Is psoas muscle area as determined by cross-sectional measurement an accurate predictor of peri-operative outcomes in adenocarcinoma of the upper gastrointestinal tract?

Mark Divey[1], Galya Chinnery[1], Anna-Lena du Toit[2], Lode van Dijk[3], Eduard Jonas[4]

[1]

Upper Gastrointestinal Surgery Unit, Department of Surgery, University of Cape Town, South Africa

[2]

Chief Dietician, Department of Dietetics, Groote Schuur Hospital

[3]

Medical Student, Department of Surgery, University of Amsterdam, Netherlands

[4]

Professor and Head Surgical Gastroenterology, Department of Surgery, University of Cape Town, South Africa

Student

Dr Mark Divey

DVYMAR002

Master's in medicine

University of Cape Town

Supervisors:

Dr Galya Chinnery: Upper Gastrointestinal Surgery Unit, Department of Surgery, University of Cape Town, Cape Town, South Africa.

Professor Eduard Jonas: Surgical Gastroenterology Unit, Department of Surgery, University of Cape Town, Cape Town, South Africa

University of Cape Town

The copyright of this thesis vests in the author. No quotation from it or information derived from it is to be published without full acknowledgement of the source. The thesis is to be used for private study or non-commercial research purposes only.

Published by the University of Cape Town (UCT) in terms of the non-exclusive license granted to UCT by the author.

University of Cape Town

This thesis is submitted in a publication-ready format with a literature review and completed manuscript.

TABLE OF CONTENTS

LIST OF TABLES AND FIGURES

DECLARARTION

I, **Mark Divey**, hereby declare that the work on which this dissertation/thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or will be submitted for another degree in this or any other university.

I empower the university to reproduce for the purpose of research either the whole or any portion of the contents in any manner whatsoever.

Signature: Signed by candidate

Date: 22/09/2021

ABSTRACT

Background

Radiologically measured psoas muscle area has been associated with poorer surgical outcomes. Our hypothesis is that patients with gastric cancer and lower psoas muscle area have poorer short-term surgical outcomes.

Methods

Individuals with gastric cancer were assessed and total psoas muscle area (TPA) in mm^2 was measured at the level of the third lumbar vertebra on staging CT, using Phillips IntelloSpace PACS Enterprise version 4.4.553.50. The psoas muscle area was normalised for height (TPA mm^2/m^2), creating the psoas muscle index (PMI). All individuals proceeding to surgery were compared in terms of PMI with correlation to short-term complications (Accordion), length of stay and mortality. In addition, PMI and tumour staging was evaluated.

Results

One hundred and seventy-seven individuals (115 males, 62 females, mean age of 60.8 ± 0.9) were evaluated of which sixty-eight underwent surgery (56 resections, 12 palliative bypasses). The surgical complication rate was 40% (27/68), major complications being Accordion 3 or higher at a rate of 16% (11/68) and mortality rate of 10% (7/68). The average length of stay was 10 ± 0.7 days. There was no statistically significant difference in PMI for males or females in respect to all complications, major complications, length of stay or mortality. PMI and tumour staging did not correlate. Males with gastric outlet obstruction had a statistically significant lower PMI (p <0.03)

Conclusions

Although low psoas muscle area has been shown to correlate with poorer surgical outcomes, we did not show this is our population undergoing surgery for gastric cancer.

[Word count: 247]

ACKNOWLEDGEMENTS

I would like to acknowledge and thank all the individuals that were involved in the study at Groote Schuur Hospital.

I would also like to thank my colleagues in the assistance and management of these individuals.

CONTRIBUTIONS

- **Dr Galya Chinnery (supervisor):** Concept for thesis, planning and supervision, manuscript preparation.
- **Professor Eduard Jonas:** Oversight of final manuscript preparation.
- **Anna-Lena du Toit:** Anthropometric data collection
- **Lode van Dijk:** Database creation and data collection.
- **Dr Karen Vickers:** Statistical support and data analysis

LITERATURE REVIEW

INTRODUCTION

Background of gastric cancer

Gastric cancer is a common and deadly form of cancer worldwide with an estimated 1 033 701 new cases and 782 685 deaths in 2018, making it the sixth most prevalent and second deadliest form of cancer.[1] 5-year survival rates for gastric cancer are dependent on stage at presentation, but given the often non-specific symptoms, up to 50% of patients present with either locally advanced or metastatic lesions and only half of those with initially resectable disease will undergo surgery.[2,3] As surgery has the best chance of curative treatment, optimising surgical outcomes should be on the forefront of management for these patients. In an attempt to minimise complications there are certain fields that need focus, with one of them being nutrition or more specifically malnutrition.

Malnutrition in gastric cancer is multifactorial due to decreased food intake with progression of the gastric lesion, as well as cachexia associated with malignancy, as contributing factors. The complex biochemical interaction with tumour necrosis factor-α, interleukin-1, interleukin-6 and leptin dysregulation leads to decreased appetite, muscle mass and adipose tissue, eventually leading to weight loss. The malnutrition that follows is associated with post-operative complications in gastric cancer surgery.[4] Avoiding post-operative complications is a clear goal, especially as they are associated with a decreased survival amongst patients that had resectable gastric cancer, and with complication rates following gastrectomy reported between 20-46%, this needs to be an area of focus.[5]

Sarcopenia

The European Working Group on Sarcopenia in Older People (EWGOP) has defined sarcopenia as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death.[6] This entity has become increasingly important in the management of many medical conditions and especially cancers. As gastric cancer has a strong association with

weight loss and subsequent malnutrition, the relationship between gastric cancer and sarcopenia is clearly a point of discussion.

There are several risk factors for the development of sarcopenia, including lifestyle lacking exercise and hormone and cytokine imbalances, especially TNF-α and IL-6. The progressive nature of cancer leads to a decreased in physical exercise and associated biochemical disturbances places individuals with gastric cancer at risk of developing sarcopenia.

LITERATURE REVIEW OBJECTIVES

This literature review aims to determine the current evidence relating sarcopenia and gastric cancer, with a focus on low psoas muscle mass and complications following surgery. Additional areas of interest include the association between psoas muscle measurements on computer topography and surgical outcomes as well as the relationship between psoas muscle volume and sarcopenia or total skeletal muscle measurement.

LITERATURE SEARCH STRATEGY

The online database, PubMed, was used for review of relevant literature. The literature was reviewed up until January 2021 and only English and full text articles were reviewed.

The following search terms were used:

- Gastric cancer
- Sarcopenia
- Psoas muscle measurement
- Surgical outcomes

SUMMARY OF FINDINGS

Psoas muscle area and gastric cancer

There are two studies published directly relating psoas muscle measurements with gastric cancer. The first was published by Taniguchi *et al* looking at the impact of pre-operative psoas muscle mass index on post-operative short and long-term outcomes in patients with gastric cancer.[7] A total of 567 patients undergoing curative gastrectomy were divided into 2 groups based on psoas muscle area on a pre-operative CT scan, low and high, so named PMI-L and PMI-H, and their outcomes after surgery were assessed. The PMI-L was an independent risk factor for post-operative pneumonia and a significantly worse recurrence free survival than the PMI-H group and may therefore be useful as a prognostic factor. Interestingly, there was no difference in post-operative complication incidence between the PMI-L or PMI-H groups nor in overall incidence of post-operative complications.

Looking at the data set, they had a high proportion of pathological stage 1 disease with 67% of the cohort. There was also no statistical significance between the PMI groups and pathological stage. The overall complication rate was 25%, on the lower end of the range of 20-46%, quoted by Li *et al*.[5] The reference range for sarcopenia was based on a review of 541 healthy liver donor patients in Japan published by Hamaguchi *et al*. Although appropriate for this specific population, it may not be accurate to apply these values elsewhere.[8]

Yamaguchi *et al* published a paper in 2017 trying to ascertain if changes in psoas muscle area post gastrectomy had any clinical significance.[9] One hundred and nineteen patients that underwent gastrectomy for malignancy had pre-operative psoas major muscle area (PMMA) measured, then regular interval measurements post-operatively for 5 years. The patients were split into two groups post-operatively, no recurrence and R2 resection/recurrence, with PMMA compared between these two groups. There was a decrease in PMMA in both groups and a significant difference at 2 years post-operatively. The PMMA was significantly lower in the R2/recurrence group, in keeping with the weight loss and cachexia associated with gastric cancer.

The authors concluded that it is important to observe PMMA change in routine imaging as a significant decrease might be associated with recurrence. The authors did state however that

recurrence in their cohort was almost exclusively diagnosed by CT imaging, thereby negating the need to look for recurrence in a patient with decreasing PMMA. Despite this, it does show the association between gastric cancer and decreasing muscle volume, specifically the psoas major muscle.

The body of work correlating psoas muscle measurements with gastric cancer post-operative complications is small and predominantly published in Asia. This provides a unique opportunity to assess the characteristics of the South African population with gastric cancer and psoas muscle measurements.

Psoas muscle area and surgical outcomes

There are a multitude of studies evaluating if psoas muscle area is related to outcomes within various fields of surgery. There has been work done in numerous areas including both malignant and benign surgery.

