Physical and Quality of Life Implications of Pelvic Exenteration

Yeqian Huang

Central Clinical School

University of Sydney

A thesis submitted in fulfilment of the requirements for the degree of Master of Philosophy

University of Sydney

2021

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Declaration

This thesis is submitted to the University of Sydney in fulfilment of the requirements for Master of Philosophy. The work presented in this thesis is, to the best of my knowledge, original except as acknowledged in the text. All assistance received in preparing this thesis has been acknowledged. I hereby declare that I have not submitted this material, either in full or in part, for a degree at the University of Sydney or any other institution.

Acknowledgements

First and foremost, I would like to thank my main supervisor, Professor Michael Solomon, for his guidance and support. Professor Solomon is the pioneer of Pelvic Exenteration surgery worldwide. His expertise, encouragement and advice have been greatly appreciated in this process. Thank you for never giving up on me and keeping me motivated during my journey.

I would also like to thank and acknowledge my co-supervisors, Associate Professor Cherry Koh and Associate Professor Daniel Steffens, for their continuous support. They were always there to listen, provide guidance and keep me on track for my timelines. Also, I want to deliver my thanks to the staff at SOuRCe (Surgical Outcomes Research Centre), especially Madhu Prasad, who has always been extremely helpful in helping me coordinate meetings with my supervisors and giving practical advice.

Last but not least, my acknowledgement to my parents for their unconditional love and support to motivate me to finish this thesis.

Abstract

Pelvic exenteration (PE) was introduced as a palliative procedure for recurrent gynaecological cancers in 1948. The rationale beyond it was that patients with recurrent cervical cancer usually had disease limited to the pelvis. With improved perioperative care and transfusion care, curative PE became achievable. Over the last few decades, it has become one of the standard treatments for advanced pelvic malignancies.

PE divides the pelvis into central, anterior, posterior and two lateral compartments and uses a compartmental approach to achieve an adequate resection margin. The surgery consists of three phases. It starts with an exploratory phase to identify any metastasis and perform adhesiolysis to prepare for resection. The resection phase uses the compartmental approach to achieve a clear resection margin (R0), followed by the reconstructive phase, which usually consists of intestinal or urinary reconstruction and perineal closure.

PE has been shown to improve the survival of advanced pelvic malignancies to a 5-year survival of 48.6% and a 10- year survival of 37.8%. Given the aggressive approach of PE to achieve a clear resection margin, it has been associated with significant morbidity, ranging from 31.6% to 86% depending on the reporting of the studies. Postoperative morbidity has been demonstrated in other studies to affect QoL, which has become an important consideration of cancer survivors, given that long-term survival is achievable with modern surgical technique and perioperative support. The study has demonstrated that patients who underwent PE returned to their baseline QoL status by six months after surgery and exceeded the QoL scores of those who did not undergo surgery by six

to nine months. Thus, PE is not only beneficial for oncological survival but also improve patients' QoL. Given the relationship between physical complications and QoL and the importance of QoL for patients, it is valuable to classify physical complications to accurately reflect the surgical morbidity and understand predictors of QoL to allow potential early interventions. In the literature, however, there is a lack of grading complication classification for PE, making it difficult to monitor and comparing surgical morbidity. The reporting of surgical complications has been inconsistent in the exenteration literature. Although Clavien-Dindo Classification (CDC) has been widely used in surgical literature to standardise the reporting of the surgical outcomes, its uptake in the exenteration literature only started to increase in the last five years. Nevertheless, it only considers the most severe complication, regardless of the number of complications a patient may have experienced, which seems practical but not entirely reflective of actual surgical morbidity for such a procedure as complicated as PE. In addition to the grading system, understanding predictors of QoL is also an area worth exploring. Although there is increasing evidence on QoL after PE, there are very few papers that identify the predictors for QoL following PE.

Chapter 1 introduces the thesis and lists the thesis aims. Chapter 2 reports complications associated with PE and assesses three grading complication systems, including CDC, comprehensive complication index (CCI) and the total number of complications using LOS, QoL and psychological and physical outcomes. The key findings of this Chapter include that it identified stronger associations between CCI, the number of complications and LOS than CDC. It also demonstrated moderate associations between three reporting classifications and predischarge 6-minute-walk-test, which is an assessment tool for patients' predischarge physical strength. These findings suggest that

the number of complications is important for patients after PE. However, all these classifications have their limitations and whether they are suitable for PE is still questionable. There may be a need to develop a new specific classification for PE.

Given locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) represent one of the largest cancer groups suitable for PE, and it is the disease of the same origin, Chapter 3 compares surgical outcomes and identifies any predictors of QoL between these two diseases. The key results of this chapter are that the predictors identified in this Chapter are more reflective of the extent of the resection. Patients with LRRC tend to undergo more extensive surgery as compared to those with LARC. However, both groups have similar QoL outcomes.

Chapter 4 discusses and concludes the implications of the findings of Chapter 2 and Chapter 3. Chapter 2 emphasises the importance of a standardised classification system to better understand the postoperative complications and subsequently provide potential intervention targets. Chapter 3 shows that patients with LRRC underwent a more extended resection but had comparable QoL outcomes. Future studies can investigate a more intense preoperative and early postoperative rehabilitation program, increasing their preoperative physical and mental strength and minimising their risks of postoperative complications.

Presentations and publications arising from this thesis

Huang Y.,Wang X., Steffens D., Young, JM., Solomon MJ., Koh CE. Grading Complications in Pelvic Exenteration. Limitations of Current Classification System. *American Society of Colon & Rectal Surgeons Annual Scientific Meeting*, San Diego, 24-28 April 2021

Huang Y.,Wang X., Steffens D., Young, JM., Solomon MJ., Koh CE. Grading Complications in Pelvic Exenteration. Limitations of Current Classification System. *Royal Australasian College of Surgeons 89th Annual Scientific Congress*, Melbourne, 10-14 May 2021

Huang Y., Steffens D., Koh CE., Young JM., Solomon MJ. Differences in surgical outcomes and quality of life outcomes in pelvic exenteration between locally advanced versus locally recurrent rectal cancer. *Royal Australasian College of Surgeons 89th Annual Scientific Congress*, Melbourne, 10-14 May 2021

Huang Y., Steffens D., Koh CE., Young JM., Solomon MJ (2021). Differences in surgical outcomes and quality of life outcomes in pelvic exenteration between locally advanced versus locally recurrent rectal cancer, A*ccepted for publication in Disease of Colon &Rectum*

Huang Y.,Wang X., Steffens D., Young, JM., Solomon MJ., Koh CE. Grading Complications in Pelvic Exenteration (2021). Limitations of Current Classification

System, *publication under review of Disease of Colon &Rectum*

Huang Y.,Wang X., Steffens D., Young, JM., Solomon MJ., Koh CE. Grading Complications in Pelvic Exenteration. Limitations of Current Classification System. *Accepted for Poster Presentation at Tripartite Colorectal Meeting, Auckland, New Zealand*, 21-24 February 2022

Huang Y., Steffens D., Koh CE., Young JM., Solomon MJ. Differences in surgical outcomes and quality of life outcomes in pelvic exenteration between locally advanced versus locally recurrent rectal cancer. *Accepted for Poster Presentation at Tripartite Colorectal Meeting, Auckland, New Zealand*, 21-24 February 2022

CHAPTER 1. Introduction

1.1 Background

In the past, palliative chemotherapy, radiation and re-irradiation were the only treatment options for most patients with extensive pelvic malignancy with the aim of symptom control and slow disease progression. The prognosis of these patients was extremely poor, with a negligible likelihood of 5-year surviva[1]. Over the last three decades, pelvic exenteration (PE) has evolved and revolutionised the outlook of patients with locally advanced primary and recurrent gastrointestinal, genitourinary, and soft tissue malignancy by offering a cure, albeit at the cost of surgical and functional morbidity[2, 3].

History of pelvic exenteration

PE was first introduced in 1948 by Alexander Brunschwig at the Memorial Hospital, New York, as a palliative procedure for recurrent cervical carcinoma. At that time, patients with recurrent cervical cancer experienced a very poor survival rate, and up to 42% of patients who died of the disease still had disease confined to the pelvis. Thus, radical resection may allow a cure for this disease, provided complete resection with a clear resection margin (R0) is achieved. After World War II, there was a significant improvement in perioperative care, managing critically ill patients after radical surgery became possible[2]. The issue with high mortality and morbidity because of intraoperative bleeding also improved with better technique. In the 1950s, Brunschwig and other pioneering surgeons started applying this new surgical approach to other pelvic malignancies, including cancers of the colorectum[4, 5], vulva[6], ovary[7], prostate[8] and pelvic sarcoma[9]. Over the last few decades, advancements in surgical techniques of urinary diversion, composite pelvic bone resection, lateral neurovascular excision

and perineal reconstruction have improved the surgical morbidity and improved complete oncological resection following PE[2]. Today, it has become the mainstay surgical treatment for advanced pelvic malignancies provided a complete resection is technically feasible[10].

Surgical approach of pelvic exenteration

PE involves 'en bloc' resection of continuously involved pelvic organs with reconstruction or diversion of visceral functions with a view to achieve complete oncological (R0) resection[2, 3]. There are various forms of PE based on anatomical compartments, determined by the site of tumour and degree of invasion into adjacent structures[11]. The surgical approach of PE is compartmental, dividing the pelvis into five compartments, including central, anterior, posterior and two lateral compartments (Figure 1)[12]. PE can be classified as total or partial exenteration. Total exenteration is defined as complete excision of all compartments, whereas partial exenteration involves the excision of at least three compartments of the pelvis[13]. PE starts with an exploratory and dissection phase, followed by a resection phase and finally a reconstructive phase. An exploratory phase involves meticulous adhesiolysis, excision of involved small bowel loops en bloc, the colonic resection and reorientation as well as dissection of all vessels and nerves the colon along its anatomical planes. The resection phase aims to achieve an R0 resection with a compartmental approach which includes complete resection of the involved compartment with soft tissue: bone junction with or without bone resection. The reconstruction phase includes urinary or intestinal reconstruction and perineal closure with or without mesh reconstruction or a myocutaneous flap[13].

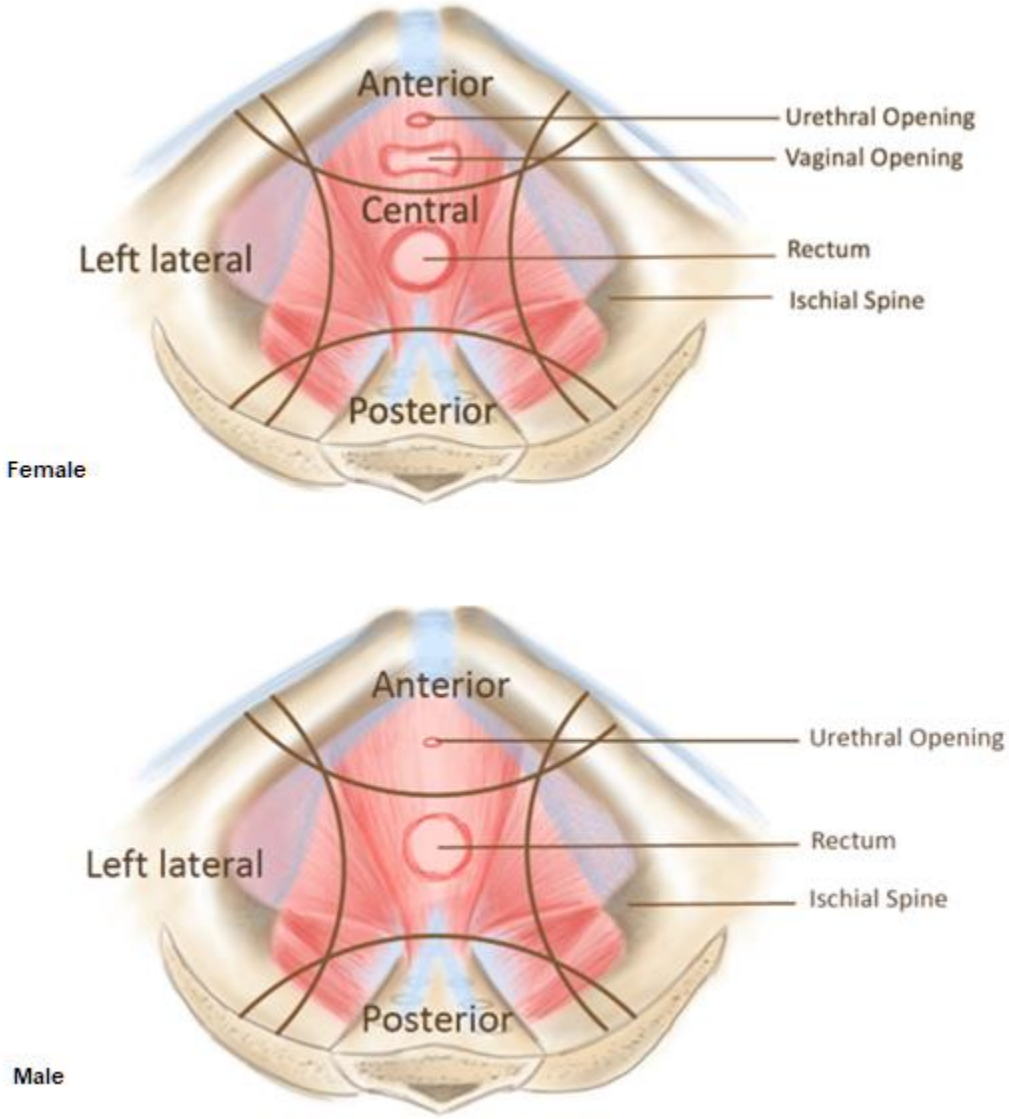

Figure 1 Compartments of the pelvis

Survival outcomes and surgical morbidity of pelvic exenteration

The rationale for such an aggressive approach is the reasonable chance of cure as well as allowing local control of the disease[14]. With an improved surgical technique and perioperative care, a cumulative 5-year survival rate of 48.6% has been reported for locally advanced or recurrent cancer[14].

Although the oncological outcomes have improved, surgical morbidity remains significant. Depending on how it is reported, complication rates ranging can vary between 31.6% to 86%[11]. Most complications following anterior PE are usually urological, including urinary leak, urinoma and urinary stricture, whereas pelvic collections are more specific to posterior PE. Other common complications include haematoma, pelvic abscess, wound infection or wound dehiscence, as well as formation of fistula[15]. Understanding postoperative complications is essential as they have been found to increase hospital LOS and healthcare costs[16]. More importantly, they can also affect postoperative QoL. Patients with complications were found to have a lower physical and mental QoL score in the short-term period after elective colorectal surgical procedures[17].

Functional outcomes of pelvic exenteration

There is a growing consensus that QoL is as essential an oncological outcome as overall survival for patients with advanced pelvic malignancies[18]. Patients who require PE often have aggressive cancer and suffer from considerable symptoms, including pain, bowel or bladder dysfunction, and/or sexual impairment[19]. PE was found to have a beneficial role in improving the QoL of patients with advanced pelvic malignancies. Young et al. (2014) published a study that compared the QoL of patients who underwent PE with those who did not have surgery. It was found that patient-reported QoL outcomes of those who underwent PE were at the lowest at the predischarge timepoint but rapidly improved at one month and continued to improve to nine months after PE. In contrast, those who did not have PE continued to decline. The QoL of those who did not have surgery declined such that their QoL was poorer than those who underwent surgery by six to nine months, depending on the domains being assessed[1]. Another

study performed by Steffens et al. (2018) demonstrated that patients returned to their baseline QoL status by six months after surgery and remained stable during the 5-year follow-up[14]. With an improved survival following the evolution of surgical technique and perioperative care, PE is not only just potentially curative but also can provide a better QoL.

