European Journal of Surgical Oncology xxx (2018) 1–6

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Poor performance in incremental shuttle walk and cardiopulmonary exercise testing predicts poor overall survival for patients undergoing esophago-gastric resection☆

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ARTICLE INFO

Article history:
Accepted 30 January 2018
Available online xxx

Keywords:
Esophageal neoplasms
Stomach neoplasms
Preoperative care
Exercise tolerance
Exercise test
Prognosis
Postoperative complications
Survival
Survival rate

ABSTRACT

Introduction: Esophageal and gastric cancer have a poor prognosis and surgical intervention is associated with considerable morbidity, highlighting the need for careful preoperative assessment. The Incremental Shuttle Walk Test (ISWT) and Cardiopulmonary exercise testing (CPET) can assess preoperative fitness. This study aims to investigate their correlation with both postoperative respiratory complications and overall survival.

Patients and methods: Patients were identified who underwent esophageal or gastric resections for cancer between 2010 and 2014 and had ISWT and/or CPET assessments. Tumor differentiation, stage, postoperative respiratory complications, and outcome were documented and then correlated with the results of the preoperative fitness assessments.

Results: Neither the ISWT result, anaerobic threshold (AT) nor VO2 Max correlated well with perioperative complications. However, ISWT ($p < 0.001$), AT ($p < 0.001$) and VO2 Max ($p < 0.001$) all correlated strongly with overall survival. No patient with a score of less than 350 m on ISWT survived beyond 3 years. In a subset of patients with ISWT results both pre and post chemotherapy ($n = 49$), those that had an improvement in result had a 19% incidence of post-operative respiratory complications compared to 45% where the result did not change or declined, though due to small numbers this only approached significance ($p = 0.08$).

Conclusion: ISWT and CPET can be useful preoperative tools to predict overall survival for patients undergoing esophago-gastric resection. Furthermore, patients that improve their functional status during chemotherapy seem to do better than those where it remains static or declines.

Introduction

The incidence of adenocarcinoma of the gastro-esophageal junction is rising faster than any other solid tumor in the western world [1,2] but unfortunately the 5 year survival of patients diagnosed with the disease remains less than 20% and only rises to 40% when patients are considered operable and treated with the most recent combinations of chemo radiotherapy and surgery [3,4]. Furthermore there are data to suggest that patients who survive less than two years never regain their preoperative quality of life after undergoing surgical resection and even those who do take up to one year to recover [5]. We are increasingly considering major surgery for patients who are older with significant co-morbidities. This is particularly relevant to the esophago-gastric cancer population as 58.5% of patients undergoing surgery are over the age of 70 [6], thus emphasizing the importance of careful multidisciplinary preoperative assessment [7].

☆ Based on the abstract presented at BASO 2015 (London), which won the BJS prize.

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https://doi.org/10.1016/j.ejso.2018.01.242
0748-7983/

The assessment of cardiopulmonary fitness before major surgery is required to identify patients who may be at increased operative risk [8] and to highlight comorbidity that can be optimized prior to surgery. Cardiopulmonary fitness assessment can also assist planning the perioperative support that patients may need following their operation as poor exercise tolerance has been correlated with increased risk of post-operative complications [9]. Neoadjuvant chemotherapy is now the standard of care for most patients undergoing treatment for esophago-gastric cancer but a significant proportion of patients will deteriorate in general fitness during their treatment, and this can be difficult to quantify.

There are a number of ways to assess cardiopulmonary fitness. Cardiopulmonary exercise testing (CPET) assesses functional capacity and is a reliable, noninvasive, and objective assessment to evaluate the response of the cardiovascular and respiratory systems to an increase in oxygen demand by measuring the anaerobic threshold (AT) and VO2 max [10,11]. An AT of greater than or less than 11 [10,12] and a VO2 Max of greater than or less than 14 [13] are associated with significant differences in operative mortality. However, it requires specialist equipment and trained operators to conduct and interpret the findings.

An alternative method is the incremental shuttle walk test (ISWT) [14] which is a simple and inexpensive method of assessing functional capacity. ISWT involves a shuttle walk exercise between two cones placed 10 m apart, which is externally paced by audio cues. The participant is required to increase their walking speed to keep up with the pre-determined pace. The result is the distance walked which equates to the number of 10 m shuttles completed. The ISWT provokes a graded cardiovascular response due to being progressive and incremental [15]. Those achieving an ISWT result of greater or less than 350 m have a lower or higher operative risk respectively [8]. Studies have suggested that ISWT and CPET tests correlate well with each other [16,17].