Womer *et al* specifically looked at total psoas muscle volume and area (TPA/TPV) in the setting of rectal cancer and whether there was an association with outcomes.[10] Their hypothesis was that smaller pre-operative TPA/TPV would be associated with increased morbidity following rectal cancer surgery. This was a retrospective review of 180 patients undergoing curative surgery for rectal cancer at the Cleveland Medical Centre. The imaging was done within 90 days of surgery and patients with a serum albumin of less than 30g/dl or reported >10% body weight loss prior to diagnosis were classified as malnourished, although this category was very small with only 8 of the 180 patients. This group did show significantly lower median TPA compared to the non-malnourished group, although with very small numbers. Looking at the main hypothesis, there was no difference in TPA or TPV for patients that experienced any post-operative complication (44% of cases), but interestingly there was a statistically significant lower TPA/TPV for those that experienced major complications (defined as Clavien-Dindo >2) compared to minor complications.

Peng *et al* assessed the impact of total psoas muscle area (TPA) on the outcomes of patients following curative surgery for pancreatic cancer.[11] This was a retrospective review of the Johns Hopkins Hospital pancreas database between 1999 and 2010. There were 557 records with imaging available within 30 days of surgery. Here the total psoas muscle area was measured using the cross-sectional area of the right and left psoas muscle at the level of L3; this was

adjusted for height and the hypothesis was that a preoperative sarcopenia would lead to worse short and long-term outcomes in patients undergoing surgery for pancreatic adenocarcinoma. Their cohort had an overall complication rate of 46.6%; including 18.7% with major complications. The presence of sarcopenia was not associated with risk of morbidity or severity of complications. The interesting aspect of this cohort was looking at the 3-year survival data, where several factors were associated with decreased survival. These factors included tumour size, poor differentiation, vascular invasion and lymph node metastasis. Sarcopenia, defined by the authors as patients in the lowest quartile for TPA, was associated with the risk of death at 3 years with a HR = 1.68 (95% 1.34-2.11; P<0.001). After controlling for tumour specific factors, sarcopenia remained independently associated with decreased survival at 3 years.

These two studies have both looked at psoas area from an oncological surgery perspective and have been associated with poorer outcomes. As malignancy is associated with cachexia, weight loss and malnutrition, this may contribute to the decrease in psoas muscle. The following three studies evaluated psoas muscle area and surgical outcomes in non-oncological surgery to evaluate if this association remains.

Lee *et al* hypothesized that decreased core muscle size, as measured by psoas cross-sectional area, will have an increased mortality after open repair of abdominal aortic aneurysms.[12] This retrospective review assessed 262 patients from 2000 to 2008 undergoing elective open AAA repair with all having a pre-operative CT scan within 90 days of surgery. The measurement of the psoas muscle area at the fourth lumbar vertebra was totalled resulting in the TPA, although not corrected for height. The cohort was followed post-operatively until death or loss to follow up. Their cohort was followed for 2.3 years, and they had 55 deaths in that period. Cox regression showed a significant association between psoas muscle area and postoperatively mortality with the effect of psoas area decreasing over time.

Zager *et al* conducted a review to see if there was an association between sarcopenia, as assessed by psoas muscle surface area (PMA), and post-operative outcomes in individuals with Crohn's disease.[13] Their retrospective review of 121 patients undergoing elective and semi-elective resections between 2009-2018 measured psoas muscle area on CT imaging done less than 30 days prior to surgery. The measurement was blinded to the researchers. The complication rate for surgery was 26% and the mean PMA was lower in those presenting with post-operative complications compared to those without complications (854.3+-226.3mm^2 vs

984.5+-267.8mm^2, P=0.02). Further division into quartiles of PMA measurement showed considerably higher rates of major and overall complications in the lowest quartile. Anastomotic leak in resectional surgery is of particular importance, and they showed a lower mean PMA in patients with a leak compared to those without leaks, although with a small number of leak cases. Within their cohort of patients, low PMA was significantly associated with post-operative complications. The patients were stratified into TPA tertiles to evaluate survival and the impact of low TPA is greatest shortly after the operation. There was a significant effect on mortality at 90 days and mortality increased as the psoas muscle area decreased to a HR = 3.01 per 1000mm^2 decrease in TPA. This remained significant after adjusting for co-morbidities.

The final paper was published by Paknikar *et al* and used psoas muscle measurement as a surrogate for frailty within the study cohort of patients undergoing both surgical and transcatheter aortic valve replacement.[14] This retrospective review included 295 patients undergoing aortic valve replacement with 156 surgical and 139 transcatheter aortic valve replacement and used psoas muscle area on imaging done less than 90 days prior to the procedure. The psoas muscle areas were significantly different between males and females, with analysis standardised by gender. A TPA 1 standard deviation below the mean increased the occurrence of early poor composite outcome by 48%. Along with this, there was an association between sarcopenia and lower 2-year survival (85.7% sarcopenia vs 93.8% without), as well as being an independent predictor of higher resource utilisation (OR 0.56 *p*=.001). The Society of Thoracic Surgeons risk score is used to predict morbidity and mortality and relies upon a multitude of variables, interestingly though, frailty is not one. There was a lack of correlation between the STS scores and TPA within the two groups, suggesting a possible unique risk assessment tool.

Although the evidence is not consistent, there are definitely signals that low psoas muscle volume is associated with poorer outcomes in surgery. There are some conflicting results regarding short- and long-term complications and survival, but there are indications present throughout the literature that low psoas muscle volumes are associated with poorer outcomes.

As psoas muscle measurement is a relatively simple task compared to total skeletal muscle measurements, it would be beneficial to determine if psoas muscle area correlates with overall skeletal muscle measurements. Specific cut-off values for low psoas muscle mass would improve the ease of use.

Psoas muscle measurements

Sarcopenia is defined by the EWGSOP2 as a syndrome involving primarily loss of strength and muscle mass with a variety of confirmatory questionnaires and tests.[6] Although the primary entity of sarcopenia is loss of strength, the measurement of muscle mass has become an important aspect. Imaging modalities such as CT and MRI are used regularly in the work-up and staging of many conditions; as such CT or MRI has become the gold standard in measuring muscle mass.[15] The measurement of skeletal muscle mass can be difficult and with the regular use of CT imaging in investigations, along with it being the gold standard of muscle measurement, the use of alternative muscle groups as a surrogate has been proposed. The EWGSOP2 does list psoas muscle measurement as a possible alternative, but further studies are required. The following articles presented use psoas muscle measurement and as the body of literature expands, this may become an easier metric for use.

Hamaguchi *et al* investigated skeletal muscle mass determined by the psoas muscle mass index (PMI) from living related liver donors and attempted to use the data to establish low muscle mass cut off values.[8] This retrospective review collected imaging data from 541 subjects with manual tracing of the psoas area at the third lumbar vertebra with corrections for height. The authors recognised the concerns in using PMI as a surrogate for total skeletal muscle mass and therefore performed simultaneous bioimpedance assessments (BIA) on a cohort of their subjects. The results showed a strong and significant correlation between PMI and the skeletal muscle index (SMI) as measured by the BIA. ($r = 0.737$, $P<0.001$). Their results have suggested that PMI can be used as a surrogate for total SMI. In addition, the authors produced cut off values for 2 standard deviations below the mean PMI in patients under the age of 50 years. These values are 6.36cm^2/m^2 for males and 3.92cm^2/m^2 for females. These values may however be population specific and not transferable. The importance of the 2 standard deviations from mean is derived from the EWGSOP recommendation, this being the value below which sarcopenia is considered present.

In a similar study, Kim *et al* measured cross sectional area of the psoas muscle at L3 in a health screening department in Korea over a 10-year period.[16] This was a larger cohort of 1422 people with no co-morbidities. The aim was to create age-specific cut off values for low skeletal muscle mass using psoas muscle measurements. The cut off values for ages 20-39 for males was 5.92cm^2/m^2 and 3.99cm^2/m^2 for females. These are similar to the values Hamaguchi

produced. Here too a statistically significant correlation was established between the PMI and SMI (r = 0.650, p<0.001). While both studies were performed in Korean populations, both confirm a statistically significant correlation between PMI and SMI.

Derstine *et al* has reported a reference range cross sectional area of the psoas muscle in 1245 potential kidney donors.[17] The cohort was a retrospective review in Michigan, USA, but unlike the previous papers, used the fourth lumbar vertebra as a reference point for psoas muscle cross sectional area and as such cannot be directly compared to Kim and Hamaguchi's work. The only cut off value of psoas muscle index at L3 outside of Asia was done by Bahat *et al*.[18] In a similar population to the previous studies, 601 individuals were evaluated during living related liver donation in Turkey. Two cut-off values were determined, one being the 5th percentile value and the other the mean minus 2 standard deviations. The PMI 5th percentile was 5.4cm^2/m^2 for males and 3.6cm^2/m^2 for females. Using 2 standards deviations from mean resulted in values of 4.6cm^2/m^2 for males and 2.7cm^2/m^2 for females. The values are slightly lower than Kim and Hamaguchi but are presently the only reported cut off values for PMI outside of Asia.

To conclude, there is unquestionably a trend towards poorer surgical outcomes with low psoas muscle mass, although limited evidence specifically in gastric cancer. While the EWGSOP has not advocated for the use of psoas muscle measurement specifically in the diagnosis of sarcopenia, there are an increasing number of studies correlating psoas muscle indexes to total skeletal muscle indexes. This allows for a unique opportunity to determine if in the South African population there too exists a correlation between low psoas muscle mass and surgical outcomes. We will be focussing on gastric cancer patients and hope to answer this question with our study.