With improved survival following the evolution of surgical technique and perioperative care, functional outcomes have become more and more of an interest for the patients. It is valuable to understand the long-term functional and psychological impacts of PE on patients with advanced pelvic malignancies. Patients' function can be affected by general health, gastrointestinal and genitourinary symptoms, pain and stoma issues and the effects of complications[20]. Initially, they often experience a significant level of fatigue and lethargy, which improves over time during recovery. Abdominal pain, distension, urinary incontinence and reduced sexual function have been reported in the postoperative period, which can adversely affect patients' function[21]. In addition to physical effects, surgery can also have psychological and social impacts. Patients are often required to adapt to a new body image and a new role in their relationships. Surgery, postoperative recovery, and follow-up can also disrupt daily living and result in a reduction of their social activities. It also requires significant work environment adjustments to accommodate restrictions imposed by the surgery, which can potentially increase financial difficulties[21, 22]. Thus, PE can still significantly impact patients' long-term functional, psychological, and social outcomes.

1.2 Gaps in the literature and current practice

Gaps in classifying surgical complications following pelvic exenteration

In the 1990s, there was a lack of consensus on how to assess and report surgical complications of PE[23-27]. The reporting system has been ad hoc with non-validated and variable classifications such as major or minor; surgical or medical. There were also other issues in assessing and documenting surgical complications without a standardised complication classification system including the interobserver variability, subjective bias from respective review, recall bias and missing data[28]. Retrospective design was the most often used clinical study in assessing surgical complications in the surgical literature because data can be easily obtained from medical records. However it is limited by its reliance on accuracy of the written record and cofounding factors. Although prospective study is encouraged when it is feasible in research studies, it is difficult to perform prospective study for surgical complications. One complication can have multiple manifestations throughout the admission. Also, the causes of some complications were not identified until later[29]. Thus retrospective analysis of surgical complications may be more suitable and could potentially generate hypothesis for future prospective studies.

In 2004, the Clavien group re-evaluated and developed Clavien-Dindo Classification (CDC), which is based on a therapy-oriented, 4-level severity grading[30, 31]. In the last decade, it has been widely used in the literature and national centre databases to uniformly report surgical outcomes[32, 33]. The CDC is intuitive and has been shown to correlate with the length of stay (LOS) in hospital[31].

Uptake of the CDC in the exenteration literature, however, was lagging. Many exenteration related studies continued to report outcomes in an ad hoc manner, although there is a trend towards using CDC over the past five years[34, 35]. In addition, CDC is also limited because it only considers the single most severe complication, ignoring others of lesser severity. Subsequently, the Comprehensive Complication Index (CCI) has been introduced in 2013, which incorporates frequency and severity of complications based on CDC classification to grade postoperative complications[30]. However, it has not been applied in the exenteration literature.

Gaps in perioperative and QoL outcomes for rectal cancers

Understanding QoL following PE is vital for both clinicians and patients to allow better pre-operative counselling and discussion. It also allows patients to understand and set expectations and have better mental preparation before such a complex procedure. Identifying predictors for QoL can even allow intraoperative modifications to be implemented should a modifiable factor be recognised as an adverse predictor of QoL outcomes. Locally advanced rectal cancer (LARC) or locally recurrent rectal cancer (LRRC) present the largest non-gynaecological malignancy group that requires PE. Although the number of QoL studies in surgery has increased significantly over the past ten years[20, 36, 37], there remain few studies on QoL of patients with LARC and LRRC[18, 22, 26]. Rausa et al. (2017) performed a systematic review on QoL of patients with LARC and LRRC and identified female gender, total PE and positive margins as negative factors for QoL[18]. However, LARC and LRRC were grouped together rather than separate entities in the review[18]. Although LARC and LRRC are diseases of the same origin with a similar surgical approach, there are intrinsic differences between these two diseases. Patients with LARC often have a virginal surgical plane, whereas patients

with LRRC often had previous treatment, including surgery and chemoradiotherapy. It can lead to adhesions and fibrosis that increase the difficulty of a clear surgical resection[38, 39].

It has been demonstrated that the QoL of patients with LARC improves rapidly after PE and continues to improve over the first year[22]. Offering PE should therefore not be subjective to a perceived poor QoL[37]. The evidence for the predictors for the change of QoL in the first year after surgery for patients with rectal cancer remains quite limited[18]. Only two studies have focused on the QoL of patients with LARC[22, 37,] and no study has compared QoL outcomes between LARC and LRRC. In addition, only one study compared surgical outcomes, including complications of patients with LARC and LRRC following PE[40].

1.3 Aims

Given the possible close association between postoperative complications and QoL, this thesis aims to assess the impacts of PE on patients following surgery from a physical and functional perspective. In particular, the complication classifications and the relationship between complications and QoL and differences in outcomes of patients with different rectal indications for PE, i.e. primary versus recurrent.

Physical perspectives

1. To comprehensively report complications associated with PE.
2. To determine if there are correlations between CDC, CCI and the number of complications and LOS, QoL, psychological and physical outcomes.

QoL perspectives

1. To compare and contrast surgical outcomes, including complications of patients with LARC and LRRC undergoing PE.
2. To identify any differences in QoL or predictors of QoL between patients with LARC and LRRC.

Chapter 2 presents an overview of morbidity following PE, followed by an assessment of current grading classifications for complications. Physical implications of PE demonstrated in Chapter 2 lead to Chapter 3, which compares the perioperative outcomes of LARC and LRRC and then explores any differences or predictors of outcomes both objectively and subjectively for patients with these two diseases. Finally, chapter 4 discusses the findings and concludes the thesis.

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CHAPTER 2. Physical morbidity and complications of pelvic exenteration. Limitations of the current classification system

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This chapter assessed three classification systems in PE and highlighted some weaknesses of current classification systems.

2.1 Abstract

Introduction

The reporting of surgical morbidity in exenteration literature has been inconsistent. Given pelvic exenteration (PE) is a highly morbid procedure, often associated with multiple complications, lack of consistent reporting makes it difficult to compare surgical outcomes across studies to determine the surgical impacts on the patients. Thus, this study aimed to comprehensively report complications associated with PE and to assess the strength of associations between three grading classifications and length of stay (LOS), quality-of-life (QoL), psychological and physical outcomes.

Methods

This was a retrospective analysis of prospectively collected data of patients who underwent PE for advanced pelvic malignancies at Royal Prince Alfred Hospital, Sydney, Australia, between December 2016 and August 2019. Complications were classified according to the Clavien-Dindo Classification (CDC), Comprehensive Complication Index (CCI) and the number of postoperative complications. Outcomes included LOS, physical component score (PCS) at 6 months, distress score at 6 months and predischarge 6-minute walk test and sit-to-stand test. Associations between the

three classifications and outcomes were investigated using Pearson's Correlation Coefficient test.

Results

198 patients were included in this study. On average, each patient had at least 2.7 complications (SD=2.4, median=2, range=0-18). CDC was moderately correlated with length of stay ($r=0.518$, $p<0.0001$), whereas CCI ($r=0.744$, $p<0.0001$) and the number of complications ($r=0.751$, $p<0.0001$) showed a strong correlation with LOS. All these classifications were moderately adversely correlated with predischarge 6MWT (CDC: $r= -0.359$, $p=0.008$; CCI: $r= -0.388$, $p=0.007$; number of complications: $r= -0.467$, $p<0.0001$). However, there was no correlation between CDC, CCI, number of complications, and distress score at 6 months, and predischarge STS time. CDC was also not correlated with predischarge 6MWT.

Conclusion

CCI and the number of postoperative complications were more strongly associated with LOS than CDC and may be a better alternative system to classify postoperative complications following PE.

2.2 Introduction

Locally advanced cancers of the pelvis are morbid conditions that commonly cause disabling symptoms. It can cause intractable pain, sepsis, obstruction and fistula formation[1]. Prior to the widespread acceptance of pelvic exenteration (PE), palliative chemotherapy and radiation were the only treatment options for these patients with the aim of symptom control and slowing disease progression. The prognosis was extremely poor, with the negligible likelihood of 5-year survival[2]. However, in the last three decades, the introduction of PE has revolutionised the outlook of patients with these advanced cancers by offering a cure, albeit at the cost of surgical morbidity, mortality and a decreased physical function[1].

Over the last decade, 5-year survival of patients with locally advanced or recurrent cancer has improved to 48.6% following PE[3]. Although the oncological outcomes have improved, surgical morbidity remains high. Depending on how it is reported, postoperative complication rates range from 31.5% to 85% have been reported[4]. Surgical complications have been found to significantly increase the postoperative length of stay (LOS) because of the need for additional investigations and treatment[5]. Furthermore, previous studies have demonstrated a strong association between complications and poorer physical and emotional outcomes[6, 7]. Postoperative complications can also significantly increase patients' anxiety after surgery, compromising their psychological wellbeing[8].

Given that PE is a highly morbid procedure, it is crucial to assess complications after PE using a standardised classification system to monitor surgical outcomes. In addition, it would allow comparisons across various studies and helps determine the physical

impacts of surgery on patients allowing for more informed consent. Until recently, reporting of surgical complications in PE has been ad hoc with non-validated and variable classifications such as major or minor, surgical or medical[9]. With increasingly widespread uptake of the Clavien-Dindo Classification (CDC) across surgical literature, the same has occurred with PE literature. A major consideration with the use of CDC in PE patients, however, is the fact that it only considers the significant complication without taking into consideration the number of complications when PE patients tend to have had multiple complications[10, 11].

The Comprehensive Complication Index (CCI) was introduced in 2013, which takes into consideration both the severity and frequency of surgical complications to address the limitations of CDC[10]. However, CCI is a relatively new classification system and is less readily accessible as it requires an online calculator[12]. As far as the authors are aware, it has not been used in the exenteration literature.

Given the inconsistencies in reporting complications of PE, the aim of this study was to comprehensively report complications associated with PE and to determine whether the CDC, CCI, or simply considering the number of postoperative complications better correlates with postoperative length of stay (LOS), psychological and physical outcomes, as well as quality of life (QoL)in PE.

2.3 Patients and Methods

Study design

This was a retrospective cohort study of consecutive patients who underwent PE at

Royal Prince Alfred Hospital (RPAH), Sydney, Australia, between December 2016 and August 2019. The decision to offer surgery is made at a dedicated multidisciplinary team meeting which reviewed all relevant clinical history and imaging[13]. Routine work-up for PE included a computed tomography scan of the chest, abdomen, pelvis, pelvic magnetic resonance imaging and positron emission tomography. The clinical and surgical data of all patients undergoing PE are collected prospectively into the Pelvic Exenteration Surgery Quality Improvement database- PESQI (Ethics protocol no: X13-0283 and HREC/13/RPAH/371), and patients were also invited to participate in a prospective QoL study (Ethics protocol number X16-0272 & HREC/11/RPAH/632). The latter also collected functional outcomes, including physical fitness tests: the 6-minute walk test (6MWT) and sit-to-stand (STS) test. This study has been approved by Sydney Local Health District Human Ethics Research Committee (X20-0297 & 2020/ETH01751).

Patient selection

PE team receives local, interstate and sometimes international referrals. A standardised referral process and discussion in MDT has been explained in the previous study [13].

Postoperative Complication

Retrospective reviews of patients' electronic medical records were performed to supplement the existing database with complication data. Perioperative complications in all patients were graded I to V with increasing severity based on the CDC grading system[11].

The frequency of each complication of grade II, III and IV was also collected for each patient. The frequency of grade I complications were not well collected given how common it was and variable documentation. Thus, patients without any complications were grouped together with patients with grade I complications. It is also difficult to decide if this had been merely a deviation or variation of "normal" recovery in such a complicated operation as the postoperative course for individual patients is complex and highly variable. Each complication was categorised using the highest interventional grade. For example, if a patient receives an antibiotic and surgery for urosepsis, it is classified as one grade III complication. CCI score was calculated using an online calculator (https://www.assessurgery.com/)[12]. It was based on the number of complications of each CDC grade to calculate an overall CCI score, ranging from 0 to 100. Grade V would score 100 automatically. The frequency of each complication of grade II, III and IV for the studied group was entered. Overall CCI score was calculated for each patient for analysis.

Outcome measures

Outcomes of interest included LOS, physical QoL as measured using the physical component score (PCS) of SF-36 version 2, distress score and predischarge functional assessments using the 6MWT and STS test. The SF-36 is a well-utilised tool that has been extensively validated to assess general health status. It has a score ranging from 0 to 100, with a higher score indicating a better outcome[14]. The psychological impact was measured using the distress thermometer, which has been shown to be an effective measure of psychological stress for oncological patients[15, 16]. A visual analogue scale was used. Distress score ranges from 0 (no distress) to 10 (extreme distress). A score of 4 or above is the cut-off for stress[17]. Patients were asked to circle a number to best

describe how much stress they had in the past week at 6-month timepoint after surgery[17]. A questionnaire was sent to them with a returned envelope attached. It was chosen as an outcome measure because surgical complications were thought to be associated with physical morbidity and distress. The timepoints for both PCS and distress score were 6 months after surgery because this was the first time point measured after surgery.

Functional status assessment using the 6MWT and STS tests was chosen as they were both simple and easy to administer bedside tests, which can objectively assess patients' functional exercise capacity of patients[18, 19]. Both tests have been validated in the clinical setting to assess physical function. For the 6MWT, patients were encouraged to walk as fast as possible for 6 mins along a 30 meter straight, indoor corridor. Standardised encouragements were offered eat minute during the test. The total distance walked and vital signs were recorded. Predicted values of the 6MWT were derived from a mathematical model of healthy Australian participates, adjusted for patient's age, height and weight. For the STS, patients were instructed to stand up and sit down as quickly as possible with their arm folded across the chest and the back against a chair. They were required to complete five repetitions[20]. The time in seconds was recorded. Predischarge timepoint was chosen as this was thought to be reflective of an early postoperative physical status.

Comparison Groups

Complications classified according to the CDC, CCI and the total number of complications were correlated with the outcomes of interest, which included LOS, PCS, distress score, 6MWT and STS. Subgroup analyses were performed for those with intra-

abdominal collection or urine leak as these are either common or of particular interest to surgeons.

Statistical analysis

All statistical analyses were performed using SPSS for Windows Version 26 (IBM Corporation, New York, USA). Categorical data were presented as frequencies (%). For normally distributed data, comparison of continuous variables was performed using the Independent Student's t test or analysis of variance (ANOVA) test, where appropriate. For non-normally distributed data, Mann-Whitney U test or Kruskal-Wallis H test was used where appropriate. Significance was defined as $p<0.05$. Baseline characteristics were compared among patients grouped by CDC grade and the number of complications. Mean CCI score was also compared according to baseline characteristics of the included patients. Categorical data were grouped using the median. LOS of patients with intraabdominal collection or urine leak were compared between conservative management and intervention groups. LOS of patients with a different total number of complications were also compared. Correlations were presented using Scatter plot and correlation analysis using Pearson's Correlation Coefficient test. Strong correlation was defined as r^2 between 0.7 and 1.0 (-0.7 and -1.0). A moderate correlation was defined as r^2 between 0.3 and 0.7 (-0.3 and -0.7). A weak correlation was defined as r^2 between 0 and 0.3 (0 and -0.3).

