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Abstract

Title of Study	Radiological and functional assessment of muscle mass in patients undergoing pancreatico-duodenectomy – does this predict outcomes?
Abstract and methodological description	Abstract It is well established that nutritional status has an impact on surgical outcomes

(1, 2), but definitions of malnutrition vary, with a large discrepancy in the incidence of malnutrition depending on the screening tool used (3).

Whilst most nutritional screening tools are validated and correlate with subjective global assessment (SGA)(4), which is considered the gold standard (5), the definition of malnutrition per se has been recognised as an “umbrella term” encompassing simple malnutrition, sarcopenia, frailty and cachexia (6).

New criteria for defining malnutrition were defined by the global leadership initiative on malnutrition (GLIM) in 2019 identifying the need to include both a phenotypic marker (such as weight loss or reduced muscle mass) and an etiologic criterion (such as poor food intake, the presence of an inflammatory condition)(7). The presence of both criteria is required to diagnose malnutrition. The authors then defined moderate or severe malnutrition based on muscle mass or body mass index (BMI) (7). Like many screening tools, this demonstrates a strong specificity when assessed against SGA, but poor sensitivity in those without a low BMI (5).

Studies exploring malnutrition in the context of surgical outcome do not use the GLIM criteria or SGA as a marker of malnutrition. SGA cannot be calculated retrospectively due to specific information required from the patient to complete the scoring criteria (ability to carry out activities of daily living, specific nutrition related symptoms, and need to carry out a clinical assessment). Instead, studies focus on tools utilising BMI and the presence of weight loss. (2, 8, 9). BMI measurements alone are not useful in determining the presence of malnutrition (10), and in clinical practice there remains concern over the underestimation of the presence of malnutrition in the patient with high a high BMI.

More recently, the importance of sarcopenia as a risk factor for post pancreatectomy complications, specifically pancreatic anastomotic leak, (11-13), and survival (14) has become a focus for research. However much of the data in the literature is flawed by the use of single measurements, and an absence of functional assessment. Sarcopenia is defined as a loss of muscle mass and functional capacity (15). Thus, the use of a radiological measure of

muscle mass as a single marker is not a true measure of sarcopenia. The addition of a simple measure, such as sit to stand tests, or hand grip strength will allow the assessment of functional ability. Hand grip strength dynamometry, as part of a nutritional assessment, has been correlated with surgical (16) and oncological outcomes (17).

Some risk factors for pancreatic anastomotic leak are not modifiable pre-operatively, and include male gender, age > 70 years, soft pancreas, narrow pancreatic duct (<3mm), jaundice and liver cirrhosis(18). Intra-operative blood loss is also associated with increased risk.

Research into the prevention of pancreatic anastomotic leak has focused primarily on surgical technique(18) and the use of somatostatin analogues to control any leaks (19). However since the development of enhanced recovery protocol, patients are progressing more quickly onto oral intake(20), which will stimulate the secretion of pancreatic enzymes, and potentially exacerbate any fistula in those at high risk, with some authors already looking at identifying evidence of early leak before implementing ERAS pathways (21).

Aside of smoking status (22), malnutrition is the only modifiable pre-operative risk factor for pancreatic anastomotic leak (18). There is not yet any data to demonstrate improvement in nutritional status reduces risk, thus the exploration of malnutrition is a basis for further research.

At present there is no definitive treatment for sarcopenia, and in the pre-operative setting there is little time for intervention, unless the patient is to undergo neo-adjuvant treatment. However, if sarcopenia truly is an independent risk factor for pancreatic anastomotic leak(11), then knowledge of this prior to surgery may allow the surgical team to stratify management and adopt a more conservative post-operative management protocol, with the aim of reducing the impact of this potentially life-threatening complication.

Aim

The aim of this study is to determine a true measure of sarcopenia in the pre-

operative setting, and analyse the impact of sarcopenia on short and long-term outcomes following pancreaticoduodenectomy.

Research question

Does sarcopenia (low muscle mass and reduced functional capacity) predict post-operative complications following pancreaticoduodenectomy?

Objectives

1) To assess the frequency of sarcopenia in patients due to undergo pancreaticoduodenectomy.
2) To ascertain any correlation between sarcopenia and post-operative complications.
3) To identify patients in whom a more conservative post-operative management plan might reduce the risk and severity of post-operative pancreatic fistulae.
4) To investigate whether radiological sarcopenia correlates with functional assessment and weight loss.
5) To investigate any correlation between malnutrition using the new GLIM criteria and surgical outcomes.

Methodology

Between 2012 and 2016, data was collected on 183 consecutive patients undergoing pancreaticoduodenectomy in a single tertiary centre, as part of a service evaluation project exploring the implementation of an enhanced recovery pathway. Included within this data set are surgical outcomes (graded using Clavien Dindo scores) and nutritional markers, including weight, MUST score and hand grip strength. There are 142 complete data sets. This data set has been selected as the 5-year survival data can now be correlated. Using this data malnutrition will be defined using the GLIM criteria.
We propose to retrospectively analyse changes in muscle mass on computerised tomography (CT) images, and sub-group patients according to the presence/absence of sarcopenia. Once sub-grouped we will correlate with

surgical outcomes.