REFERENCES

1. Bray, F., et al., *Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries.* CA: A Cancer Journal for Clinicians, 2018. 68(6): p. 394-424.
2. Mansfield, P., *Clinical features, diagnosis, and staging of gastric cancer*, in *UpToDate*, K.K. Tanabe, J, Editor.: UpToDate, Waltham, MA (Accessed on January 11, 2021).
3. Recio-Boiles, A. and H.M. Babiker, *Gastric Cancer*, in *StatPearls*. 2020: Treasure Island (FL).
4. Kubota, T., et al., *Nutrition update in gastric cancer surgery.* Ann Gastroenterol Surg, 2020. 4(4): p. 360-368.
5. Li, J., et al., *Impact of postoperative complications on long-term outcomes of patients following surgery for gastric cancer: A systematic review and meta-analysis of 64 follow-up studies.* Asian J Surg, 2020. 43(7): p. 719-729.
6. Cruz-Jentoft, A.J., et al., *Sarcopenia: revised European consensus on definition and diagnosis.* Age Ageing, 2019. 48(4): p. 601.
7. Taniguchi, Y., et al., *Impacts of Preoperative Psoas Muscle Mass and Visceral Fat Area on Postoperative Short- and Long-Term Outcomes in Patients with Gastric Cancer.* World J Surg, 2020.
8. Hamaguchi, Y., et al., *Proposal for new diagnostic criteria for low skeletal muscle mass based on computed tomography imaging in Asian adults.* Nutrition, 2016. 32(11-12): p. 1200-5.
9. Yaguchi, Y., et al., *Clinical Significance of Area of Psoas Major Muscle on Computed Tomography after Gastrectomy in Gastric Cancer Patients.* Ann Nutr Metab, 2017. 71(3-4): p. 145-149.
10. Womer, A.L., et al., *Do psoas muscle area and volume correlate with postoperative complications in patients undergoing rectal cancer resection?* Am J Surg, 2018. 215(3): p. 503-506.
11. Peng, P., et al., *Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma.* J Gastrointest Surg, 2012. 16(8): p. 1478-86.
12. Lee, J.S., et al., *Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair.* J Vasc Surg, 2011. 53(4): p. 912-7.

13. Zager, Y., et al., *Low psoas muscle area is associated with postoperative complications in Crohn's disease.* Int J Colorectal Dis, 2021. 36(3): p. 543-550.
14. Paknikar, R., et al., *Psoas muscle size as a frailty measure for open and transcatheter aortic valve replacement.* J Thorac Cardiovasc Surg, 2016. 151(3): p. 745-751.
15. Beaudart, C., et al., *Sarcopenia in daily practice: assessment and management.* BMC Geriatr, 2016. 16(1): p. 170.
16. Kim, J.S., et al., *Simple Age Specific Cutoff Value for Sarcopenia Evaluated by Computed Tomography.* Ann Nutr Metab, 2017. 71(3-4): p. 157-163.
17. Derstine, B.A., et al., *Quantifying Sarcopenia Reference Values Using Lumbar and Thoracic Muscle Areas in a Healthy Population.* J Nutr Health Aging, 2017. 21(10): p. 180-185.
18. Bahat, G., et al., *Cut-off values of skeletal muscle index and psoas muscle index at L3 vertebra level by computerized tomography to assess low muscle mass.* Clin Nutr, 2021 Jun;40(6):4360-4365. doi: 10.1016/j.clnu.2021.01.010. Epub 2021 Jan 16. PMID: 33516603

PUBLICATION-READY MANUSCRIPT

TITLE PAGE:

Is psoas muscle area as determined by cross-sectional measurement an accurate predictor of peri-operative outcomes in adenocarcinoma of the upper gastrointestinal tract?

Mark Divey[1], Galya Chinnery[1], Anna-Lena du Toit[2], Lode van Dijk[3], Eduard Jonas[4]

[1]

Upper Gastrointestinal Surgery Unit, Department of Surgery, University of Cape Town, South Africa

[2]

Chief Dietician, Department of Dietetics, Groote Schuur Hospital

[3]

Medical Student, Department of Surgery, University of Amsterdam, Netherlands

[4]

Professor and Head Surgical Gastroenterology, Department of Surgery, University of Cape Town, South Africa

Word count: 2222

Short Title: Psoas muscle area and gastric cancer surgical outcomes

Key words: Psoas muscle area, Gastric cancer

Disclosures: Nil

Conflicts of interest: No conflicts of interest declared

Funding information: Nil

MANUSCRIPT:

Is psoas muscle area as determined by cross-sectional measurement an accurate predictor of peri-operative outcomes in adenocarcinoma of the upper gastrointestinal tract?

INTRODUCTION

Gastric cancer is the sixth most prevalent and second deadliest form of cancer, with an estimated 1 033 701 new diagnoses and 782 685 attributable deaths in 2018.[1] The 5-year survival rates are largely dependent on stage at presentation, with up to 50% presenting with either locally advanced or metastatic disease. Even with resectable disease, only half of patients eventually undergo surgery.[2,3] Neoadjuvant therapy with surgery provides the best chance of curative treatment and as surgery is the definitive step in treatment, optimising surgical outcomes must be on the forefront of management. The presence of gastric cancer negatively influences nutrition; in addition pre-operative malnutrition has confirmed poorer outcomes in gastric cancer surgery.[4,5] Post-operative complication rates are in the range of 20-46%, resulting in decreased survival amongst individuals with resectable cancers.[6] As malnutrition increases risk of post-operative complications it clearly is a focus point in improving outcomes.

The European Working Group on Sarcopenia in Older People (EWGOP) has defined sarcopenia as a syndrome characterised by progressive and generalised loss of skeletal muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of life, and death.[7] Malnutrition, weight loss and subsequent loss of muscle mass is a hallmark of gastric cancer. This loss of muscle mass may provide a potential prognostication of surgical outcomes in gastric cancer leading to a potential field of further investigation. Cross-sectional imaging is performed routinely for gastric cancer staging, providing an opportunity to evaluate skeletal muscle quantity simultaneously. The correlation between psoas muscle area and skeletal muscle area in cross-sectional imaging has been demonstrated and provides a simple and reliable tool for quantifying low muscle mass.[8,9] Our hypothesis is that a decreased psoas muscle area as assessed on initial cross-sectional imaging is associated with poorer outcomes in gastric cancer surgery. The data also allows us to evaluate the relationship between stage and psoas muscle area.

METHODS

Study design and oversight

This single centre study aimed to retrospectively assess psoas muscle area in gastric cancer and to investigate potential correlation with surgical outcomes. Ethics approval was obtained from the University of Cape Town's Human Research Ethics Committee, HREC number 841/2017.

Study population

Gastric cancer patients presenting to the Upper Gastrointestinal Unit at Groote Schuur Hospital between 1st January 2014 and 31st December 2020 were selected from an approved database. Clinical and pathological information was collected, including demographics, anthropometrics, staging, type of surgery, complications of surgery and length of stay. Complications were scored using the Accordion grading system for surgical complications.[10]

Study procedure

The psoas muscles were assessed using computed topography (CT) imaging performed during staging work-up. In individuals undergoing surgery, all evaluated imaging was performed within 90 days of the operation. The total psoas muscle area (TPA) was measured in mm^2 as the sum of the left and right psoas muscles (See Appendix for measurement graphic) on axial images at the level where both transverse processes of the 3rd lumbar vertebrae are visible. The area was measured by outlining the left and right psoas muscles, to provide a measurement in mm^2, with calculations performed using the programming available on Phillips IntelloSpace PACS Enterprise version 4.4.553.50. Two reviewers independently assessed the axial psoas muscle areas with the average applied as the final value. A psoas muscle index (PMI) was then calculated using the TPA divided by height squared ($PMI = TPA/m^2$).

Statistics

All values are expressed as a mean with standard error reported. The T-test was used when comparing PMI between groups and Chi-squared test used when PMI values were grouped to compare stages. For all analyses, $p < 0.05$ was considered significant.

RESULTS

Clinical and pathological characteristics

There were 183 records and 6 were excluded as there was missing data, including anthropometric measurements and incomplete staging. Complete datasets were available in 177 and these were included for analysis. The clinical and pathological characteristics of the 177 participants are described in Table 1. The mean age at presentation was 59,1±1,6 years for females and 61,1±1,1 for males. The majority, 52% (n=92), of our cohort presented with stage 4 disease, when using the AJCC staging criteria. The anatomical distribution of the cancers were 85% (n=151) non-cardia and 15% (n=26) cardia. Within the larger non-cardia group a substantial proportion (28%, n=50) presented with gastric outlet obstruction (GOO).

Anthropometric measurements

The anthropometric measurements of the cohort were reported as body mass index (BMI) and PMI. The mean PMI was 414,3±13,4 for females and 590,4±17,2 for males. The range was variable, with males having a slightly higher distribution (Figure 1).