2.4 Results

Characteristics of the included sample

A total of 198 patients were included in this study. Characteristics of the study

population were summarised in Table 1 and Table 2. Only 90 patients had PCS scores at 6 months. 49 patients had distress score at 6 months. 54 patients had pre-discharge 6MWT, whereas 44 patients had pre-discharge STS test outcomes.

Postoperative complications

112 patients (56.6%) had CDC grade II complications whereas 48 patients (24.2%) and 8 patients (4.0%) had grade III and grade IV complications, respectively. Overall inpatient mortality was 1.0% (n=2). The mean number of complications which was grade II or above were 2.7±2.4. The most common complications were the need for postoperative blood transfusion (n=102, 51.5%), urine leak (n=76, 38.4%), electrolyte derangements (n=48, 24.2%) and intraabdominal collection (n=43, 21.7%).

Of those who had an intraabdominal collection, 13 patients were managed with antibiotics alone, whereas 30 patients required percutaneous drainage of the collection. Patients who required interventional drainage had a significantly longer LOS (60.9±43.4 vs. 30.2±10.9, p=0.004). Amongst patients who had a urine leak, 54 patients were managed conservatively whereas 22 patients required an intervention either in the form of insertion of percutaneous nephrostomy (n=6, 27.3%) or surgery (n=8, 36.4%) or both (n=7, 31.8%). There was missing data for one patient who suffered from urine leak and required an intervention. There was a statistically significant difference in the LOS between the conservatively managed group and the intervention group (33.1±27.3 vs. 56.7±42.8 respectively, p<0.0001).

Correlation of CDC with postoperative outcomes

Table 1 summarised the postoperative outcomes of patients in each CDC group. Operative times, intraoperative blood loss, the likelihood of needing intraoperative blood transfusion and ICU stay increased with CDC grades ($p<0.001$, $p=0.023$, $p<0.0001$ and $p<0.0001$). Additionally, patients with a higher CDC grade complication also had a lower PCS score ($p=0.033$).

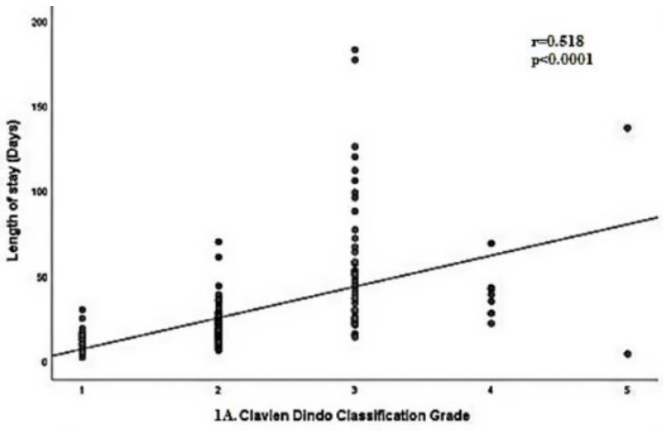
CDC grade was moderately correlated with LOS ($r=0.518$, $p<0.0001$, Figure 1A). Patients with grade III complications were found to have a much longer length of stay as compared to the rest of the groups ($p<0.0001$) (Table 1). CDC was also moderately adversely correlated with predischarge 6MWT distance ($r= -0.359$, $p=0.008$, Figure 1D). There was a weak association between CDC and PCS ($r= -0.292$, $p=0.005$, Figure 1B) however there was no association between CDC and distress score at 6 months ($r=0.113$, $p=0.438$) and STS time ($r=0.145$, $p=0.348$) (Figure 1C and 1E). There were no differences in distress score at 6 months, predischarge 6MWT and STS test amongst patients with complications of different CDC grades (Table 1).

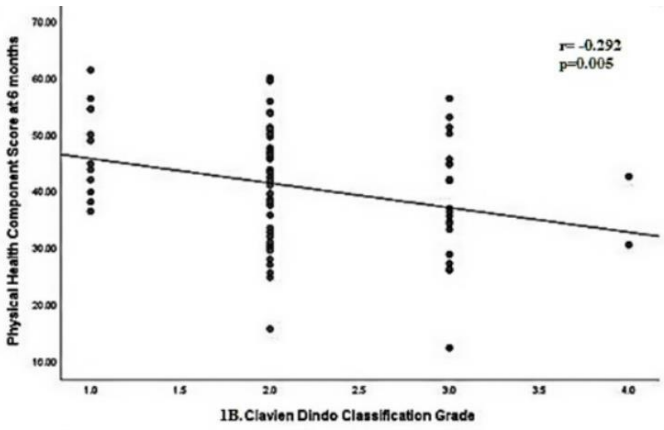
Table 1. Characteristics of the included sample according to CDC grade

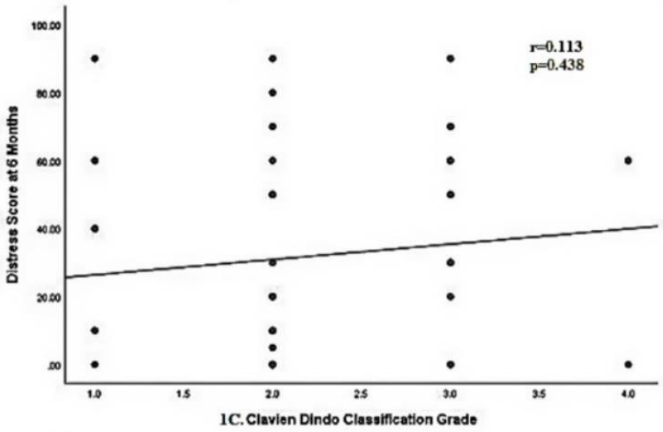
CDC Grade	Overall	0/1	2	3	4	5	P value
Number of patients	198	28 (14.1)	112 (56.6)	48 (24.2)	8 (4.0)	2 (1.0)	
Age (years)	58.5 ±13.0	54.9±14.0	59.2±13.3	58.8±13.7	63.5±12.0	63.5±12.0	0.487
Sex							0.131
Male	100 (50.5)	13 (46.4)	54 (48.2)	26 (54.2)	7 (85.7)	0 (0)	
Female	98 (49.5)	15 (53.6)	58 (51.8)	22 (45.8)	1 (12.5)	2 (100)	
Indications for surgery							0.310
Primary rectal	65 (32.8)	13 (46.4)	29 (25.9)	18 (37.5)	4 (50.0)	1 (50.0)	
Recurrent rectal	58 (29.3)	7 (25.0)	34 (30.4)	14 (29.2)	3 (37.5)	0 (0)	
Other primary	25 (12.6)	2 (7.1)	17 (15.2)	5 (10.4)	0 (0.0)	1 (50.0)	
Other recurrent	45 (22.7)	6 (21.4)	28 (25.0)	111 (22.9)	0 (0)	0 (0)	
Other	5 (2.5)	0 (0)	4 (3.6)	0 (0)	1 (12.5)	0 (0)	
Neoadjuvant radiotherapy	98 (49.7)	13 (46.4)	55 (49.5)	27 (56.3)	3 (37.5)	0 (0)	0.494
Neoadjuvant chemotherapy	108 (54.8)	15 (53.6)	60 (54.1)	29 (60.4)	3 (37.5)	1 (50.0)	0.802
Operative time (hours)	9.6±3.1	6.6±2.5	9.4±2.7	11.4±2.7	9.9±1.9	15.7±0.5	<0.0001
Intraoperative blood loss (mls)	2919.2±2817.7	1284.4±697.5	2900.8±2531.0	3240.4±3140.6	3850.0±5113.0	6750.0±4596.2	0.023
Intraoperative blood transfusion	141 (71.2)	8 (28.6)	81 (72.3)	45 (93.8)	5 (62.5)	2 (100.0)	<0.0001
Resection margin							0.715
R0	163 (82.3)	22 (78.6)	2 (84.8)	3 (79.2)	6 (75.0)	2 (100.0)	
R1/2	32 (16.2)	6 (21.4)	14 (12.5)	10 (20.8)	2 (25.0)	0 (0)	
Not assessed	3 (1.5)	0 (0)	3 (0)	0 (0)	0 (0)	0 (0)	
ICU stay (days)	4.1±3.3	2.2±1.6	3.6±1.9	5.0±4.0	9.9±6.8	10.5±9.2	<0.0001
Length of stay (days)	29.2±27.3	12.3±6.1	20.6±9.9	55.5±38.6	38.3±14.5	70.5±94.0	<0.0001
Mean number of complications	2.7±2.4	0	2.3±1.2	4.8±3.0	4.4±2.1	6.5±2.1	<0.0001
PCS Score at 6 months*	40.7 ±9.9	47.5±8.0	40.7±9.4	37.3±10.7	36.5±8.5	-	0.033
Distress score at 6 months#	31.7±28.9	35.7±32.1	25.5±27.4	44.2±28.4	30.0±42.4	-	0.300
Predischarge 6-minute walk test (meters)†	334.0±118.6	422.9±107.3	339.9±120.3	291.5±104.8	250.0±69.5	-	0.061
Predischarge sit-to-stand test (seconds)‡	16.6±13.0	12.5±6.8	17.0±16.0	16.6±5.5	25.1±11.1	-	0.149

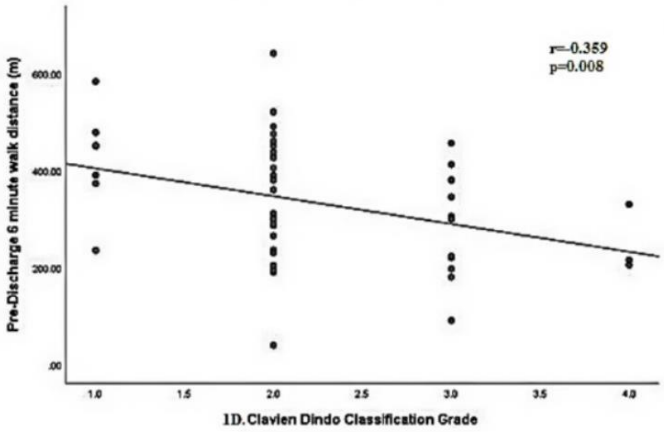
Data presented as mean ± standard deviation or frequency (percentage). ICU=Intensive care unit; * n=90; # n=49 † n=54;‡ n=44

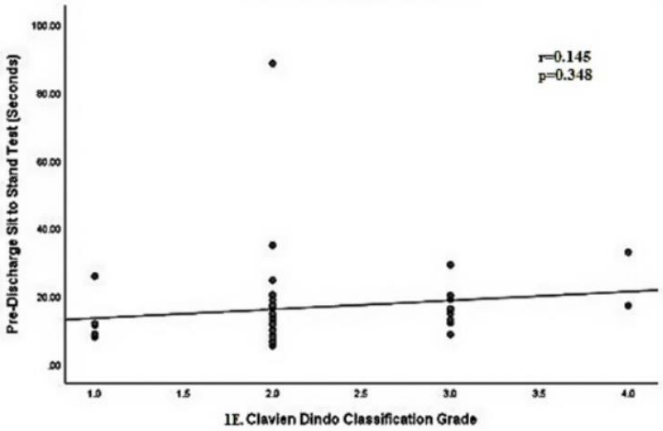
Figure 1. Correlations with CDC











Correlation of CCI with postoperative outcomes

The mean CCI was 39.1±17.4. A distribution of CCI score was demonstrated in Figure 2. Patients with longer operative time ($p<0.0001$), more intraoperative transfusion ($p=0.001$), longer ICU stay ($p=0.039$), and longer LOS ($p<0.001$) had a higher mean CCI scores. A lower CCI (less complications) score was also associated with a greater 6MWT distance ($p=0.026$) and a shorter time in the STS test ($p=0.029$) (Table 2).

CCI score was strongly correlated with LOS ($r=0.744$, $p<0.0001$, Figure 3A), moderately negatively correlated with predischarge 6MWT distance ($r= -0.388$, $p=0.007$, Figure 3D) and weakly adversely correlated with PCS ($r= -0.295$, $p=0.009$, Figure 3B). There was no association between CCI score and distress score at 6 months ($r=0.155$, $p=0.328$, Figure 3C) and predischarge STS time ($r=0.210$, $p=0.207$, Figure 3E).

Table 2 Differences in CCI score based on different clinical variables

Variables	Mean CCI ±SD	p
Age		0.646
<59.5	39.1±18.8	
≥59.5	39.1±15.8	
Sex		0.766
Male	39.2±18.1	
Female	39.1±16.7	
Indications for surgery		0.315
Primary rectal	41.1±18.9	
Recurrent rectal	40.4±15.8	
Other primary	40.0±25.0	
Other recurrent	34.0±9.9	
Other	41.0±18.4	
Neoadjuvant radiotherapy		0.650
Yes	38.7±15.2	
No	39.6±19.4	
Neoadjuvant chemotherapy		0.822
Yes	38.9±16.6	
No	39.4±18.4	
Operative time (hours)		<0.001
<9.8	33.3±12.3	
≥9.8	43.4±19.2	
Intraoperative blood loss (mls)		0.252
<2000	37.4±13.5	
≥2000	42.2±19.2	
Intraoperative blood transfusion		0.001
Yes	41.1±18.1	
No	31.3±11.5	
Resection margin		0.241
R0	39.0±18.0	
R1/2	40.9±14.1	
Not assessed	29.6±0	
ICU stay (days)		0.039
<3	33.9±10.5	
≥3	41.3±19.1	
Length of stay (days)		<0.001
<22	29.2±11.0	
≥22	46.2±17.6	
PCS Score at 6 months*		0.474
<41.8	39.9±18.3	
≥41.8	36.7±13.5	
Distress Score at 6 months#		0.493
<20	37.7±14.9	
≥20	43.1±18.8	
Predischarge 6-minute walk test (meters)†		0.026
<310.5	40.9±13.5	
≥310.5	32.2±11.7	
Predischarge sit-to-stand test (seconds)‡		0.029
<14.4	31.0±11.6	
≥14.4	39.2±10.7	

*Patients without complications or with grade 1 complications were excluded. Data presented as mean ± standard deviation or frequency (percentage). ICU=Intensive care unit; *n=78, , #n=42 † n=47, ‡ n=38*

