity?

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