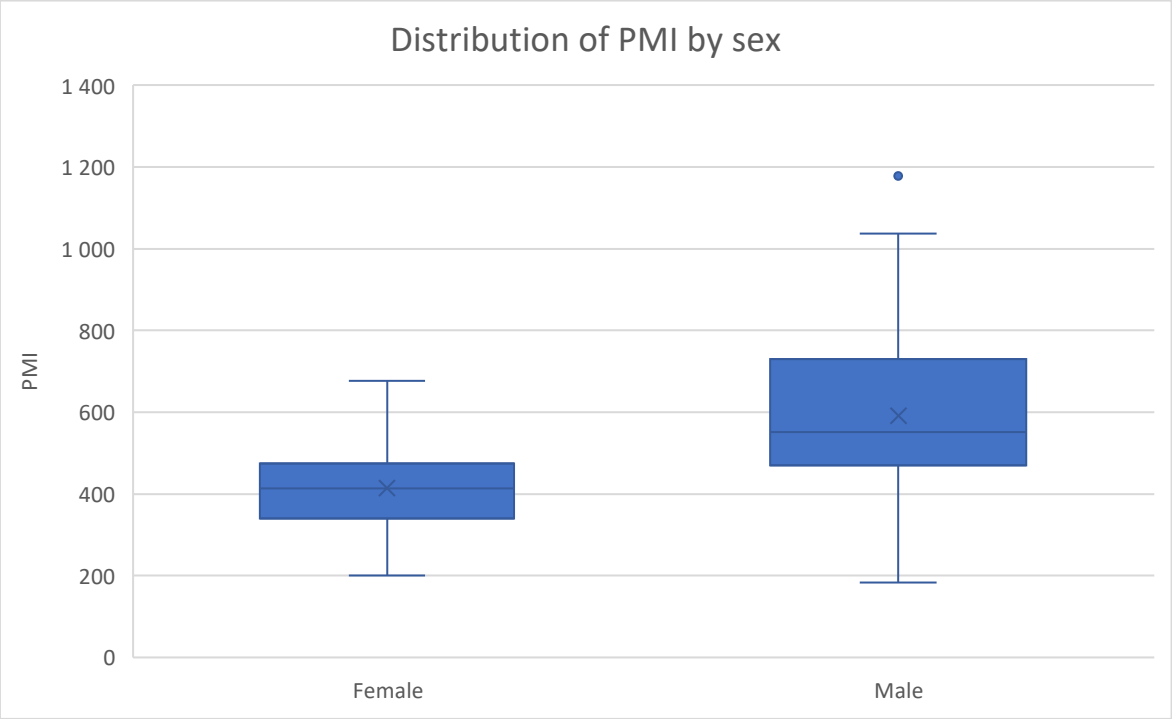


Figure 1: Distribution of PMI by sex

There was no correlation between age and PMI in either sex (Figure 2).

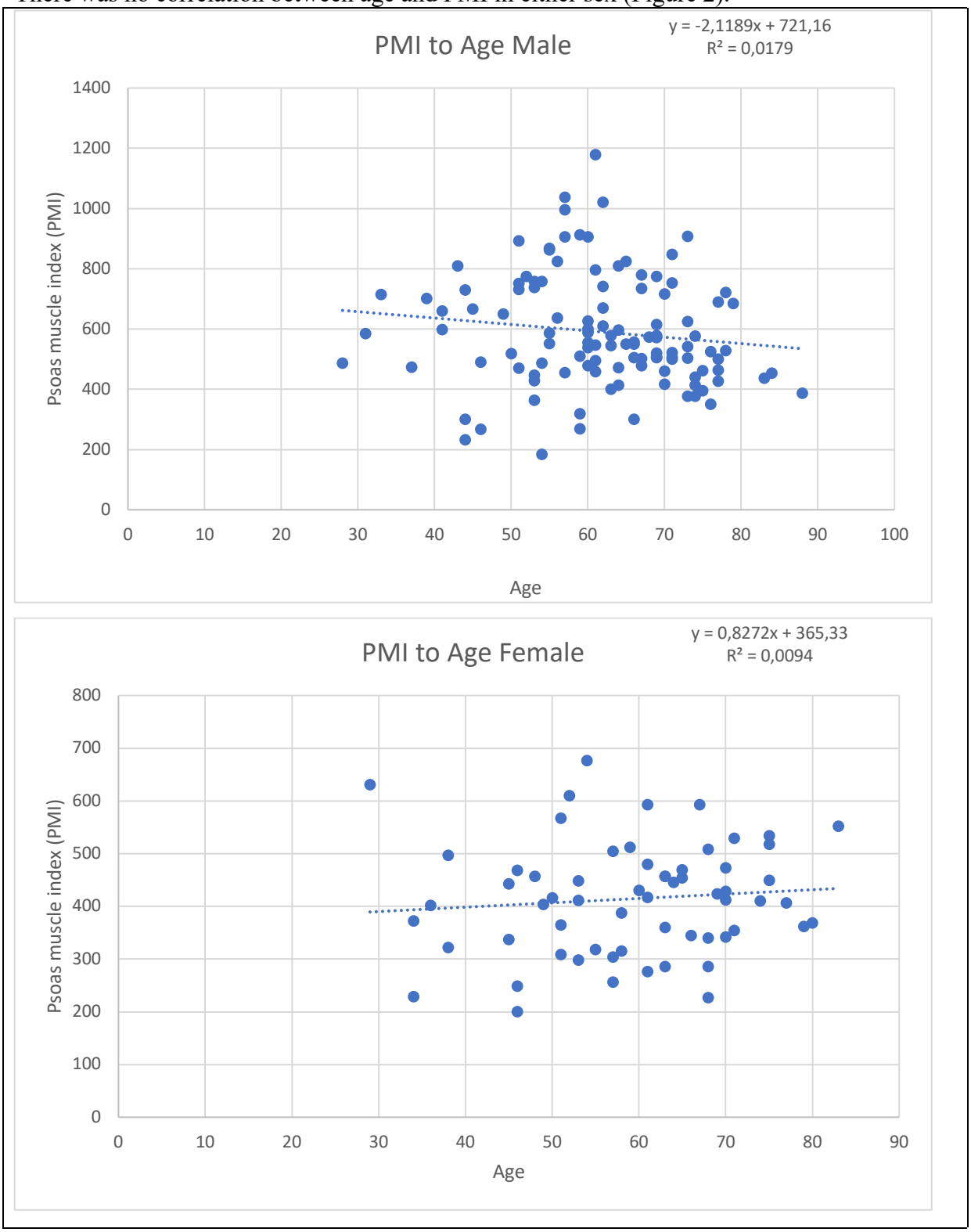


Figure 2: PMI to Age

While the PMI is not dependant on the BMI, there is a slight correlation for both sexes with females showing a stronger correlation but no statistical significance. The mean PMI for females presenting with GOO (401 $mm^2/m^2 \pm 24$) was slightly lower than without (421 mm^2/m^2

± 15), but was not statistically significant (*p* value of <0.4). However, the mean PMI for males with GOO (517mm^2/m^2±36) was statistically significant (*p* value <0.03) compared to those without (609mm^2/m^2±19).

The anthropometric characteristics of the 68 individuals that underwent surgery are represented on Table 2. Thirty-six (53%) had a subtotal gastrectomy, 20 (29%) a total gastrectomy and 12 (18%) a gastrojejunostomy due to non-resectable disease at surgical exploration. The bypass group were included in the surgical outcomes cohort as a gastrointestinal anastomosis was performed.

The outcomes of the surgical cohort were evaluated for complications, length of hospital stay and mortality (Table 2). Severe complications were defined as Accordian grades 3-6. The overall complication rate was 40% (n=27), with 16% (n=11) defined as severe. There were seven deaths resulting in a 10% surgical mortality. Overall, the mean PMI was not statistically significant between individuals with or without complications, including severe complications. However, it did approach significance for males when comparing no complications to all complications (*p* = 0.07). All mortalities occurred in the male group with no statistical significance to PMI.

The mean length of post-operative stay was 10±0,7 days. The PMI did not correlate to length of stay for either sex. The cohort was then grouped into a short (< 10days) and long (> 10days) post-operative stay. Ten days was judged to be an appropriate post-operative stay for a major operation. Again the mean PMI was no different between these two groups.

The entire cohort was then evaluated for correlation between presenting AJCC cancer stage and PMI.[11] The expanded TNM classification was initially used with no correlation. We redefined cancer stage as either early disease (as reflected by no nodal disease), localised nodal disease and metastatic disease using the clinical staging, with interestingly still no correlation found between PMI and stage (Figure 3).