Figure 2. Distribution of CCI scores

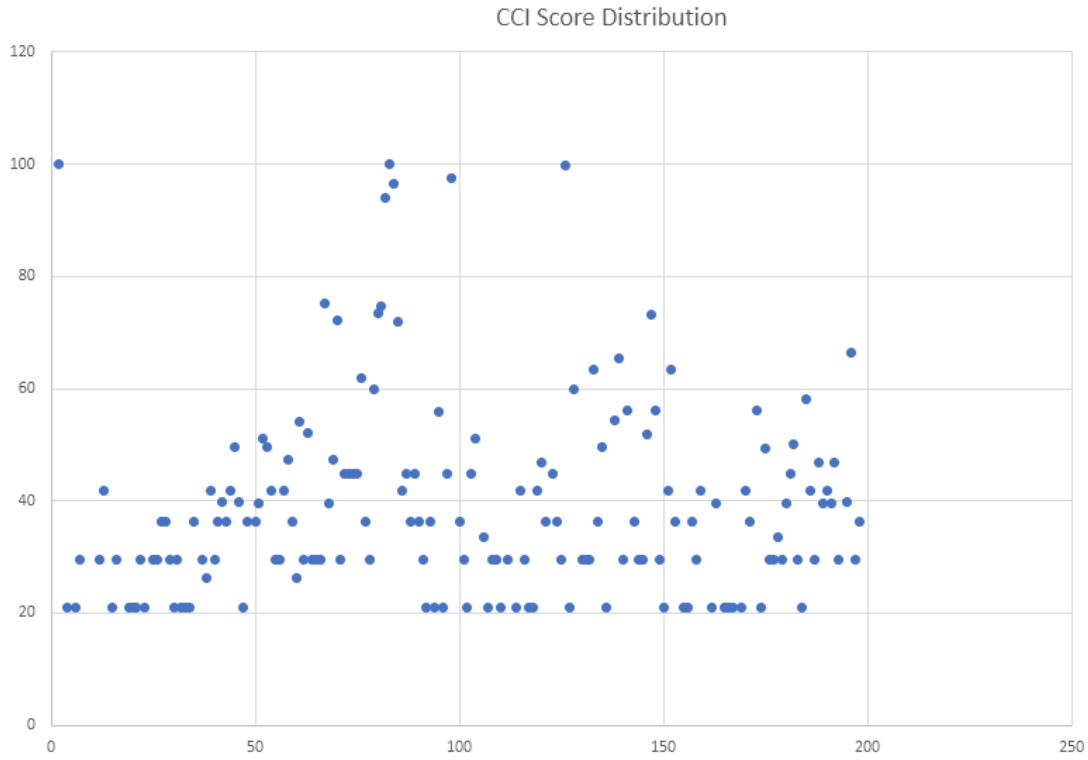
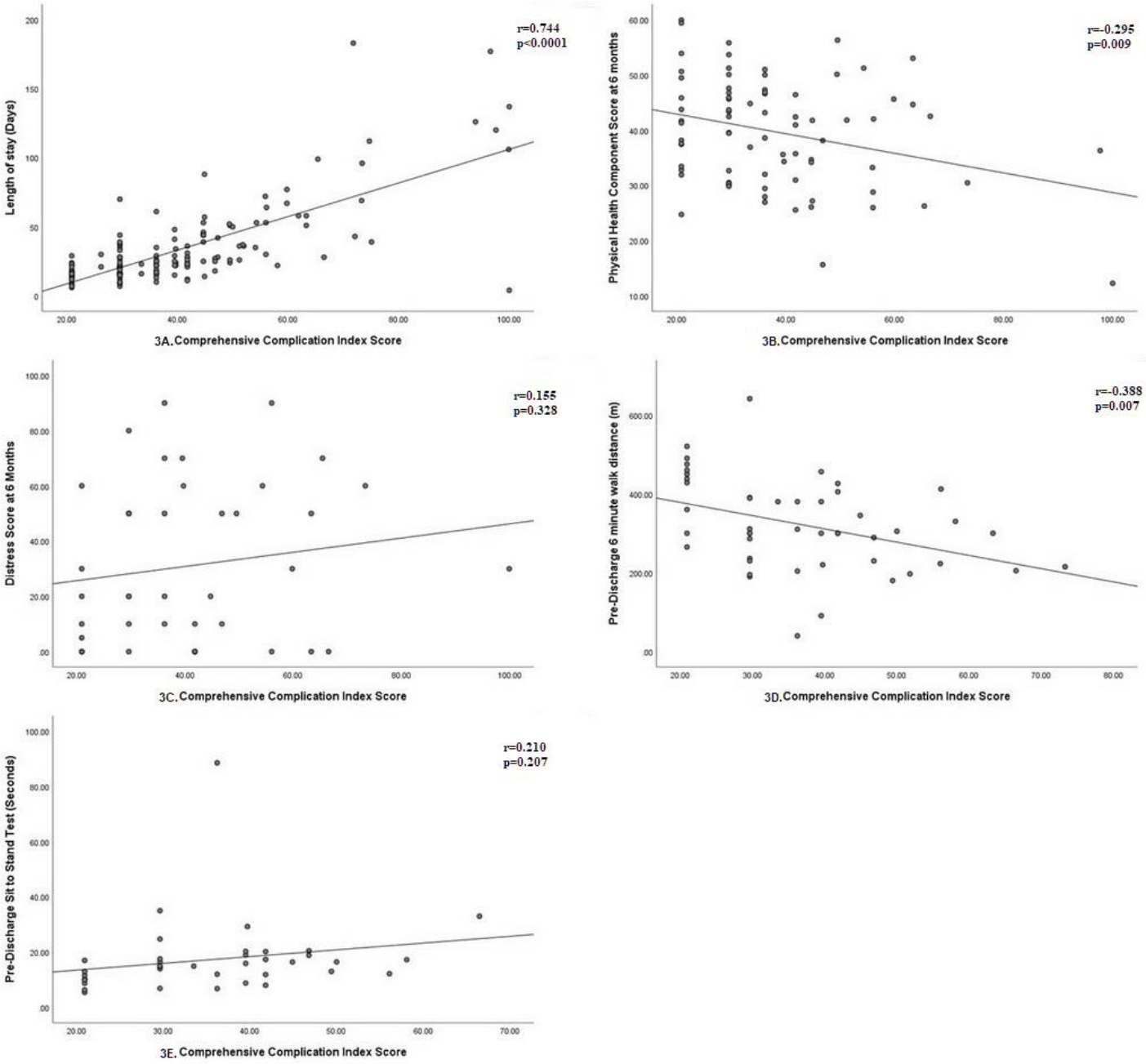


Figure 3. Correlations with CCI



Correlation of total number of complications with postoperative outcomes

Patients with >4 complications had the longest operative time ($p<0.0001$), ICU stay ($p=0.005$) and LOS ($p<0.0001$). These patients were found to have the shortest walking distance in 6MWT($p=0.004$) and spent longer time to complete STS test ($p=0.023$) (Table 3).

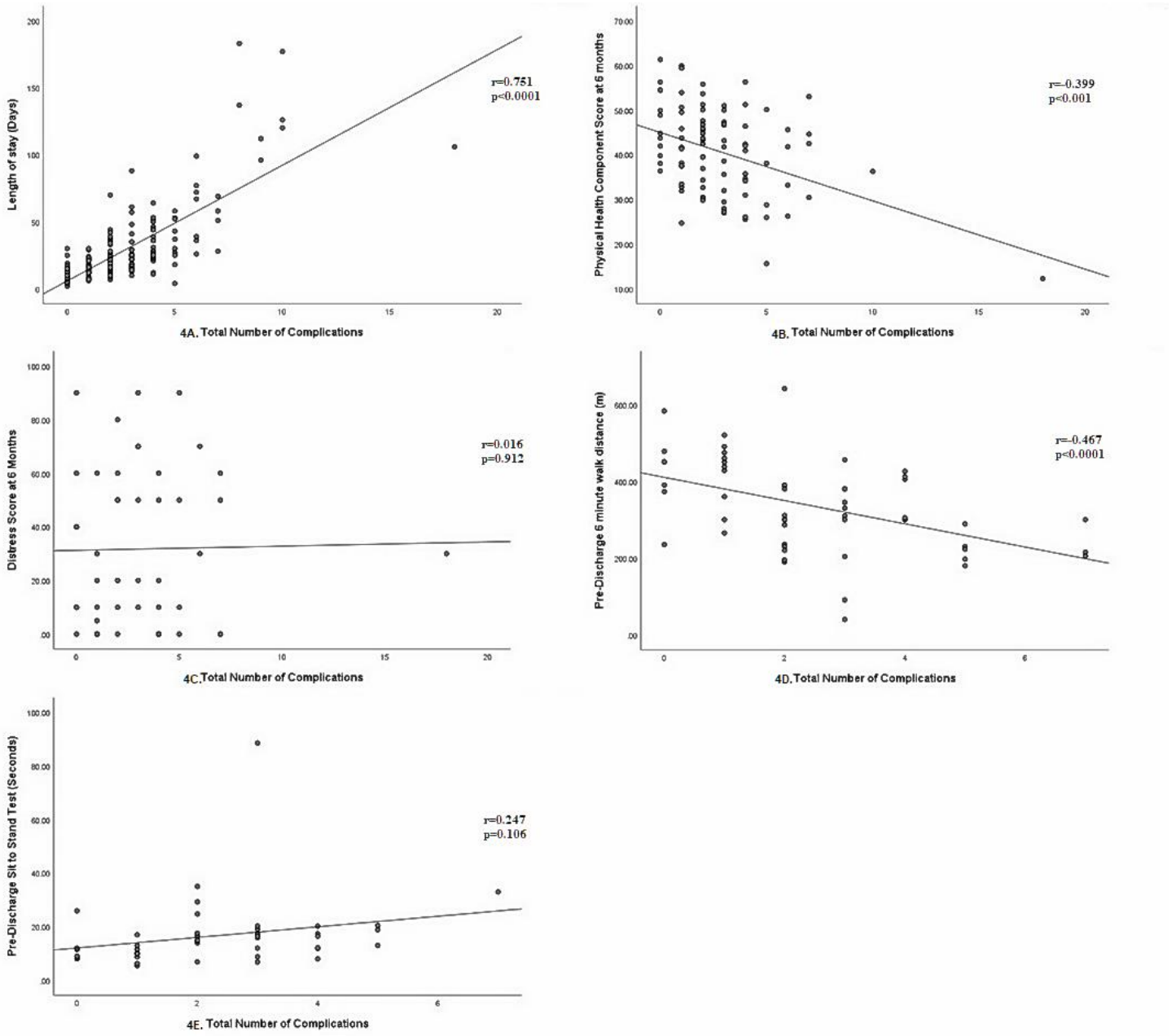
It was demonstrated that there was a strong association between the number of complications and LOS ($r=0.751$, $p<0.0001$) (Figure 4A). Patients with >4 complications had a much longer LOS than those with ≤4 complications (Table 2). The number of complications was also moderately adversely associated with PCS score at 6 months ($r= -0.399$, $p<0.001$, Figure 4B) and predischarge 6MWT distance ($r= -0.467$, $p<0.0001$, Figure 4D). There were no strong associations between total number of complications and distress at 6 months ($r= 0.016$, $p=0.912$, Figure 4C) and pre-discharge STS time ($r=0.247$, $p=0.106$, Figure 4E).

Table 3. Characteristics of the included sample according to number of complications

Number of complications	Overall	1	2	3	4	>4	P value
Number of patients	170	35 (17.7)	47 (23.7)	32 (16.2)	27 (13.6)	29 (14.6)	
Age (years)	58.2±13.2	54.5±14.5	59.9±12.4	60.7±12.8	58.3±12.7	57.2±12.3	0.279
Sex							0.344
Male	87 (51.2)	21 (60.0)	26 (55.3)	12 (37.5)	12 (44.4)	16 (55.2)	
Female	83 (48.8)	14 (40.0)	21 (44.7)	20 (62.5)	15 (55.6)	13 (44.8)	
Indications for surgery							0.534
Primary rectal	52 (30.6)	11 (31.4)	15 (31.9)	8 (25.0)	6 (22.2)	12 (41.1)	
Recurrent rectal	51 (30.0)	8 (22.9)	11 (23.4)	11 (34.4)	12 (44.4)	9 (31.0)	
Other primary	23 (13.5)	8 (22.9)	5 (10.6)	3 (1.8)	3 (1.8)	4 (2.4)	
Other recurrent	39 (22.9)	8 (22.9)	14 (29.8)	8 (25.0)	6 (22.2)	3 (10.3)	
Other	5 (2.9)	0 (0)	2 (4.3)	2 (6.3)	0 (0)	1 (3.4)	
Neoadjuvant radiotherapy	85 (50.3)	14 (40.0)	24 (52.2)	18 (56.3)	17 (63.0)	12- (41.4)	0.324
Neoadjuvant chemotherapy	93 (55.0)	18 (51.4)	25 (54.3)	18 (56.3)	17 (63.0)	15 (51.7)	0.906
Operative time (hours)	10.1±2.7	8.4±2.8	9.7±2.8	9.6±2.2	11.6±2.9	11.8±2.1	<0.0001
Intraoperative blood loss (mls)	3110.2±2910.1	2350.4±2199.2	3120.0±2781.4	2965.0±3289.6	3582.9±2742.8	3534.0±3217.2	0.306
Intraoperative blood transfusion	133 (78.2)	22 (62.9)	36 (76.6)	23 (71.9)	24 (88.9)	28 (96.6)	0.047
Resection margin							0.206
R0	141 (82.9)	31 (88.6)	2 (78.)	29 (0.6)	21 (77.8)	23 (79.3)	
R1/2	26 (15.3)	4 (11.4)	7 (14.9)	3 (9.4)	6 (22.2)	6 (20.7)	
Not assessed	3 (1.8)	0 (0)	3 (6.4)	0 (0)	0 (0)	3 (1.8)	
ICU stay (days)	4.4±3.4	3.5±2.0	3.6±2.0	3.6±1.7	4.2±1.9	7.7±6.1	0.005
Length of stay (days)	32.0±28.4	15.9 ±6.0	22.7±11.5	27.3±16.3	33.6±13.6	69.9±46.5	<0.0001
PCS Score at 6 months*	39.6±9.8	42.6±10.1	41.6±8.1	38.9±8.9	38.9±9.5	35.0±11.9	0.208
Distress Score at 6 months#	31.1±28.7	15.6±20.9	37.8±26.4	51.7±31.3	17.5±24.3	35.5±31.1	0.090
Predischarge 6-minute walk test (meters)†	320.9±115.4	418.6±83.5	312.9±120.9	283.6±132.5	358.0±62.1	229.9±42.9	0.004
Predischarge sit-to-stand test (seconds)‡	17.3±13.7	10.2±3.5	18.9±8.3	22.7±25.1	14.3±4.4	21.3±8.4	0.023

*Patients who had no complications or grade 1 complications were excluded Data presented as mean ± standard deviation or frequency (percentage). ICU=Intensive care unit; *n=78, #n=42, † n=47, ‡ n=38*

Figure 4. Correlations with number of complications



2.5 Discussion

This study demonstrated a moderate correlation between CDC and LOS, whereas a strong correlation was identified between CCI, the number of complications and LOS. All three classification systems were moderately negatively correlated with predischarge 6MWT distance. A weak association was established between CDC, CCI and PCS score, whereas the number of complications was moderately adversely associated with PCS.

In the last five years, there has been increasing use of CDC in reporting surgical complications in the exenteration literature. It is interesting to note that while CDC is increasingly utilised internationally, its correlation with LOS after PE was only modest. By contrast, CCI and the number of complications had better correlations than CDC after PE. It is even more worth noting that the correlation between LOS and the number of complications is even better, albeit only marginally so, compared to CCI, suggesting the number of complications is the main driver of LOS in these patients.