As part of a perioperative enhanced recovery program an assessment of patient fitness was undertaken at initial presentation with OG cancer. The intention was to provide a baseline level of physical function with a subsequent reassessment after neoadjuvant treatment in order to determine the need for optimization and any deconditioning effect of the preoperative regimen. If a patient requires optimization, they are referred to physiotherapy to complete 4–6 weeks of exercise intervention, in the form of supervised cardiovascular and strengthening exercises which are specific and tailored to the patient's needs. In addition to the physiotherapy assessments, all patients undergoing major surgical resections will have an anesthetic pre-operative assessment. This will often include a CPET but this usually occurs after the completion of neo-adjuvant treatment.

The aim of the study was to evaluate preoperative assessments in predicting postoperative respiratory complications and longer term outcome and to determine whether ISWT could quantify the effects of de-conditioning from neo-adjuvant chemotherapy.

Patients and methods

All patients with esophageal or gastric cancer were assessed at initial presentation using a perioperative Enhanced Recovery protocol during the time period 2010–2014. This included a clinical assessment, nutritional assessment and physical activity review using an ISWT as per the published protocol [14]. A proportion of patients also underwent CPET testing [13]. Patients underwent neoadjuvant chemotherapy and surgery or surgery alone according to disease stage. Specifically, data on preoperative clinical stage (based on clinical, endoscopic and radiological information), comorbidity, postoperative pathological stage, postoperative respiratory complications and overall survival were recorded.

The results obtained from CPET and ISWT were correlated by creating scatter plots of the outcome measures and then deriving the R^2 value for their correlation. To determine if there was an association between the preoperative assessments and respiratory complications patients were divided into groups based on previously published cut offs (ISWT Score of less than 350 m versus 350 or higher, anaerobic threshold less than 11 versus 11 or higher, and VO_2 max less than 14 versus 14 or higher). The incidence of respiratory complications was compared between groups using the Chi squared test. To determine if a change in shuttle walk score post neoadjuvant chemotherapy influenced the incidence of post-operative respiratory complications patients were categorized into a decline in score if it fell by >10%, no change in score if it stayed within 10% of the pre-chemotherapy value or an increase in score if it rose by >10%. The incidence of respiratory complications was again compared between groups using the Chi squared test. Multivariable analysis of factors associated with respiratory complications was performed using binary logistic regression.

In order to evaluate if the results from preoperative assessments of fitness correlated with overall survival and cancer specific survival (only considering deaths caused by recurrence of the cancer) the defined groups were compared using Kaplan-Meier survival curves and the Log-rank Mantle-cox test [18,19]. Multivariable analysis was performed using a backwards stepwise cox regression model to determine if each of the assessments was independently prognostic [20]. Both sets of data were combined in IBM SPSS Version 24 (IBM Corp, New York, United States) to allow for statistical analysis. The project was approved by Royal Marsden Committee for Clinical review as a Service Evaluation project (reference SE445).

Results

Patient details

Eighty-one patients who had undergone at least one ISWT assessment were included. The patient demographics, tumor differentiation, TNM stage, Mandard regression score and length of follow up are shown in Table 1.

Comparison of preoperative assessments

73 of the 81 (90%) patients had both ISWT and CPET assessments. ISWT value and AT and ISWT and VO_2 Max correlated poorly with each other ($R^2 = 0.101$ and 0.312 respectively, Supplementary Fig. 1a and 1b). AT and VO_2 Max showed weak correlation ($R^2 = 0.506$, Supplementary Fig. 1c).

Correlation of preoperative assessments with respiratory complications

Neither the ISWT result (Fig. 1a, $p = 0.58$), AT (Fig. 1b, $p = 0.24$) nor VO_2 Max (Fig. 1c, $p = 0.65$) recorded at a single time point individually correlated with the incidence of postoperative respiratory complications.

In a subset of patients with ISWT results both pre and post chemotherapy ($n = 45$), those that had an improvement in ISWT had a 19% incidence of post-operative respiratory complications compared to 45% in those where the ISWT score stayed the same or declined (Fig. 1d, $p = 0.08$).

To determine which preoperative features were associated with post-operative respiratory complications binary logistic regression was carried out with the change (increase or decrease) in ISWT score during chemotherapy, preoperative tumor stage and age entered into the model. In this subset of patients ($n = 45$) only the

Please cite this article in press as: Whibley J, et al., Poor performance in incremental shuttle walk and cardiopulmonary exercise testing predicts poor overall survival for patients undergoing esophago-gastric resection, European Journal of Surgical Oncology (2018), https://doi.org/10.1016/j.ejso.2018.01.242