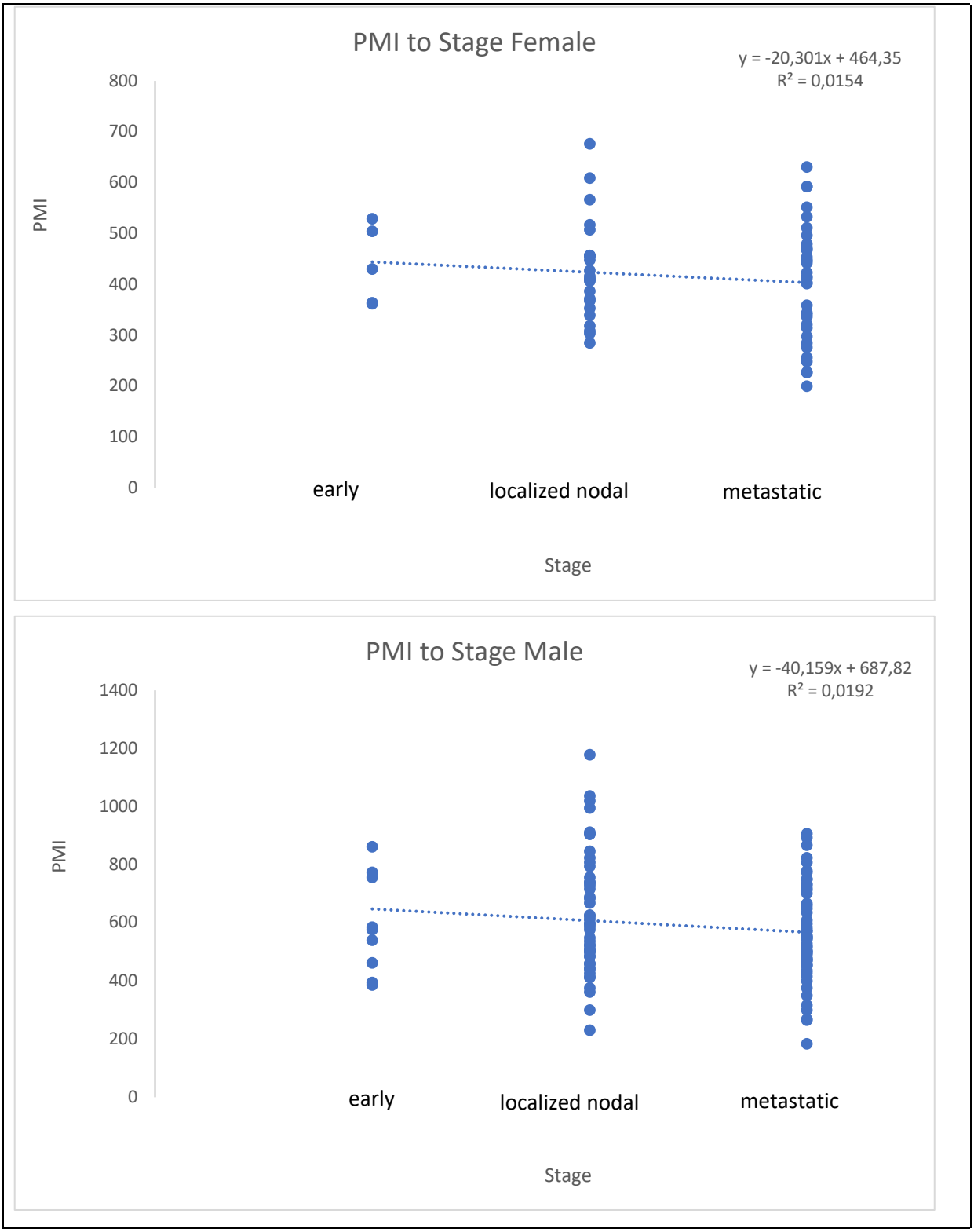


Figure 3: PMI to early, localized nodal and metastatic groups

While there was no significant correlation between PMI and staging, we noticed extremely low PMI was never found in early stage disease. In order to examine this further we grouped individuals into PMI categories. The PMI range within the female cohort was split into four groups, <200, 201-400, 401-600 and >600 and compared to the stage of cancer at presentation.

A Chi-squared statistics test was performed and the mean PMI was not statistically significant depending on the stage of disease (p=0.98). Similarly, for males the PMI groups were represented as <300, 301-600, 601-900 and >901. Again, the mean PMI was not quite reaching statistical significance in relation to stage of cancer (p=0.07) (Figure 4).

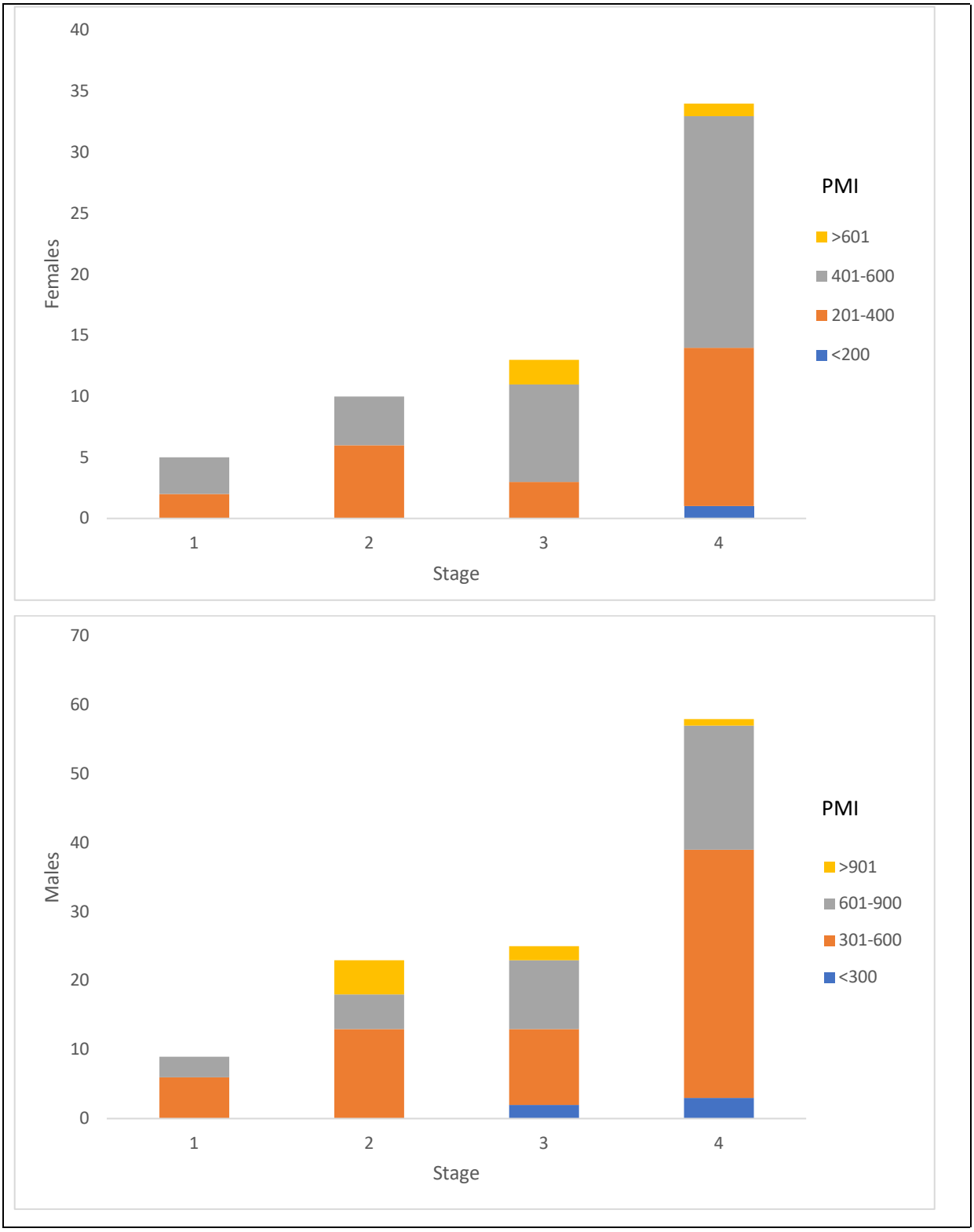


Figure 4: PMI grouping to stage at presentation

DISCUSSION

Our South African gastric cancer cohort is unique. The Asian gastric cancer population generally presents with early distal lesions, whereas Western populations generally present with late proximal disease.[3] Our local population unfortunately presents with advanced and often metastatic disease of the distal stomach at primary evaluation. There is no active screening for this moderately low incidence cancer in our population with the additional obstacle of delayed access to scarce endoscopic resources. This is compounded by the endoscopic services clustered in larger metropolitan health care facilities, with rural communities having significant referral delays.

From unpublished local institutional numbers, less than 10% of gastric cancers presenting through our multidisciplinary oncology meetings will be potential surgical candidates. Local surgical complication rates are similar, although of the higher side, of reported international rates of 20-46%.[6] The mortality rate was in keeping with Western low volume centres reporting 10-20% mortality.[12] Although on the higher side of reported morbidity and mortality, there is very limited data from the African continent and therefore we are unable to compare our outcomes to others on the continent.

Recognising our high morbidity rate and suspecting poor nutrition to play a role in outcomes, it is our institutional practice to offer routine nutrition prehabilitation in patients deemed to be at risk of malnutrition. Currently nutritional risk is assessed clinically due to a shortage of available objective measurements of nutrition, such as bioimpedance or DEXA body composition scan. Our rationale behind psoas muscle measurements as a surrogate for skeletal muscle mass, and as such overall nutrition was cost. As all gastric cancer staging includes a routine CT scan, this is readily available for assessment at no added financial burden.

Psoas muscle area in gastric cancer outcomes has been previous found to be a possible useful prognostic factor in a Japanese cohort of patients. Low psoas muscle area was an independent risk factor for post-operative pneumonia and worse disease-free survival in the long-term.[13] Contrary to the Japanese cohort, our results also showed no significant difference in short-term outcomes. However comparing outcomes between these two populations should be done cautiously as a high proportion of their cohort (67%) present with stage 1 disease. The Japanese have the ability to group their cohort into low and high psoas muscle mass following research in living-related liver donors that defined a normal value.[8] We believe the cut-off points used

in the Japanese population are not transferable to our local population. This does present an interesting area for future research. A defined normal PMI value specific to the South African population will impact surgical outcomes evaluation.