In some ways, this is not surprising because PE patients commonly experience multiple complications with varying severity. Using the CDC, which only considers the most severe complication, may limit its utility[10, 21]. Anecdotally, it has been observed that some patients with multiple and less severe complications may have longer LOS compared to those with more severe complications. The converse is also true with some patients who developed severe occult sepsis requiring readmission to ICU but responding rapidly with antimicrobial therapy. In these cases, patients may only require transient physiological support but scored a higher complication grade. For example, a

patient may require ICU admission for urosepsis (classified as CDC grade IV) after ileal conduit formation and be discharged to the ward the day after. On the other hand, a patient may require multiple operations for perineal wound dehiscence (CDC grade III) and suffer from longer stay and more mental stress. It was reflected by the fact that patients with CDC grade III had the longest LOS in this study. Additionally, as CDC only provides generic criteria, it can be challenging to grade some complications and be subject to bias by the grader[22]. For example, insertion of a nasogastric tube for ileus is variable with different surgeons and not specified in CDC grading. However, ileus is not an uncommon complication after gastrointestinal surgery and can significantly affect patients' postoperative recovery.

On the other hand, the CCI combines both number of complications as well as the severity of complications, making it more user-friendly. It was developed using 30 scenarios presenting the five most common complications of each grade CDC I to IVb, giving each complication with different frequencies a relative severity[10]. It contains a continuous scale from 0 to 100, with a higher score indicating worse complication[10]. Given the complexity of PE and the fact that patients often suffer from multiple complications, CCI correlates better with LOS than the CDC classification and may be a better audit tool and predictor of outcomes.

However, CCI also has several drawbacks. It was validated mainly using liver surgery, which is far less complicated than PE. It was developed based on the subjective perception of patients and physicians on the scenario. These patients did not experience the actual complications. Whether those patients' perceptions of complications are

transferrable to patients who underwent PE is still questionable. Patients' perceptions can also be affected by their pre-existing medical conditions[10]. Although CCI is a comprehensive grading system, it is resource-intensive for accurate data collection during a patient's journey as patients often have multiple complications following PE. Accurately collecting all complications, especially of low grades, can be challenging.

Other than LOS, there is a corresponding reduction in the physical strength assessed by 6MWT using the number of complications. These findings indicate that not only does complications impact LOS, more importantly, it also affects patients' well-being and physical status at the time of discharge. Considering the high postoperative complication rates after PE, interventions that may reduce and minimise complications should be considered. Although cost was not assessed in this study, it has been established that postoperative complications can increase treatment-related costs of PE[23].

LOS was chosen in this study as one of the outcomes measures as it is readily available and can be accurately calculated[11]. However, for complex gastrointestinal surgery like PE, other factors such as geographical distance can significantly affect LOS significantly[24]. It may not accurately reflect the physical and QoL impacts of PE on patients. Additionally, no correlation between the three classifications and distress score at 6 months was identified in this study. It could be due to the small numbers in this study. Also, six months was the first postoperative time point recorded at our centre. Distress scores at 1 month and 3 months are likely to be more sensitive and appropriate. However, this data was not available at our institution.

Given that each classification has its advantages and limitations, there is no perfect classification to grade complications after PE at the present days. CCI is a potential classification but requires validation in PE surgery. It also requires intense data entry which may pragmatically limit its use in PE service. The most ideal system should be easy to use in the clinical setting and requires low level of resources to maintain. It would be ideal if the usual postoperative medication regimens including analgesia and antiemetics can be defined in the classification systems. The common complications that are specific to PE such as ileus requiring nasogastric tube alone can also be included. CCI could be potentially modified to overcome the limitations of current system to be used for PE with refined criteria. The feasibility of the potential classification should be trialled and validated before implementation.

Other systems including National Surgical Quality Improvement Program (NSQIP) has been used in the literature to provide surgical morbidity data[25]. However, NSQIP only started at our centre within the last 12 months. The period of this study was not covered in NSQIP database. In addition, the data is collected in a different way and not collected for all patients in NSQIP database. Also, our database was collected prospectively and designed specifically for PE. The research officers collected all data including complication data prospectively. The data used in this study was retrospectively coded the data and supplemented the data collection. The data was also supplemented by the regular morbidity and mortality meetings in PE. In addition, the research officers sat down with the clinical supervisors regularly to go through the data. Random audits were also performed to make sure the data collection was as accurate as possible. Our research officers are all experienced and trained in collecting data for PE.

This study has several limitations. Firstly, data for the specific number for grade I complications was not available in this study, so they have been grouped with no complications. It limited the calculation of the CCI score and may falsely undermine the correlation between CCI and LOS following PE. Secondly, we did not have distress score and PCS scores earlier than at the 6-month follow-up. In addition, not all patients had PCS score at 6 months, distress score at 6 months, predischarge 6MWT and STS test. There is a high rate of missing data on those scores in this study. Significances may not be present given small numbers of a relatively uncommon operation.

The data collection depends on staff availability, and we tend to combine a number of indications for their return to allow data collection e.g. stomal therapy appointment, follow-up with PE surgeon. Physiotherapists may not be available at the time especially if they were not the main reason why the patient was having the appointments. This accounts for the large number of missing data. In addition, a lot of our patients, at least 35%, are interstate or regional patients. Our policy is always to refer back to the referring surgeon for ongoing reviews. Hence, only in strenuous situations, they tend to come back for a review. The underlying reasons for the missing data could potentially bias the results. More data is warranted. Prior to conducting this study, as a pilot, medical records were reviewed with co-supervisors for the first ten patients to ensure accurate data collection. Given my clinical experience as a surgical registrar, I was able to determine the CDC grade based on the medical records. Therefore, it is difficult to determine the reproducibility and validity of the results of this study.

2.6 Conclusions

Complications are common after PE. They increased LOS and diversely affected functional outcomes and increased distress. Of the classifications assessed, the CCI and number of complications correlate better with LOS and functional outcomes, but further studies are necessary.

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CHAPTER 3. Quality of life implications of pelvic exenteration surgery. A comparative study: locally advanced versus locally recurrent rectal cancer

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This chapter provided an overview of perioperative outcomes and compared QoL outcomes between patients with locally advanced and locally recurrent rectal cancers, highlighting any differences in QoL between these two cancers after pelvic exenteration.

3.1 Abstract

Introduction

It is challenging to treat locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC). Although pelvic exenteration (PE) remains the only curative options for these two diseases, the disease pathophysiology and anatomy of resection appears to be inherently different. There is, however, limited evidence on the differences in surgical and quality of life (QoL) outcomes between the two. Therefore, the aim of this study was to compare surgical outcomes of patients with LARC and LRRC undergoing PE and identify any differences or predictors of QoL between these two diseases.

Methods

This was a cohort study of patients with LARC or LRRC who underwent PE at Royal Prince Alfred Hospital, Sydney, Australia and were included in a QoL and outcome study between July 2008 and March 2019.

Results

271 patients were included in this study, with 111 patients diagnosed with LARC and 160 patients diagnosed with LRRC. LARC patients received higher rates of neoadjuvant chemoradiotherapy ($p<0.001$), R0 resection (88% vs. 74%, $p=0.003$) and had greater median overall survival (75.1 vs. 45.8 months) than LRRC, although the latter was clinically but not statistically significant. There was no difference in bone resection, obturator and sciatic nerve resection, flap reconstruction, nor total cystectomy.

There was a higher blood loss ($p<0.001$), longer LOS ($p=0.039$) and longer operative time ($p=0.002$) in the LRRC group. Patients with LRRC had a higher mean baseline PCS and a higher FACT-C score when compared to those with LARC. However, despite the more complicated surgery and increased recovery time, there were no significant differences in complications or QoL outcomes between LARC and LRRC at any time points postoperatively up to 12 months.

Conclusion

Patients with LRRC tend to require a more extensive surgery with a longer operative time and more blood loss, and longer recovery from surgery, but despite this, their QoL is comparable to those with LARC.

3.2 Introduction

Patients with locally advanced rectal cancer (LARC) or locally recurrent rectal cancer (LRRC) often suffer from considerable symptoms, including pain, bowel, bladder or sexual dysfunction[1]. The only curative option for these very advanced cancers and most recurrent rectal cancers is a multi-visceral "en bloc" resection, i.e. pelvic exenteration (PE). A clear resection margin is the most important for survival and quality of life and is also related to postoperative complications[2]. PE is now established as the procedure of choice to improve local control and improve survival[3-5]. The five-year survival has improved to 52-60% for patients with LARC and 28-40% for patients with LRRC[5, 6].

Although LARC and LRRC are different disease entities of the same organ of origin, the surgical approach to resectability is contrasted by the different pathophysiology of recurrent disease and the loss of the previous TME anatomical planes. It is of interest to compare the surgical and quality of life (QoL) outcomes between the two following PE to better inform our patients of the likely results of surgical intervention. While the number of QoL studies have increased significantly over the past ten years in the surgical literature, there remain relatively few studies that have investigated QoL of patients with LARC and LRRC either collectively or separately[3, 6, 7]. Additionally, no studies have directly compared QoL outcomes between the two diseases[4-6, 8]. As far as the authors are aware, there has only been one study that compared surgical outcomes between LARC and LRRC after PE[9].

Therefore, the current study aimed to compare surgical outcomes of patients with LARC and LRRC undergoing PE and identify any differences in QoL or predictors of

QoL between patients with LARC and LRRC.

3.3 Patients and Methods

Study Design

This was a cohort study of prospectively collected data of consecutive patients with rectal cancer who underwent PE at Royal Prince Alfred Hospital, Sydney, Australia, between July 2008 and March 2019 and were part of a prospective QoL study. This study has been approved by Sydney Local Health District Human Ethics Research Committee (X19-0215&2019/ETH10689).

Inclusion and exclusion criteria

Patients diagnosed with a LARC and LRRC who also consented to enrol in a prospective QoL study were included in this study. A LARC was defined as a tumour staged as a T4 rectal cancer on pelvic magnetic resonance imaging (MRI) with contiguous involvement of an adjacent structure. LRRC was described as a local recurrence that occurred at least six months after initial treatment of primary rectal cancer. Other exclusion criteria included patients aged ≤18 years at the time of surgery and patients who underwent PE for other advanced pelvic malignancies or conditions other than cancer. As with previous publications from the authors' institution, PE was defined as the removal of the rectal tumour and rectum and at least >50% of two or more compartment organs and/or bone or neurovascular resection[10]. Patients were divided into two groups (LARC vs. LRRC).

Patient recruitment and QoL Measures

All patients were discussed at a dedicated multidisciplinary team meeting that reviewed relevant clinical history and imaging[11]. Routine investigations included a CT scan of the chest, abdomen and pelvis, pelvic MRI and positron emission tomography. Patients deemed to have the resectable disease were reviewed by the responsible surgeon, who was also responsible for patient recruitment. Potential participants are provided with an information pack that includes participant information sheet, consent form and QoL questionnaire in a reply-paid envelope. Patients that returned their signed consent form and completed the QoL questionnaire entered the study and were followed up via postal mail, email, or phone-based on participants' preferences.

QoL measures were collected prospectively in a longitudinal manner using the same questionnaire. From 2008 and 2019, QoL measures were collected at baseline and subsequently at 6 monthly intervals to 5 years. For this study, only data from baseline, 6 months and 12 months were used. A clinical database routinely collected relevant clinical data, including patient demographics, surgical data, pathology data and complications. The main outcome measures included a generic (Short Form 36 Version 2, SF-36v2) and a disease-specific QoL instrument (Functional Assessment of Cancer Therapy- Colorectal (FACT-C).

The SF-36v2 is a well-validated and reliable QoL assessment tool comprising 36 questions. It consists of eight multi-item scales of functional health and wellbeing. Additionally, it can be combined into the physical component score (PCS) and mental component score (MCS). Each component has a score ranging from 0 to 100[12, 13]. The

FACT-C score is a reliable and valid measure to assess colorectal cancer-specific QoL[14]. It comprises 27 items relating to physical, social, emotional, and functional health and a further ten questions specific to colorectal cancer. The FACT-C score range from 0 to 136. For both instruments, a higher score indicates better QoL[13].

Perioperative outcomes

Clinical factors including gender, age, use of neoadjuvant therapy, margin status, need for major nerve or bony resection, or perineal flap reconstruction, estimated blood loss (ml), length of stay (days) in hospital, postoperative complications and surgical resection compartments were compared. Neoadjuvant therapy included neoadjuvant chemotherapy and/or radiotherapy. R0 resection was defined as a microscopically clear margin of ≥0.5mm. R1 was defined as a microscopically involved margin, whereas R2 was defined as a macroscopically involved margin. Length of stay was defined as the duration of hospital stay after the operation. Survival was calculated from the last follow-up date or date of death from the date of surgery.

Statistical analyses

All statistical analyses were performed using SPSS for Windows Version 26 (IBM Corporation, New York, USA). Correlations between clinical variables and QoL scores at 6 months and 12 months were explored. Categorical data were presented as frequencies (%), and continuous data as mean (standard deviation, SD). A comparison of continuous variables was performed using the independent t-test. Categorical variables were analysed using the Chi-square test or Fisher' exact test where appropriate.

Univariate analysis was performed using logistic regression. Variables with a $p<0.2$ on the univariate analysis were entered in a multivariate logistic regression analysis. Age, neoadjuvant chemoradiotherapy, and surgical margin were forced into the model to minimise potential confounding factors. To avoid duplication, the same data point that is collected variable across multiple fields are eliminated if the p value <0.2 for one. For instance, if the p value of bony resection was <0.2 in univariate analysis, data for pubic bone and sacrum was not entered in multivariate analysis to avoid duplicate data.

Similarly, if the p value for nerve resection was less than 0.2 in univariate analysis, data for obturator nerve and sciatic nerve were entered in multivariate analysis. Survival analysis was performed using the Kaplan-Meier curve. A $p<0.05$ was considered statistically significant.

3.4 Results

Patient characteristics

A total of 271 patients with rectal cancer underwent PE between July 2008 and March 2019. 111 patients (41.0%) had LARC, whereas 160 patients (59.0%) had LRRC. Table 1 summarises the characteristics of patients with rectal cancer. Patients with LARC were significantly younger than those with LRRC ($p=0.047$). A significantly higher percentage of patients received neoadjuvant chemoradiotherapy ($p<0.001$) and achieved R0 resection (88% vs. 74%$p=0.003$) in the LARC group. More patients with LRRC required an obturator nerve resection (13.8% vs. 10.8%) and a sciatic nerve resection (n=15% vs. 7%), although there were no statistical significances. Patients with LRRC also had a higher blood loss ($p<0.001$), longer LOS ($p=0.039$) and longer

operative time (p=0.002) (Table 1).