Primary outcome measures

1) Length of stay
2) Grade III and above post-operative complications (Clavien-Dindo)

Secondary outcome measures

1) Completion of adjuvant chemotherapy

Inclusion criteria

1) Patients who have undergone pancreaticoduodenectomy between 2012 -2016 who have the following:
a. Pre-operative CT images are available
b. Pre-operative grip strength measurements
c. Pre-operative body weight and % weight loss prior to surgery
d. Documented post-operative complications classified using Clavien-Dindo

Exclusion criteria

1) The presence of ascites or intra-abdominal collections, which will distort the muscle mass measurements
2) The presence of metal implants in the image field
3) The presence of significant abdominal hernia in the image field
4) CT images where the abdominal wall is outside of the image field

Muscle mass analysis

Image selection will take place with the support of a Consultant Radiologist to ensure images are correctly selected at the third lumbar vertebra (L3). L3 (5cm above L4/5) has been identified as the area where muscle mass is best correlated with whole body muscle volume (23).
Once identified, scans will be coded, and analysed by a different researcher,

thus blinding the analysis. Nutritional data will be not be collected until after image analysis is completed to further reduce the risk of confirmation bias.

Muscle will be determined using tissue specific Hounsfield units (HU) of -29 to 150 for skeletal muscle, -190 to -30 for subcutaneous and inter-muscular adipose tissue, and -150 to -50 for visceral adipose tissues. The measurement of HU allows for the analysis of the quality of the muscle, as the presence of fat within the muscle will reduce the HU (23).

Body composition analysis will be undertaken using Slice-o-matic 5.0 (Tomovision, Canada).

Staff training

Prior to data collection, all investigators will undertake training and repeated assessment of a series of images to ensure intra and inter investigator coefficient of variation (CV%) is < 2.5%, in line with best practice (24). Every 25th image will be re-analysed by 2 investigators to ensure the CV% remains <2.5%.

Three measurements will be taken for each scan and the mean measurement used for analysis.

Statistical analysis

Data will be analysed for correlations between muscle mass, hand grip strength, weight loss, surgical outcomes and length of stay. Survival data will be analysed by Kaplan Meier estimations, with further sub-grouping according to nutritional status and oncological findings. Initiation and completion of adjuvant chemotherapy will also be associated with presence/absence of sarcopenia.

Limitations

The retrospective nature of this project may result in inability to achieve

complete data sets. However, the service evaluation project was conducted prospectively, with 100% complete data for post-operative complications, and a total of 142 complete data sets for nutritional data. Demographic and complication analyses will be undertaken for the 41 patients in whom there are incomplete data sets to ensure the analysed data is representative of the whole sample population.

Selection bias has been largely removed by the use of consecutive data sets. All CT images have been imported onto the hospital PACS system where they can be analysed using Slice-o-matic. Previous plans for this project involved the use of a free software package (Image J), but this introduced significant limitations, as Image J is not able to analyse imported images. This would introduce a large geographical selection bias, as most pre-operative CT scans are carried out in other “spoke” hospitals, and therefore would be excluded from the analysis. Therefore, the use of Slice-o-matic is required, compared to a free piece of software.

There is a possibility of selection bias due to the need for the whole abdomen to be included within the image field, therefore those patients whose abdominal circumference exceeds the radiological field would be excluded. Initial analysis of the data set indicates only 13/183 (7%) patients had a body mass index (BMI) over 30 kg/m2, 2 (1%) had a BMI over 35 kg/m2 and all BMI’s were under 40kg/m2 with the highest body weight being 120kg. Therefore, the impact of this should be minimal.

Researchers will be blinded when undertaking image analysis, Clavien-Dindo scoring was completed by surgical registrars, who had no access to the remaining data set, and length of stay data was collected retrospectively, thus reducing confirmation bias.

Confounding variables

Data on variables that may also impact both the change in nutritional status pre-operatively and post-operative outcomes were also collected during the original service evaluation. For example, pre-operative jaundice, smoking

status, as well as the presence of diabetes, pancreatic exocrine insufficiency and gastric outflow obstruction were all collected. Multivariate analysis will be undertaken to ascertain any independent predictors between the variables and outcomes.

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Timetable

Name	Staff recruitment
Date	30.09.2021

Name	Staff training
Date	30.10.2021

Name	Data Collection
Date	30.10.2022

Name	Data Analysis
Date	30.12.2022

Name	Write up
Date	30.01.2023

Name	Submit for publication
Date	30.01.2023

Funding

Name	Slico-o-matic software, initial and year one licence. $4500 (current conversion $1 = £0.72. ~ £3227),
Amount	3227.0

Name	Publication Fees
Amount	2000.0

Name	Statistical support
Amount	250.0

Details of ethical approval

The original project was performed as a service evaluation (HRA form 2012). This current project is classified as audit, due to the retrospective nature of the study.

Institutional approval information

Original letter of approval for the service evaluation audit in 2013.
Current instititional audit permissions submitted for this retrospective project

Declaration

Confirm Declaration: Yes

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