Surprisingly in our analysed cohort the PMI did not show correlation with short-term surgical outcomes. A further interrogation of PMI was done in relation to gastric cancer staging. Again unexpectedly, PMI did not show any correlation to tumour stage. Looking at the extremes of the distribution curves seen in Figure 4, very low PMI was close to being statistically enough to show significance. The PMI was statistically lower in males presenting with GOO as would be expected with restricted caloric intake secondary to an obstruction. While 44% of females presented with GOO, there was no statistical significance in PMI, unlike their male counterparts. We cannot explain this, although sample size may play a role. The spectrum of gastric cancer in South Africa has been reported in a single centre,[14] there have been no published reports of surgical outcomes in gastric cancer in South Africa, so this serves to be the first of its kind. The ability to audit outcomes in surgery is crucial and so this allows outcomes to be compared to international data, along with documenting local outcomes for future referencing.

The clear limitation to this study was the small sample size with complete anthropometric information and even smaller surgical group. The surgical interventions in gastric cancer in the Cape Town Metro West are generally grouped together to a single centre, that being Groote Schuur Hospital, but there still remains a vast discrepancy between public and private health care facilities and our cohort may not be a true representation of the local population. Psoas muscle measurements have been correlated with total skeletal muscle volumes,[8,9] but are still not accepted as a measure for sarcopenia by the EWGOP, although there have been studies linking low psoas muscle area and volume to poorer surgical outcomes.[15-18] This leads to a possible new prognostic factor, unfortunately which we were unable to demonstrate.
The use of psoas muscle area as opposed to psoas muscle density is another possible limitation. Increased adiposity may lead to muscle with a higher fat content, thereby increasing size without function. This confounding factor can be evaluated by using density of the muscle to ascertain fat content.[19] The use of uncontrasted and arterial phasing of the CT images is required for density measurements, depending on methodology. As we did not have consistent uncontrasted and arterial phasing of the CT images, we excluded this from our study. Almost half of the South African female population are classified overweight or obese and as such we

speculate muscle density may be more accurate in our population,[20] and should be considered in future research.

CONCLUSION

We showed no correlation between PMI and short-term surgical outcomes in gastric cancer surgery at Groote Schuur Hospital. This is in contrast to previously published international literature. It is clear that nutrition is of great importance to surgical outcomes and a reliable, easily reproduceable, cost-effective surrogate marker for nutrition would aid in patient discussions and surgical decision making. Future considerations should include enlarging the cohort, including psoas muscle density in conjunction with area and including long-term outcomes. A South African population specific normal range PMI is imperative.

Table 1: Demographics, anthropometrics and tumour stage

	Female	**Male**	**Combined**
Cases	62	115	177
Average age (years)	59,1 (±1,6)	61,7 (±1,1)	60,8 (±0,9)
Anthropomorphic characteristics			
BMI	23,9 (±0,8)	22,9 (±0,5)	23,2 (±0,4)
BMI range	15,6 - 39,6	11,1 - 38,0	11,1 - 39,6
PMI average	414,3 (±13,4)	590,4 (±17,2)	528,7 (±13,6)
PMI range	200,0 - 676,7	183,5 - 1178,2	183,5 - 1178,2
Tumour Site			
Cardia	8	18	26
Non-cardia	54	97	151
Gastric outlet obstruction			
Yes	27	23	50
No	35	92	127
Stage			
1	5	9	14
2	10	23	33
3	13	25	38
4	34	58	92

Table 2: Anthropometrics of cohort undergoing surgery with outcomes

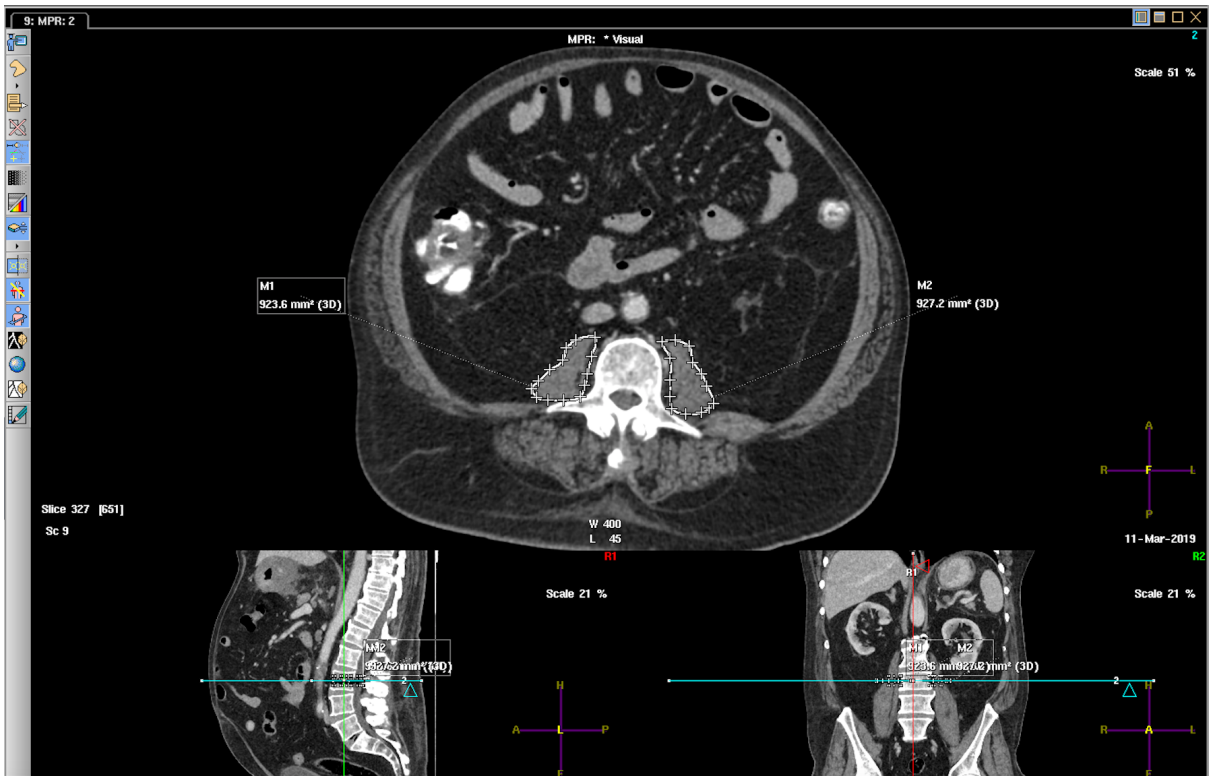
	Female	**Male**	**Combined**
Surgery performed	21	47	68
Type of surgery			
Total gastrectomy	6	14	20
PMI average	444,7 (±51,6)	582,2 (±48,6)	541,0 (±39,4)
Subtotal gastrectomy	11	25	36
PMI average	405,9 (±20,6)	616,7 (±37,1)	552,3 (±31,0)
Bypass	4	8	12
PMI average	431,2 (±76,8)	579,9 (±68,9)	530,4 (±54,8)
Overall			
PMI average	428,3 (±22,0)	590,4 (±26,7)	533,6 (±22,0)
No complications	16	24	40
PMI average	430,6 (±24,0)	641,0 (±42,4)	556,8 (±31,6)
All complications	5	22	27
PMI average	393,8 (±54,9)	560,6 (±31,5)	529,7 (±30,0)
Severe complication	1	10	11
PMI average	609,8 (±0)	583,0 (±163,0)	585,5 (±154,8)
Death	0	7	7
PMI average	N/A	564,6 (±54,7)	564,6 (±54,7)
Length of stay	8,9 (±0,8)	10,5 (±1,0)	10,0 (±0,7)

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians. 2018;68(6):394-424.
2. Mansfield P. Clinical features, diagnosis, and staging of gastric cancer. In: Tanabe KK, J, editor. UpToDate. UpToDate, Waltham, MA (Accessed on January 11, 2021).
3. Recio-Boiles A, Babiker HM. Gastric Cancer. StatPearls. Treasure Island (FL)2020.
4. Zheng HL, Lu J, Li P, Xie JW, Wang JB, Lin JX, et al. Effects of Preoperative Malnutrition on Short- and Long-Term Outcomes of Patients with Gastric Cancer: Can We Do Better? Ann Surg Oncol. 2017;24(11):3376-85.
5. Kubota T, Shoda K, Konishi H, Okamoto K, Otsuji E. Nutrition update in gastric cancer surgery. Ann Gastroenterol Surg. 2020;4(4):360-8.
6. Li J, Zhang Y, Hu DM, Gong TP, Xu R, Gao J. Impact of postoperative complications on long-term outcomes of patients following surgery for gastric cancer: A systematic review and meta-analysis of 64 follow-up studies. Asian J Surg. 2020;43(7):719-29.
7. Cruz-Jentoft AJ, Bahat G, Bauer J, Boirie Y, Bruyere O, Cederholm T, et al. Sarcopenia: revised European consensus on definition and diagnosis. Age Ageing. 2019;48(4):601.
8. Hamaguchi Y, Kaido T, Okumura S, Kobayashi A, Hammad A, Tamai Y, et al. Proposal for new diagnostic criteria for low skeletal muscle mass based on computed tomography imaging in Asian adults. Nutrition. 2016;32(11-12):1200-5.
9. Kim JS, Kim WY, Park HK, Kim MC, Jung W, Ko BS. Simple Age Specific Cutoff Value for Sarcopenia Evaluated by Computed Tomography. Ann Nutr Metab. 2017;71(3-4):157-63.
10. Strasberg SM, Linehan DC, Hawkins WG. The accordion severity grading system of surgical complications. Ann Surg. 2009;250(2):177-86.
11. Amin MB, Greene FL, Edge SB, Compton CC, Gershenwald JE, Brookland RK, et al. The Eighth Edition AJCC Cancer Staging Manual: Continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. CA Cancer J Clin. 2017;67(2):93-9.
12. Baiocchi GL, Giacopuzzi S, Marrelli D, Reim D, Piessen G, Matos da Costa P, et al. International consensus on a complications list after gastrectomy for cancer. Gastric Cancer. 2019;22(1):172-89.