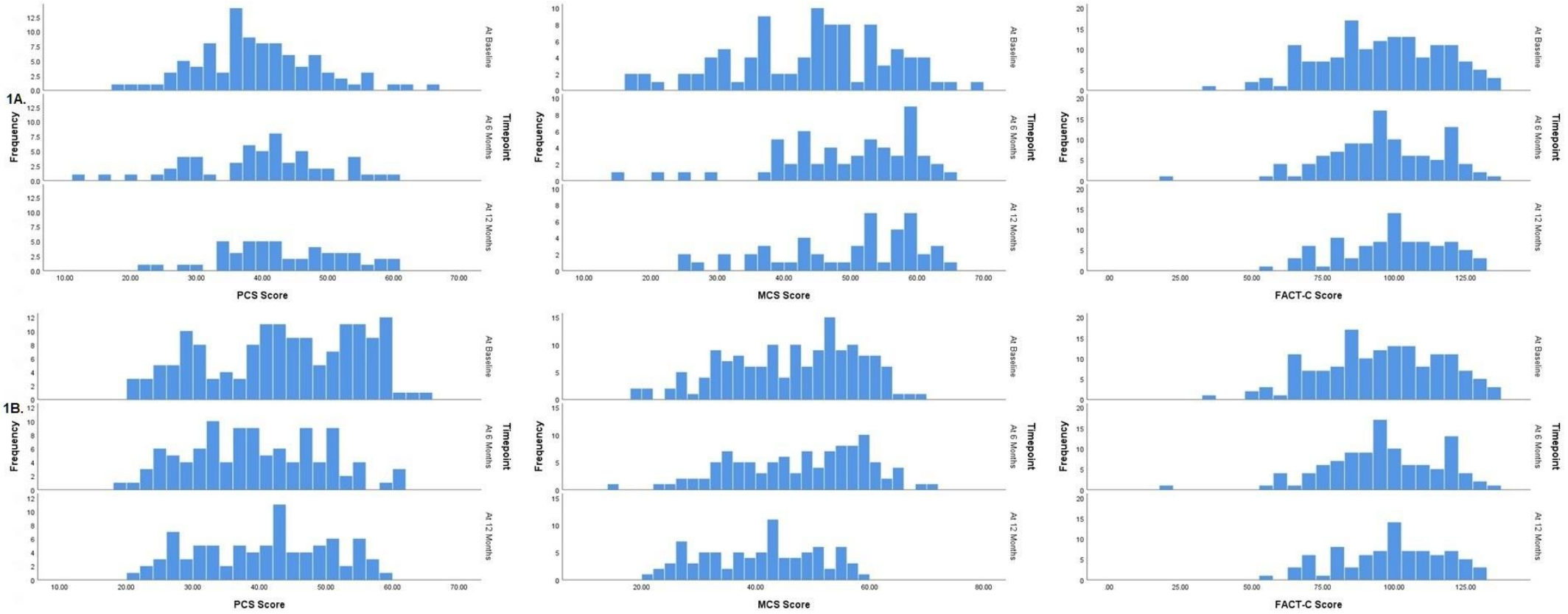
Patients with LARC had a lower mean baseline PCS (38.6±9.2 vs. 43.1±11.3, p=0.001) and a lower FACT-C (85.8±20.9 vs. 95.3±20.9, p=0.001) when compared to those with LRRC. However, there were no significant differences in QoL scores between LARC and LRRC at any time points postoperatively (Table 1 and Figure 1).

Table 1. Demographic, surgical outcomes and quality of life data of the included sample

Variables	Overall (N=271)	LARC (N=111)	LRRC (N=160)	P Value
Age, years	58.6±12.6	58.2 ±14.2	61.3 ±9.6	0.047
Sex				
Male	180 (66.4)	74 (66.7)	106 (66.3)	0.943
Female	91 (33.6)	37 (33.3)	54 (33.8)	
Neoadjuvant Chemoradiotherapy	196 (72.3)	102 (91.9)	94 (61.8)	<0.001
Surgical Margin				
R0	215 (79.3)	98 (88.3)	117 (73.6)	0.003
R1-R2	55 (20.3)	13 (11.7)	42 (26.4)	
Bony Resection	189 (69.7)	71 (64.0)	118 (74.2)	0.071
Pubic bone	22 (8.1)	6 (5.4)	16 (10.0)	0.173
Sacrum	160 (59.0)	61 (55.0)	99 (62.3)	0.229
Obturator Nerve Resection	34 (12.5)	12 (10.8)	22 (13.8)	0.473
Sciatic Nerve Resection	32 (11.8)	8 (7.2)	24 (15.0)	0.051
Flap reconstruction	61 (22.5)	21 (19.1)	40 (25.0)	0.254
Cystectomy				
Partial/total	180 (66.4)	70 (63.1)	110 (68.8)	0.330
No	91 (33.6)	41 (36.9)	50 (31.3)	
Blood loss, mL	2968.3±2428.3	2280.8±1948.1	3420.5±2606.7	<0.001
Length of hospital stay, days	25.9±16.7	23.4±15.2	27.6±17.6	0.039
Operative time, hours	10.1±3.5	9.3 ±3.2	10.6±3.6	0.002
Postoperative complication	251 (92.6)	101 (91.0)	150 (93.8)	0.694
Compartments				
All compartments	94 (34.7)	33 (29.7)	61 (38.1)	0.153
Anterior	170 (62.7)	65 (58.6))	105 (65.6)	0.237
Posterior	185 (68.3)	64 (57.7)	121 (75.6)	0.002
Central	219 (80.8)	91 (82.0)	128 (80.0)	0.684
Right lateral	173 (63.8)	61 (55.0)	112 (70.0)	0.011
Left lateral	184 (67.9)	59 (53.2)	125 (78.1)	<0.0001
Quality of Life				
Baseline				
PCS	41.4±10.8	38.6±9.2	43.1±11.3	0.001
MCS	45.0±11.6	43.4±11.7	46.0±11.4	0.091
FACT-C Total	91.6±21.4	85.8±20.9	95.3±20.9	0.001
6 Months				
PCS	38.9±10.0	39.0±10.3	38.9±10.0	0.945
MCS	47.7±11.3	48.6±10.8	47.2±11.6	0.451
FACT-C Total	95.4 ±0.5	94.0±22.3	96.2±19.6	0.547
12 Months				
PCS	41.1±9.7	42.6±9.2	40.3±9.9	0.188
MCS	48.6±10.2	48.8±10.9	48.5±9.9	0.875
FACT-C Total	98.1±19.1	97.0±21.3	98.7±17.8	0.620
Median survival (Months) (95%CI)	57.5 (41.4-73.6)	75.1 (47.5-102.8)	45.8 (31.8)	0.118
1-year OS (%)	89.3	91.0	88.1	
3-year OS (%)	63.2	67.0	57.4	
5-year OS (%)	48.7	59.0	42.4	

Data presented as frequency (%) or mean (Standard deviation); LARC: Locally advanced rectal cancer; LRRC: Locally recurrent rectal cancer; PCS: Physical component score; MCS: Mental component score; PCS and MCS scores ranges from 0-100. FACT-C: Functional Assessment of Cancer Therapy-Colorectal Cancer. FACT-C Total score ranges from 0 to 136. A higher PCS, MCS, or FACT-C Total score indicates a better quality of life; CI- confidence interval; OS- Overall Survival

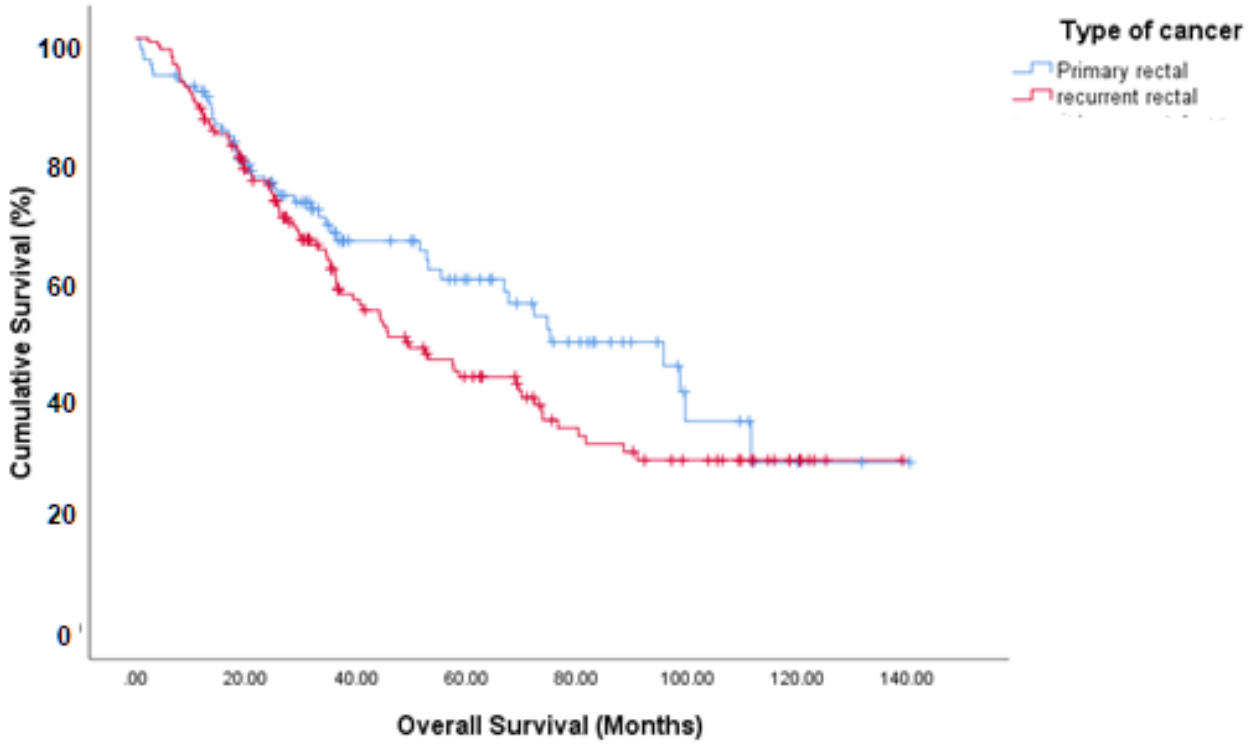
Figure 2 Histograms of QoL scores for LARC and LRRC (1A-LARC, 1B-LRRC)



Survival

The overall median overall survival (OS) of patients with rectal cancers was 57.5 months (95%CI= 41.4-73.6). The median OS of patients with LARC was longer than those with LRRC (75.1 months vs. 45.8 months) with a 5-year OS of 59.0% for LARC and 42.4% for LRRC, although this was not statistically significant (p=0.118) (Table 1 and Figure 2).

Figure 2. Overall survival of LARC vs. LRRC



Predictors of QoL Outcomes- LARC

In the multivariate analysis, increasing age was found to be associated with a better FACT-C score at 6 and 12 months (beta= 0.462, 95%CI=0.013-0.912, p=0.044 and beta=0.491, 95%=0.042-0.940, p=0.033 respectively). Having a sciatic nerve resection was associated with a poorer PCS score at 6 months (beta=-27.360, 95%CI=-47.333- -7.387, p=0.008). Increasing hospital stay was correlated with a lower FACT-C score at 12 months (beta= -0.557, 95%CI=-1.103- -0.100, p=0.018). Additionally, increasing blood loss and LOS were also negatively correlated with a PCS score at 12 months (beta= -0.001, 95=-0.003-0.000, p=0.020 and -0.258, 95%=-0.443- -0.072, p=0.008 respectively) (Table 2).

Table 2. Univariate and multivariate analysis investigating the association between locally advanced rectal cancer surgical outcomes and changes in quality of life

Variables	FACT-C at 6 Months				PCS at 6 Months				MCS at 6 Months			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)		Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	p
Male sex	-6.870 (-19.915-6.175)	0.296	-	-	-1.425(-7.546-4.696)	0.643			**-4.438 (-10.761-1.886)**	0.165	-4.438 (-10.761-1.886)	0.165
Age, years	**0.462 (0.013-0.912)**	0.044	0.462 (0.013-0.912)	0.044	0.088 (-0.124-0.300)	0.407	0.067 (-0.164-0.298)	**0.561**	**0.130 (-0.091-0.351)**	0.243	0.148 (-0.073-0.370)	0.184
Neoadjuvant chemoradiotherapy	12.359 (-14.246-38.965)	0.356	12.992 (-12.829-38.813)	**0.317**	**2.616 (-7.074-12.306)**	0.591	3.526 (-5.858-12.910)	0.453	1.584 (-8.607-11.775)	0.756	5.757 (-4.574-16.088)	0.268
R1/2 surgical margin	2.598 (-15.665-20.861)	0.776	3.803 (-14.108-21.714)	0.672	3.122 (-5.212-11.457)	0.456	3.048 (-6.089-12.186)	0.505	-5.633 (-14.292-3.027)	0.198	-6.449 (-15.054-2.155)	0.139
Any bony resection	-2.354 (-15.750-11.042)	0.726	-	-	-2.982 (-8.952-2.989)	0.321	-	-	-0.344 (-6.669-5.981)	0.914	-	-
Pubic bone	11.968 (-14.652-38.588)	0.371	-	-	-1.596 (-12.345-9.153)	0.767	-	-	-3.923)15.166-7.320)	0.487	-	-
Sacrum	0.402 (-11.880-12.648)	0.948	-	-	-3.021 (-8.558-2.517)	0.279	-	-	-1.427 (-7.292-4.438)	0.628	-	-
Obturator nerve	-13.230 (-36.402-9.941)	0.257	-	-	-9.673 (-20.102-0.756)	0.068	-3.215 (-15.310-8.879)	0.595	0.923 (-10.368-12.214)	0.870	-	-
Sciatic nerve	-19.217 (-51.324-12.890)	0.235	-	-	-10.870 (-25.502-3.762)	0.142	-27.360 (-47.333-7.387)	0.008	8.148 (-7.367-23.663)	0.297	-	-
Flap reconstruction	2.179 (-11.791-16.150)	0.756	-	-	1.643 (-4.740-8.026)	0.608			0.381 (-6.335-7.097)	0.910	-	-
Cystectomy	-2.975 (-15.486-9.536)	0.635	-	-	-5.006 (-10.526-0.613)	0.080	-3.865 (-9.647-1.918)	0.185	-4.211 (-10.172-1.750)	0.162	-3.699 (-10.000-2.602)	0.244
Blood loss (mL)	-0.001 (-0.004-0.002)	0.524	-	-	**-0.001 (0.003-0.000)**	0.150	-0.001 (-0.002-0.001)	0.472	0.000 (-0.002-0.001)	0.744	-	-
Length of hospital stay, days	-0.072 (-0.437-0.292)	0.692	-	-	-0.015 (-0.185-0.154)	0.857	-	-	-0.107 (-0.283-0.069)	0.228	-	-
Operative time, hours	-1.088 (-3.019-0.843)	0.264	-	-	-0.191 (-1.100-0.719)	0.676	-	-	-0.286 (-1.239-0.668)	0.551	-	-
Presence of postoperative complication	13.230 (-9.941-36.402)	0.257	-	-	3.750 (-6.959-14.459)	0.486	-	-	5.808 (-5.375=16.990)	0.302	-	-

Variables	FACT-C at 12 Months				PCS at 12 Months				MCS at 12 Months			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)		Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
Male sex	-11.508 (-24.257-1.242)	0.076	-10.315 (-23.630-3.000)	**0.125**	**-4.998 (-10.4799-0.483)**	0.073	-1.874 (-7.704-3.956)	0.519	-0.920 (-7.680-5.839)	0.785	-	-
Age, years	0.356 (-0.074-0.785)	0.102	0.491 (0.042-0.940)	**0.033**	**0.033 (-0.157-0.222)**	0.732	0.110 (-0.072-0.292)	0.230	0.073 (-0.152-0.299)	0.517	3.173 (-3.276-9.621)	0.327
Neoadjuvant chemoradiotherapy	-11.706 (-24.032-10.621)	0.297	-5.272 (-27.681-17.137)	**0.637**	**-0.194- (-9.911-9.522)**	0.968	2.545 (-6.261-11.350)	0.562	-2.989 (-14.542-8.564)	0.605	-1.126 (-12745-10.494)	0.846
R1/2 surgical margin	-1.559 (-21.986-18.868)	0.879	-	-	-2.864 (-11.613-5.885)	0.513	-3.785 (-11.406-3.836)	**0.332**	**-0.173 (-10.653-10.307)**	**0.974**	-0.531 (-11.023-9.960)	0.919
Any bony resection	-2.522 (-15.495-10.450)	0.697	-	-	-2.638 (-8.173-2.898)	0.343	-	-	**6.200 (-0.211-12.612)**	0.058	6.200 (-0.2111-12.612)	0.058
Pubic bone	28.583 (-14.348-71.515)	0.187	30.066 (-10.775-70.907)	0.145	2.479 (-16.324-21.282)	0.792	-	-	12.500 (-9,635-34.635)	0.262	-	-
Sacrum	-4.753 (-17.067-7.562)	0.441	-	-	-2.774 (-8.043-2.494)	0.295	-	-	1.669 (-4.669-8.007)	0.599	-	-
Obturator nerve	1.420 (-24.375-27.215)	0.912	-	-	-3.449 (-14.501-7.602)	0.533	-	-	4.167 (-9.009-17.343)	0.528	-	-
Sciatic nerve	-2.042 (-45.781-41.697)	0.926	-	-	5.542 (-13.205-24.288)	0.555	-	-	9.438 (-12.828-31.703)	0.398	-	-
Flap reconstruction	3.311 (-11.039-17.661)	0.645	-	-	**-0.536 (-6.721-5.649)**	0.862	-	-	**1.759 (-5.600-9.118)**	0.633	-	-
Cystectomy	-7.376 (-20.022-5.269)	0.247	-	-	-4.190 (-9.570-1.190)	0.124	-3.528 (-9.297-2.242)	0.224	-3.197 (-9.711-3.316)	0.328	-	-
Blood loss (mL)	-0.003 (-0.006-0.001)	0.107	0.000 (-0.004-0.004)	**0.923**	**-0.002 (-0.003--0.001)**	**0.003**	-0.001 (-0.003-0.000)	0.020	0.000 (-0.002-0.001)	0.569	-	-
LOS, days	-0.465 (-0.890- -0.041)	0.032	-0.557 (-1.103- -0.100)	0.018	-0.267 (-0.442--0.092)	0.004	-0.258 (-0.443- -0.072)	0.008	-0.126 (-0.351-0.100)	0.269	-	-
Operative time, hours	-2.014 (-4.027- -0.001	0.050	-0.804 (-3.172-1.563)	0.496	-0.819 (-1.689-0.050)	0.064	0.586 (-0.550-1.721)	0.303	-0.359 (-1.430-0.712)	0.503	-	-
Presence of postoperative complication	-3.267 (-25.835-19.302)	0.772	-	-	3.344 (--6.323-13.012)	0.490	-	-	0.550 (-11.035-12.135)	0.924	-	-

Data presented as odds ratio (95% confidence intervals Univariate variables in bold were entered into multivariate analysis (P<0.2). R0 surgical margin forced into multivariate analysis. Only significant results (p<0.05) in multivariate analysis were present. PCS: Physical Component Score; MCS: Mental component score; FACT-C: Functional Assessment of Cancer Therapy-Colorectal Cancer.

Predictors of QoL Outcomes- LRRC

In the multivariate analysis, having an obturator nerve resection was found to be associated with a better FACT-C score at 6 months (beta= 11.713, 95%CI=1.215-22.210, p=0.029). Nevertheless, increasing LOS was negatively associated with FACT-C and PCS score at 6 months (beta=-0.253 95% CI= -0.0489- -0.018, p=0.036 and beta=-0.127, 95%=-0.242- -0.012, p=0.031 respectively). Having a bony resection was also correlated with a lower PCS score at 6 months and at 12 months (beta=-6.466, 95%+-10.921- -2.010, p=0.005 and beta=-6.161, 95%=-11.389- -0.933, p=0.02 respectively) (Table 3).

Increasing operative time was found to be associated with a lower FACT- C score and PCS score at 12 months (beta=-1.370, 95%= -2.505- -0.235, p=0.019, beta=-0.688, 95%=-1.337- -0.040, p=0.038). In addition, having a positive resection margin was found to be associated with a lower MCS at 12 months (beta=-0.565, 95%=-10.577- -0.533, p=0.030) (Table 3).

Table 3. Univariate and multivariate analysis investigating the association between locally recurrent rectal cancer surgical outcomes and changes in quality of life

Variables	FACT-C at 6 Months				PCS at 6 Months				MCS at 6 Months			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
					6 Months Postoperatively							
Male sex	-0.898 (-8.953-7.157)	0.825	-	-	-1.918 (-6.074-2.238)	0.362	-	-	0.068 (-4.794-4.930)	0.978	-	-
Age, years	0.277 (-0.152-0.707)	0.203	0.384 (-0.041-0.809)	0.076	-0.073 (-0.292-0.147)	0.513	-0.060 (-0.276-0.156)	0.582	-0.001 (-0.257-0.256)	0.996	0.028 (-0.234-0.290)	0.833
Neoadjuvant chemoradiotherapy	0.699 (-7.218-8.616)	0.861	-0.282 (-8.088-7.523)	0.943	1.242 (-2.796-5.279)	0.543	0.310 (-3.578-4.198)	0.874	-0.364 (-5.135-4.406)	0.880	-0.271 (-5.110-4.567)	0.912
R1/2 surgical margin	2.008 (-6.679-10.696)	0.648	3.418 (-5.098-12.134)	0.420	-6.393 (-10.591- -2.195)	0.003	-3.914 (-8.267-0.439)	0.077	1.344 (-3.753-6.441)	0.602	1.034 (-4.145-6.212)	0.693
Any bony resection	-1.774 (-10.008-6.459)	0.670	-	-	-8.140 (-12.150-4.129)	0.000	-6.466 (-10.921--2.010)	0.005	1.558 (-3.422-6.537)	0.536	-	-
Pubic bone	6.395 (-8811-21.602)	0.406	-	-	-2.459 (-10.210-5.291)	0.531	-	-	5.112 (-3.881-14.105)	0.262	-	-
Sacrum	-3.289 (-10.821-4.244)	0.389	-	-	-4.122 (-7.976- -0.268)	0.036	0.983 (-4.828-6.793)	0.737	-0.380 (-4.930-4.170)	0.869	-	-
Obturator nerve	11.062 (0.406-21.718)	0.042	11.713 (1.215-22.210)	0.029	-3.189 (-8.689-2.311)	0.253	-	-	7.511 (1.230-13.792)	0.020	-	-
Sciatic nerve	1.977 (-8.888-12.841)	0.719	-	-	-3.637 (-9.291-2.016)	0.205	-	-	2.703 (-3.915-9.322)	0.420	-	-
Flap reconstruction	0.120 (-8.576-8.816)	0.978	-	-	-2.174 (-6.642-2.293)	0.337	-	-	-0.508 (-5.736-4.720)	0.847	-	-
Cystectomy	-4.125 (-11.985-3.736)	0.300	-	-	-5.422 (-9.336- -1.509)	0.007	-3.256 (-7.312-0.800)	0.114	-1.442 (-6.158-3.275)	0.546	-	-
Blood loss (mL)	<0.001 (-0.002-0.002)	0.992	-	-	-0.001 (-0.002-0.000)	0.003	0.000 (-0.001-0.000)	0.302	<0.001 (-0.001-0.001)	0.912)	-	-
Length of hospital stay, days	-0.196 (-0.431-0.040)	0.103	-0.253 (-0.489--0.018)	0.036	-0.185 (-0.302- -0.069)	0.002	-0.127 (-0.242- -0.012)	0.031	-0.061 (-0.203-0.080)	0.393	-	-
Operative time, hours	-0.047 (-1.191-1.098)	0.936	-	-	-0.750 (-1.306- -0.193)	0.009	0.407 (-0.290-1.105)	0.249	0.148 (-0.522-0.819)	0.662	-	-
Presence of postoperative complication	-4.684 (-18.999-9.632)	0.518	-	-	-3.663 (-11.3954.069)	0.350	-	-	0.245 (-8.803-9.293)	0.957	-	-

Variables	FACT-C at 12 Months				PCS at 12 Months				MCS at 12 Months			
	Univariate		Multivariate		Univariate		Multivariate		Univariate		Multivariate	
	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P	Beta (95%CI)	P
Male sex	-2.514 (-11.020-5.992)	0.558	-	-	-2.500 (-7.164-2.164)	0.289	-	-	-1.277 (-5.941-3.386)	0.587	-	-
Age, years	0.002 (-0.436-0.440)	0.993	0.006 (-6.369-11.233)	0.583	0.024 (-0.219-0.267)	0.845	0.032 (-0.209-0.273)	0.790	0.029 (-0.213-0.271)	0.815	-0.027 (-0.299-0.244)	0.840
Neoadjuvant chemoradiotherapy	2.336 (-5.673-10.344)	0.563	2.496 (-6.006-10.999)	0.560	2.008 (-2.526-6.542)	0.381	1.891 (-2.285-6.067)	0.369	4.068 (-0.402-8.537)	0.074	2.847 (-1.742-7.436)	0.220
R1/2 surgical margin	2.081 (-7.058-11.220)	0.652	1.875 (-7.442-11.191)	0.689	-4.048 (-8.982-0.887)	0.107	-2.877 (-7.778-2.024)	0.245	-5.000 (-9.865--0.135)	0.044	-5.565 (-10.577--0.553)	0.030
Any bony resection	-9.548 (-17.665- -1.431)	0.022	-2.854 (-14.285-8.576)	0.559	-9.321 (-13.587- -5.054)	0.000	-6.161 (-11.389--0.933)	0.022	-3.278 (-7.930-1.374)	0.165	1.832 (-4.121-7.785)	0.541
Pubic bone	-9.385 (-24.376-5.607)	0.217	-	-	-5.597 (-13.356-2.161)	0.155	-	-	-0.506 (-8.320-7.307)	0.898	-	-
Sacrum	-10.193 (-17.770--2.616)	0.009	-	-	-5.538 (-9.800- -1.276)	0.012	-	-	-2.568 (-6.938-1.802)	0.246	-	-
Obturator nerve	-1.300 (-12.072-9.472)	0.811	-	-	-4.357 (-10.104-1.389)	0.135	0.515 (-5.676-6.707)	0.868	-2.014 (-7.793-3.764)	0.490	-	-
Sciatic nerve	-0.833 (-11.969-10.303)	0.882	-	-	-5.147 (-11.043-0.748)	0.086	-4.935 (-10.816-0.945)	0.099	1.908 (-4.049-7.865)	0.526	-	-
Flap reconstruction	1.372 (-7.487-10.231)	0.759	-	-	-2.832 (-7.661-1.997)	0.247	-	-	2.055 (-2.768-6.877)	0.399	-	-
Cystectomy	-8.067 (-16.005- -0.128)	0.046	-3.723 (-13.207-5.761)	0.436	-7.093 (-11.347- -2.838)	0.001	-2.819 (-7.592-1.954)	0.243	-1.715 (-6.206-2.777)	0.450	-	-
Blood loss (mL)	-0.002 (-0.004- -0.001)	0.005	-0.001 (-0.003-0.001)	0.182	-0.001 (-0.001- -0.001)	0.001	0.000 (-0.001-0.000)	0.312	-0.001 (-0.002-0.000)	0.134	0.000 (-0.001-0.001)	0.373
LOS, days	-0.045 (-0.299-0.209)	0.724	-	-	-0.129 (-0.268-0.011)	0.070	-0.015 (-0.158-0.128)	0.835	0.049 (0.093-0.190)	0.494	-	-
Operative time, hours	-1.619 (-2.669- -0.569)	0.000	-1.370 (-2.505--0.235)	0.019	-1.222 (-1.785- -0.658)	0.000	-0.688 (-1.337- -0.040)	0.038	-0.075 (-0.696-0.545)	0.810	-	-
Presence of postoperative complication	-5.692 (-20.773-9.389)	0.455	-	-	-5.269 (-13.620-3.081)	0.213	-	-	-2.551 (10.919-5.816)	0.546	-	-

Data presented as odds ratio (95% confidence intervals Univariate variables in bold were entered into multivariate analysis (P<0.2). R0 surgical margin forced into multivariate analysis. Only significant results (p<0.05) in multivariate analysis were present. PCS: Physical Component Score; MCS: Mental component score; FACT-C: Functional Assessment of Cancer Therapy-Colorectal Cancer.

3.5 Discussion

Patients with LARC had higher R0 rates (88% vs. 74%) and increased survival (59% vs. 42% for 5-year OS) than LRRC, although the latter was clinically but not statistically significant. These results overall fare positively compared to the current published literature. LRRC often required a more extensive surgery with a higher likelihood of requiring nerve resection and more blood transfusion, resulting in longer operating time and length of surgery. Despite a more extended resection and a lower R0 rate, patients with LRRC had similar survival and QoL outcomes as those with LARC. Of note, better baseline QoL scores were observed in the LRRC group. This could be explained by the fact that more LARC patients had undergone neoadjuvant chemoradiotherapy, which may have affected their baseline function.

Neoadjuvant chemoradiotherapy has become the standard treatment for LARC, improves local oncological control, and helps resectability for primary patients[15]. However, re-irradiation for patients with recurrent disease after prior radiotherapy to the pelvis remains controversial worldwide. While re-irradiation is not offered at our centre for LRRC, it is interesting that 61% of LRRC received chemoradiotherapy as they had not previously received treatments as part of their primary treatment. The debate about re-irradiation continues with some data of acceptable toxicities in Phase I studies; some have increased complications such that an RCT is needed to balance the pros and cons[5, 9, 16-19].

Increasing age was found to be a positive predictor of QoL for patients with LARC, whereas sciatic nerve resection, increasing blood loss and LOS were negatively

associated with QoL scores for those patients. On the other hand, any bony resection, positive surgical margin, increasing operative time and length of stay were all negative predictors of QoL scores for patients with LRRC. Apart from age, the predictors identified for both diseases are more reflective of the extent of surgery.

Patients with LRRC are more likely to be offered more radical and extensive surgery. Understanding the extra TME anatomy is paramount to surgical planning with MRI. This pathophysiology of the attachments of recurrent rectal cancer is crucial as it is more likely to involve neurovascular structures, muscles, and ligaments in the lateral compartments genitourinary anterior and bony sacral structures posteriorly. The surgical anatomy and resectability of LRRC must not focus on the TME planes of primary rectal cancer surgery. In the only international benchmark study comparing radicality of planned surgical approaches, it was found that compared to French centres, there is a higher rate of broader and more radical resection in Australia, which demonstrated a higher R0 resection rate for LRRC in Australia[20].