13. Taniguchi Y, Kurokawa Y, Takahashi T, Saito T, Yamashita K, Tanaka K, et al. Impacts of Preoperative Psoas Muscle Mass and Visceral Fat Area on Postoperative Short- and Long-Term Outcomes in Patients with Gastric Cancer. World J Surg. 2020.
14. Benamro F, Sartorius B, Clarke DL, Anderson F, Loots E, Olinger L. The spectrum of gastric cancer as seen in a large quaternary hospital in KwaZulu-Natal, South Africa. S Afr Med J. 2017;107(2):130-3.
15. Womer AL, Brady JT, Kalisz K, Patel ND, Paspulati RM, Reynolds HL, et al. Do psoas muscle area and volume correlate with postoperative complications in patients undergoing rectal cancer resection? Am J Surg. 2018;215(3):503-6.
16. Peng P, Hyder O, Firoozmand A, Kneuertz P, Schulick RD, Huang D, et al. Impact of sarcopenia on outcomes following resection of pancreatic adenocarcinoma. J Gastrointest Surg. 2012;16(8):1478-86.
17. Lee JS, He K, Harbaugh CM, Schaubel DE, Sonnenday CJ, Wang SC, et al. Frailty, core muscle size, and mortality in patients undergoing open abdominal aortic aneurysm repair. J Vasc Surg. 2011;53(4):912-7.
18. Zager Y, Khalilieh S, Ganaiem O, Gorgov E, Horesh N, Anteby R, et al. Low psoas muscle area is associated with postoperative complications in Crohn's disease. Int J Colorectal Dis. 2021;36(3):543-50.
19. Tzeng YH, Wei J, Tsao TP, Lee YT, Lee KC, Liou HR, et al. Computed Tomography-Determined Muscle Quality Rather Than Muscle Quantity Is a Better Determinant of Prolonged Hospital Length of Stay in Patients Undergoing Transcatheter Aortic Valve Implantation. Acad Radiol. 2020;27(3):381-8.
20. Goetjes E, Pavlova M, Hongoro C, Groot W. Socioeconomic Inequalities and Obesity in South Africa-A Decomposition Analysis. Int J Environ Res Public Health. 2021;18(17).

PSOAS MUSCLE MEASUREMENT



The total psoas muscle area (TPA) was measured in mm^2 as the sum of the left and right psoas muscles on axial images at the level where both transverse processes of the 3rd lumbar vertebrae are visible. The area was measured by outlining the left and right psoas muscles, to provide a measurement in mm^2, with calculations performed using the programming available on Phillips IntelloSpace PACS Enterprise version 4.4.553.50

ETHICS APPROVAL

UNIVERSITY OF CAPE TOWN

FACULTY OF HEALTH SCIENCES
Human Research Ethics Committee

HUMAN RESEARCH ETHICS COMMITTEE
07 JAN 2021
HEALTH SCIENCES FACULTY
UNIVERSITY OF CAPE TOWN

FHS017: Annual Progress Report / Renewal

Record Reviews/Audits/Collection of Biological Specimens/Repositories/Databases/Registries

HREC office use only (FWA00001637; IRB00001938)			
This serves as notification of annual approval, including any documentation described below.			
☐ Approved	Annual progress report	Approved until/next renewal date	30·12·2021
☐ Not approved	See attached comments		
Signature Chairperson of the HREC/ Designee		Date Signed	7/1/21

Note: Please note that incomplete submissions will not be reviewed.
Please email this form and supporting documents (if applicable) in a combined pdf-file to hrec-enquiries@uct.ac.za.

Please clarify your plan for research-related activities during COVID-19 lockdown

Principal Investigator to complete the following:

1. Protocol information

Date (when submitting this form)	6 January 2021		
HREC REF Number	841/2017	Current Ethics Approval was granted until	30 December 2020
Protocol title	Is sarcopenia as determined by psoas cross-sectional area measurement an accurate predictor of peri-operative outcome in adenocarcinoma of the upper gastrointestinal tract? (Substudy R031/2015)		
Principal Investigator	Galya Chinnery		
Department / Office Internal Mail Address	E23 Room 19 New Groote Schuur Hospital		
1.1 Does this protocol receive US Federal funding?		☐ Yes	x No

2. Protocol status (tick ✓)

☑	Research-related activities are ongoing
☐	Data collection is complete, data analysis only

Please indicate (in the block below) the titles and HREC reference numbers of any projects currently making use of the Database/registry/repository.

3. Protocol summary

Total number of records or specimens collected, reviewed or stored since the original approval		97
Total number of records or specimens collected, reviewed or stored since last progress report		97
Have any research-related outputs (e.g. publications, abstracts, conference presentations) resulted from this research? If yes, please list and attach with this report.	☐ Yes	☑ No

4. Signature

Signature of PI		Date	6 January 2021

INSTRUCTIONS TO AUTHOR SAJS

Submission Preparation Checklist

As part of the submission process, authors are required to check off their submission's compliance with all of the following items, and submissions may be returned to authors that do not adhere to these guidelines.

- Named authors' consent to publication and meet the requirements of authorship as set out by the journal.
- The submission has not been previously published, nor is it before another journal for consideration.
- Any conflict of interest (or competing interests) as indicated by the author(s).
- A covering letter signed by ALL authors as a supplementary file.
- Written confirmation of Research Ethics Committee approval must be submitted as a supplementary file.
- Authors' details, including full names, current position, department and place of work, email addresses as well as ORCID as a supplementary file.

- The text complies with the stylistic and bibliographic requirements as per the Authors' Guidelines:

    - A style template is available under the Author Guidelines. The manuscript is in Microsoft Word format. The text is 1,5-spaced, in 12-point Times New Roman font, and contains no unnecessary formatting.
    - Illustrations/figures are high resolution/quality (not compressed) and in an acceptable format (preferably TIFF or PNG) and submitted as supplementary files.
    - Tables must be submitted as supplementary files (not included in the manuscript).

- Where possible, references are accompanied by a digital object identifier (DOI) and PubMed ID (PMID)/PubMed Central ID (PMCID)
- An structured abstract or summary has been included where applicable.
- Please provide the names and email addresses of three possible reviewers for this manuscript.

Author Guidelines

Submitted manuscripts that are not in the correct format and without the required supporting documentation specified in these guidelines will be returned to the author(s) for correction and will delay publication.

AUTHORSHIP

Named authors must consent to publication **by signing a covering letter** which should be submitted as a supplementary file. Authorship should be based on substantial contribution to:

(i) conception, design, analysis and interpretation of data;

(ii) drafting or critical revision for important intellectual content; and

(iii) approval of the version to be published. These conditions must all be met (uniform requirements for manuscripts submitted to biomedical journals; refer to **www.icmje.org**); and

(iv) exact contribution of each author must be stated.

DECLARATION OF CONFLICT OF INTEREST

Authors must declare all sources of support for the research and any association with a product or subject that may constitute a conflict of interest. If there is no conflict of interest to declare please include the following: The authors declare no conflict of interest.

FUNDING SOURCE

All sources of funding should be declared. Also define the involvement of study sponsors in the study design, collection, analysis and interpretation of data; the writing of the manuscript; the decision to submit the manuscript for publication. If the study sponsors

had no such involvement, this should be stated as follows: No funding source to be declared.

RESEARCH ETHICS COMMITTEE APPROVAL

The submitting author must provide written confirmation of Research Ethics Committee approval for all studies including case reports. The ethics committee as well as the approval number should be included.

STATISTICAL ANALYSIS

Authors are advised to involve medical statisticians at the protocol stage of their research project: to plan sample size, and the selection of appropriate statistical tests for analysis and presentation.

PROTECTION OF PATIENT'S RIGHTS TO PRIVACY

Identifying information should not be published in written descriptions, photographs, and pedigrees unless the information is essential for scientific purposes and the patient (or parent or guardian) gives informed written consent for publication. The patient should be shown the manuscript to be published. Refer to **www.icmje.org**.

ETHNIC CLASSIFICATION

The rationale for analysis based on racio-ethnic-cultural categorisation should be indicated.

CATEGORIES OF SUBMISSIONS

Shorter items are more likely to be accepted for publication, owing to space constraints and reader preferences.

Original articles

Original articles on research relevant to surgery should not exceed 3 000 words, no more than 30 references, with up to 6 tables or figures. A structured abstract under the following headings, Background, Methods, Results, and Conclusions is a requirement and should not exceed 250 words.

Scientific letters/short reports

Short reports should not exceed 1 500 words with a maximum of 10 references. Only one table or illustration is permissible. A structured abstract under the following headings, Background, Methods, Results, and Conclusions, is a requirement and should not exceed 250 words.

Case reports

Case reports should not exceed 1 500 words with no more than 10 references. Figures are limited to 2 figures and may include images or photographs. The case report should have three headings: Summary (not exceeding 100 words), Case report (with no introduction) and Discussion. Case reports will be published online only. The summary and the URL will appear in the printed version.

Video case reports (SAJS-VIDEO)

Video case reports should not exceed 1 500 words with 10 references and 6 figures. Heading should include Summary (not exceeding 100 words) and Case description (with three subheadings: Introduction, Case presentation and Discussion). The video file format must be only MP4 or MOV and should not exceed 300 MB and 8 minutes. Video case reports will be published online only. The summary and the URL will appear in the printed version.

How to do it

How to do it submissions should address a practical aspect of surgical or interventional (endoscopic or radiological) patient management in which a best practice technique or method to advance optimal patient management is presented in a standardised format. The submission should be structured with a short contextual introduction focussing on the indications for the procedure, followed by numbered sequential points that explain and

illustrate the procedure and its complications. The total word count should not exceed 1500 words with a maximum of 10 references and 6 figures. Five keywords should be included.

Editorials

Opinions, etc. should not exceed 1 000 words and are welcome, but unless invited, will be subjected to the SAJS peer review process.

Review articles

Review articles relevant to surgery should not exceed 5 000 words, with a maximum of 50 references and no more than 6 tables or figures. A summary of 250 words or less is required.

Letters to the editor

Letters to the editor should be 400 words or less with only one image or table.

Obituaries

Obituaries should be 900 words or less and should be accompanied by a photograph.

MANUSCRIPT PREPARATION

Refer to articles in recent issues for the presentation of headings and subheadings. If in doubt, refer to 'uniform requirements' - **www.icmje.org**. Manuscripts must be provided in **UK English**.

The manuscript should contain the title, abstract, keywords, article text and references.

The title page should be submitted as a supplementary file and should include:

- Qualification, affiliation and contact details of ALL the authors.
- Email addresses of all author must be provided.
- ORCID number of ALL authors must be provided – if authors do not have ORCID, please register at https://orcid.org/.
- Disclaimers: Acknowledgements, Declaration of conflict of interest, Funding declaration, Ethics declaration and ORCID.

- A signed copy of the title page including the declarations must be provided in PDF format. An unsigned copy of the title page MUST be submitted in MSWord format.

Abbreviations

All abbreviations should be spelt out when first used and thereafter used consistently, e.g. 'intravenous (IV)' or 'Department of Health (DoH)'.

Scientific measurements

Scientific measurements must be expressed in SI units except blood pressure (mmHg) and haemoglobin (g/dl). Litres is denoted with a lowercase 'l' e.g. 'ml' for millilitres). Units should be preceded by a space (except for %), e.g. '40 kg' and '20 cm' but '50%'. Greater/smaller than signs (> and 40 years of age) should also be preceded by a space e.g. > 20 years. No spaces should precede ± and °, i.e. '35±6' and '19°C'.

Numbers should be written as grouped per thousand-units, i.e. 4 000, 22 160…

Quotes should be placed in single quotation marks: i.e. The respondent stated: '…'
Round **brackets** (parentheses) should be used, as opposed to square brackets, which are reserved for denoting concentrations or insertions in direct quotes.

General formatting

The manuscript must be in Microsoft Word or RTF document format. Text must be 1,5-spaced, in 12-point Times New Roman font, and contain no unnecessary formatting (such as text in boxes, except for Tables). *The manuscript must be free of track changes.*

ILLUSTRATIONS AND TABLES

If tables or illustrations submitted have been published elsewhere, the author(s) should provide consent to republication obtained from the copyright holder.

Tables may be embedded in the manuscript file **and** provided as **'supplementary files'**. They must be numbered in Arabic numerals (1,2,3…) and referred to consecutively in the text (e.g. 'Table 1'). Tables should be constructed carefully and simply for intelligible data

representation. Unnecessarily complicated tables are strongly discouraged. Tables must be cell-based (i.e. not constructed with text boxes, tabs or enters) and accompanied by a concise title and column headings. Footnotes must be indicated with consecutive use of the following symbols: * † ‡ § ¶ || then ** †† ‡‡ etc.

Figures must be numbered in Arabic numerals and referred to in the text e.g. '(Figure 1)'. Figure legends: Figure 1: 'Title…'. All illustrations/figures/graphs must be of **high resolution/quality**: 300 dpi or more is preferable, but images must not be resized to increase resolution. Unformatted and uncompressed images must be attached as '**supplementary files**' upon submission (not embedded in the accompanying manuscript). TIFF and PNG formats are preferable; JPEG and PDF formats are accepted, but authors must be wary of image compression. Illustrations and graphs prepared in Microsoft PowerPoint or Excel must be accompanied by the original workbook.

REFERENCES

Authors must verify references from the original sources. *Only complete, correctly formatted reference lists will be accepted.* Reference lists may be generated with the use of reference manager software, but the final document must be delinked from the reference database or otherwise generated manually. Citations should be inserted in the text as superscript, e.g. These regulations are endorsed by the World Health Organization,[2] and others.[3,4-6] The superscript reference number should come after the punctuation mark.

All references should be listed at the end of the article in numerical order of appearance in the **Vancouver style** (not alphabetical order). Approved abbreviations of journal titles must be used; see the List of Journals in Index Medicus. Names and initials of all authors should be given; if there are more than six authors, the first three names should be given followed by et al. First and last page, volume and issue numbers should be given. **Wherever possible, references must be accompanied by a digital object identifier (DOI) link and PubMed ID (PMID)/PubMed Central ID (PMCID).** Authors are encouraged to use the DOI lookup service offered by **CrossRef**. Crossref DOIs should always be displayed as a full URL link in the form https://doi.org/10.xxxx/xxxxx

Journal references: Price NC, Jacobs NN, Roberts DA, et al. Importance of asking about glaucoma. Stat Med 1998;289(1):350-355. [http://dx.doi.org/10.1000/hgjr.182] [PMID: 2764753]

Book references: Jeffcoate N. Principles of Gynaecology. 4th ed. London: Butterworth, 1975:96-101. *Chapter/section in a book:* Weinstein L, Swartz MN. Pathogenic Properties of Invading Microorganisms. In: Sodeman WA jun, Sodeman WA, eds. Pathologic Physiology: Mechanisms of Disease. Philadelphia: WB Saunders, 1974:457-472.

Internet references: World Health Organization. The World Health Report 2002 - Reducing Risks, Promoting Healthy Life. Geneva: World Health Organization, 2002. http://www.who.int/whr/2002 (accessed 16 January 2010).

Other references (e.g. reports) should follow the same format: Author(s). Title. Publisher place: publisher name, year; pages. Cited manuscripts that have been accepted but not yet published can be included as references followed by '(in press)'. Unpublished observations and personal communications in the text must not appear in the reference list. The full name of the source person must be provided for personal communications e.g. '...(Prof. Michael Jones, personal communication)'.

COVERING LETTER

A covering letter to the editor is mandatory and must include statements that the manuscript has not been published previously and is not under review elsewhere. It should state details of any prior publication of the research in abstract form or in Congress proceedings. The letter must declare if any of the authors have a conflict of interest and that the requirements for submission, including ethics approval and patient permission for case reports have been fulfilled. All authors must sign the covering letter.

Please provide the names and email addresses of three possible reviewers for this manuscript.

REVIEW PROCESS

Manuscripts, after vetting by the editorial team, are assigned for peer-review to 3 reviewers, conversant with the particular field of research. The reviewers and the authors are blinded to each other's identity. The turn-around time for review and initial editorial decision notification aims to be within 6 weeks of submission.

PROOFS

A PDF proof of an article may be sent to the corresponding author before publication to resolve remaining queries. At that stage, **only** typographical changes are permitted; the corresponding author is required, having conferred with his/her co-authors, to reply within 2 working days in order for the article to be published in the issue for which it has been scheduled.

CHANGES OF ADDRESS

Please notify the editorial department of any contact detail changes, including email, to facilitate communication.

CHARGES

There is no charge for the publication of manuscripts.

COPYRIGHT NOTICE

The South African Journal of Surgery (SAJS) reserves copyright of the material published. The work is licensed under a Creative Commons Attribution-Non-Commercial Works 4.0 South Africa License. Material submitted for publication in the SAJS is accepted provided it has not been published elsewhere. The SAJS does not hold itself responsible for statements made by the authors.

PRIVACY STATEMENT

The SAJS is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only

for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the SAJS for the stated purposes of the journal. Queries with regard to privacy may be directed to robyn@jesser-point.co.za.

Copyright Notice

The *South African Journal of Surgery (SAJS)* reserves copyright of the material published. The work is licensed under a Creative Commons Attribution-Noncommercial Works 4.0 South Africa License. Material submitted for publication in the *SAJS* is accepted provided it has not been published elsewhere. The *SAJS* does not hold itself responsible for statements made by the authors.

Privacy Statement

The *SAJS* is committed to protecting the privacy of the users of this journal website. The names, personal particulars and email addresses entered in this website will be used only for the stated purposes of this journal and will not be made available to third parties without the user's permission or due process. Users consent to receive communication from the *SAJS* for the stated purposes of the journal. Queries with regard to privacy may be directed to robyn@jesser-point.co.za.