For LARC, some debate whether resection margins are planned before or after neoadjuvant treatment[21]. By contrast, patients with LRRC often have had previous treatments, including surgery and radiotherapy. Thus, recurrent disease is commonly associated with loss of normal anatomical tissue planes due to adhesions and fibrosis and sometimes some degree of previous sepsis[5, 21].

In addition to the variations in the intrinsic nature of LARC and LRRC, the surgical planning can also be different between these two diseases. Organ preservation is more

advocated in patients with LARC, whereas a more aggressive approach is usually applied to recurrent disease. For example, in the case of bladder involvement, especially in the case of previous irradiation and/or major sacrectomy leading to neuropathic bladders, a planned total cystectomy can be preferred over partial cystectomy for functional and QoL implications alone[22].

Despite a more aggressive surgical approach resulting in more blood loss, longer operating time and LOS, patients with LRRC had similar complication rates. More interestingly, their QoL was equivalent to those with LARC following PE. The reasons for this are elusive but may be multifactorial and brings up the psychological theories of "cognitive dissonance reduction and of "reconceptualization". Reconceptualization is a known phenomenon in cancer survivors, which could happen to patients with LRRC who have a baseline "recurrent" cancer mentality with an expected poorer prognosis than primary cancer group, so inherently they have lower expectations. Recurrence of cancer allows patients to contemplate their priorities and personal expectations of life, strengthening inter-social relations. Subsequently, patients' expectation that they may not be offered surgery and treatment allows for an appreciation of daily life, and the evaluation of symptoms improves, leading to an improved baseline QoL in those with LRRC compared with LARC seen in this paper[23]. Additionally, patients with LRRC have often undergone one or more surgeries previously and may have more mental preparation for the surgical journey and often have been previously exposed to stoma care. This may explain why LRRC patients have a higher baseline FACT-C score. Cognitive dissonance reduction means that if an extensive operation is planned with high rates of complications expected and then this occurs, current QoL measures more accurately measures "expectations" rather than true

current QoL[24].

Increasing age was found to be positively associated with FACT- C scores for patients with LARC. Better coping mechanisms could explain it in the older population. Hart et al. (2013) have identified that older age was associated with lower levels of depression and the adverse effects of a diagnosis of colorectal cancer. In addition, they found more adaptive appraisals of their cancer diagnosis in the older population[25].

The study performed by Bhangu et al. (2013) compared 55 patients with LARC with 45 patients with LRRC[9]. They also identified a higher positive margin rate, higher blood loss, and longer length of stay and operative time in LRRC. However, there was no statistical significance in the latter three factors. These results were similar to the findings in this study. Additionally, there was a recent systematic review that reported outcomes of patients with LARC and LRRC[6]. In this review, a median R0 resection rate of 82.6% (range 66-95.5%) and 58.0% (range 31.8% -71.4%) was reported for LARC and LRRC respectively[6]. These results are consistent with the R0 rate of this study.

There is limited literature on differences in surgical outcomes between LARC and LRRC. The PelvEx Collaborative group published a multicentre study that investigated the trend of operative and surgical outcomes of LARC and LRRC[7]. They reported a flap reconstruction rate of 29.4% for LARC and 24.4% for LRRC between 2014 to mid-2015. In this study, the flap reconstruction rate for LARC was lower than their finding, whereas it is similar for patients with LRRC. The bony resection rate in this study was

88.3% for those with LARC and 73.6% for those with LRRC, which were much higher than the results of the PelvEx Collaborative group (12.8% for LARC and 24.4% for LRRC between 2014 to mid-2015). This significant increase most likely reflects more complex referrals to our quaternary unit with more advanced disease and a higher preponderance of recurrent rectal cancer involving neurovascular lateral compartments and the posterior bone compartments. Our more radical conceptual approach to LRRC may also contribute to this more aggressive and radical surgical approach[26].

There are several limitations to this study that need to be considered. Firstly, his study was from a single experienced quaternary referral national and state-wide centre, which could potentially limit its generalizability. Secondly, the R0 resection rates of patients with LRRC were higher than the findings reported in the literature. Our evidence has previously demonstrated that R0 not only relates to survival but also complications and longer-term QoL[27]. The higher R0 rate may improve the results for LRRC in this study. In addition, it was also limited by the sample size. A post-hoc power calculation was performed. With the sample size acquired in our study, we would have greater than 70% power to be able to detect a difference of 3 points in QoL scores between groups at 12 months follow-up or 90% to detect a significant difference of 4 points between groups. However, this is also the largest study of the similar type despite the sample size.

3.6 Conclusions

Patients with LRRC are more likely to present with more complicated disease and tend to require a longer operation with more blood loss and an increased LOS compared to LARC. Although LRRC often requires more complex and extensive resection, QoL

outcomes of patients with LARC and LRRC remain similar in all postoperative time points measured. It affirms the beneficial role of PE in QoL outcomes and surgical outcomes in not only advanced primary rectal but also recurrent rectal cancer.

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CHAPTER 4. Discussion and conclusions

4.1 Overview of principal findings

PE is one of the most invasive gastrointestinal surgery for advanced pelvic malignancies. In modern clinical practice, oncological outcomes do not only consist of survival benefits, but also emphasise on patient-centred outcomes which include QoL[1]. Thus, with the improved survival, surgical morbidity and functional outcomes are now more critical long-term considerations for patients who underwent PE. Thus, this thesis aimed to investigate the physical and functional impacts of PE on patients with advanced pelvic malignancies.

Surgical morbidity associated with PE remains significant. However, it is difficult to understand it without a standard classification system in the contemporary literature [2]. Chapter 2 provides an overview of surgical morbidity associated with PE and investigated the associations between the three grading classifications and length of stay (LOS) and physical outcomes, including physical component score (PCS) at 6 months, distress score at 6 months, distance for pre-discharge 6 minute-walk test and time for the sit-to-stand test. Chapter 2 identifies a strong and a moderate association between the Comprehensive Complication Index (CCI) and the number of complications with LOS and PCS at 6 months, respectively. CCI and the total number of complications were more strongly associated with outcomes than Clavien-Dindo Classification grade and maybe better classifications to evaluate post exenteration complications.

Thus, in addition to appreciating the significance of surgical complications of PE, understanding functional outcomes using QoL measures following PE were also paramount. Chapter 3 compares perioperative outcomes of patients with LARC with those with LRRC and determined the impacts of PE on QoL of patients with rectal cancer. Chapter 3 demonstrates that patients with LRRC tend to have more advanced disease and require more extensive surgery. However, the QoL remains similar between LARC and LRRC despite the differences in perioperative outcomes.

4.2 Contribution of this thesis to current knowledge and practice

PE is one of the most invasive oncological procedures and has an immense effect on physical, sexual and psychological functioning. Patients bring their cultural, psychological background and a range of fears and personal expectations to the decision- making process. Also, clinical cancer history, length of illness history and patients' symptoms are also important determinants of patients' cognitive acceptance of PE. Due to variabilities amongst patients, it is essential to assess the preoperative functioning to determine the best care strategies[3].

Patients who are eligible undergo PE are reviewed by treating surgeon to discuss the surgical procedure in detail. They will also be reviewed by allied health team including dietitian, stoma therapist, physiotherapist, and clinical psychologist at the preadmission clinic to understand the postoperative course from different perspectives. Given that PE is a complex oncological procedure and patients are often focused on the cancer treatment, they may underappreciate the profound functional and long-term effects that PE may have on themselves. It is important that clinicians manage these patients be

cognisant of this and encourage patients to take this into consideration while making decisions about treatment. Additionally, an unhurried consultation with support person of the patient's choice, provision of reading material and the opportunity to discuss the procedure over separate consultations may all help set realistic expectations after the procedure as well as understanding the potential functional consequences.

The significant findings of Chapter 2 address the issue that there has been no study that investigated the applicability of available classifications on PE. The selection of a valid grading classification has been variable in different centres, making it hard to compare the morbidity of PE across the literature. Although Chapter 2 demonstrates a strong association between CCI and LOS, as well as between the number of complications and LOS, all the investigated classifications are limited by their weaknesses. The lack of appropriate grading classification in the current literature will provide a direction for future research. With appropriate grading classification, it will facilitate the understanding of the surgical morbidity, improve communication between units that offer this procedure and allow clinicians to counsel patients better by discussing the balance of survival and QoL benefits against surgical risks for individuals to aid preoperative decision-making.

The information provided in Chapter 3 is also valuable for preoperative discussion and decision-making. It helps set the expectations and prepare patients with LRRC mentally, especially for the immediate postoperative course, given that those patients tend to have more extensive surgery. Despite the differences in perioperative outcomes, QoL outcomes at 6 months and 12 months postoperatively remain similar between patients

with LARC and those with LRRC. Understanding that patients with rectal cancer are likely to have equivalent and acceptable recovery of QoL is vital to facilitate the decision-making progress for surgery, especially for those who are suffering from significant disabling symptoms. In addition, it was found that patients with LRRC often underwent more extensive surgery. Therefore, they may benefit from a preoperative fitness program and more psychological consultations to increase their physical strength and mental wellbeing prior to surgery. Given that patients with LRRC tend to have a higher physical baseline but experience more complicated surgery, individualised preoperative intense physiotherapy program could be implemented to further enhance the preoperative physical strength. In addition, planned preoperative psychological consultations could also be helpful to develop a positive coping mechanism and be more prepared for the upcoming surgery.

4.3 Implications for future research

Standardising the classification grading system for PE is paramount. Chapter 2 demonstrates that there is a strong association between CCI and LOS. CCI is a comprehensive grading system that overcomes the weaknesses of the CDC system by considering all complications of varying degrees. Future studies may focus on validating CCI in the PE literature, not only using postoperative LOS but also considering QoL outcomes as an essential quality target for patient-centred care [4]. However, given that it is a quite complex and resource intense grading system to use in clinical practice, it may also be worthwhile to develop and test a new specific grading system suitable but simpler than the CCI for PE which is easy to use in clinical practice and classifies common but essential complications such as postoperative ileus and considers all the complication of varying severities.

Due to the importance of the number of complications as demonstrated in Chapter 2, it is also worthwhile investigating the relationships of the number of complications and CDC grade. A new classification could be developed to include a mathematical formulation which could upgrade the complications based on the number of complications. For example, the effects of a certain number of lower grade complications can be equivalent to the effects of single a higher-grade complication. Surgical morbidity has also been also suggested to be a potential significant and long-term negative predictor of patients' postoperative psychological wellbeing[5]. It is also worthwhile exploring the relationship between mental health score and three classification systems in the future study.

Given that the association between postoperative complication and QoL was demonstrated, more research should be conducted to investigate the benefits of a specialised enhanced recovery program for PE. Often patients will have higher needs for rehabilitation after PE. They may require more aggressive physiotherapy and ensure adequate nutrition intake to minimise the risks of complications.

It was difficult to assess the long-term QoL outcomes of patients as most patients have not reached the five-year mark at our centre. It will be useful to have collaborative data from multiple centres to further assess the long-term effects of PE on QoL outcomes. Given that the potential association between postoperative complication and QoL was demonstrated, more research should be conducted to investigate the benefits of a specialised enhanced recovery program for PE. Often patients will have higher needs for rehabilitation after PE. They may require more aggressive physiotherapy and ensure

adequate nutrition intake to minimise the risks of complications.

In addition, patients with LRRC can be a specific target group for a trial of preoperative fitness and psychological training program in preparation for an extensive resection. Patients eligible for PE are usually assessed by allied health and a psychologist at the pre-admission clinic. However, more exercise sessions with physiotherapists and psychological counselling sessions can increase patients' baseline function and QoL.

It may be worthwhile looking into LOS of patients with different complication frequencies within the same CDC grade group. There may be an equivalent effect on LOS between the certain frequencies of a lower grade complication and a single higher-grade complication. For example, patients with more than four grade II complications may have similar LOS to those with a single grade III complication. With the limited sample size, it was difficult to identify any predictors for change in QoL over the first year after PE for patients with LARC and LRRC. However, this is also the largest study of its type despite the sample size. With available data, it was identified that several predictors that are related to complexity of operation were related to QoL changes. It could be an area of interest for future research. It is a highly specialised procedure and will require collaborative efforts to collect sufficient data to allow more comprehensive analysis to identify any predictors for change in QoL after PE. By changing potentially modifiable predictors will likely benefit patients' postoperative QoL outcomes.

4.4 References

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CHAPTER 5. Appendices

5.1 Authorship Contribution Statement and Declaration by Co-Authors

STATEMENT OF CONTRIBUTIONS

Candidate Declaration

Chapter 2, titled "Physical Morbidity and Complications of Pelvic Exenteration. Limitations of the Current Classification System", has been submitted for publication. The contribution of the candidate is as follows:

- Study Concept and Design
- Data Collection and Analysis
- Data Interpretation
- Manuscript Preparation and Drafting
- Final Approval of Manuscript

The contributions of co-authors are as follows:

Dr Xiaomeng Wang- Study Concept and Design, Data Collection and Analysis, Final approval of the manuscript

A/Professor Cherry Koh- Study Concept and Design, Critical Review of Manuscript, Final Approval of Manuscript

A/Professor Daniel Steffens- Study Concept and Design, Critical Review of Manuscript, Final Approval of Manuscript

Professor Jane Young- Study Concept and Design, Critical Review of Manuscript, Final Approval of Manuscript

Professor Michael Solomon- Study Concept and Design, Critical Review of Manuscript, Final Approval of Manuscript

Candidate's Signature:

[REDACTION]

Dr Yeqian Huang

20th June 2021

Declaration by Co-Authors

The undersigned certifies that the above declaration accurately reflects the candidate's contribution to the work presented in this thesis and the contributions of each co-author. There have been no conflicts of interest.

X [REDACTION]

Professor Michael Solomon

X [REDACTION]

A/Professor Daniel Steffens

X [REDACTION]

A/Professor Cherry Koh

X [REDACTION]

Professor Jane Young

X [REDACTION]

Dr Xiaomeng Wang

STATEMENT OF CONTRIBUTIONS

Candidate Declaration

Chapter 3, titled "Quality of Life Implications of Pelvic Exenteration Surgery. A Comparative Study: Locally Advanced versus Locally Recurrent Rectal Cancer", has been submitted for publication.

The contribution of the candidate is as follows:

- Study Concept and Design
- Data Collection and Analysis
- Data Interpretation
- Manuscript Preparation and Drafting
- Final Approval of Manuscript

The contributions of co-authors are as follows:

A/Professor Daniel Steffens- Study Concept and Design, Critical Review of Manuscript, Final Approval of Manuscript

A/Professor Cherry Koh- Study Concept and Design, Critical Review of Manuscript, Final Approval of Manuscript

Professor Jane Young- Study Concept and Design, Critical Review of Manuscript, Final Approval of Manuscript

Professor Michael Solomon- Study Concept and Design, Critical Review of Manuscript, Final Approval of Manuscript

Candidate's Signature:

[REDACTION]

Dr Yeqian Huang

20th June 2021

Declaration by Co-Authors

The undersigned certifies that the above declaration accurately reflects the candidate's contribution to the work presented in this thesis and the contributions of each co-author. There have been no conflicts of interest.

X [REDACTION]

Professor Michael Solomon

X [REDACTION]

A/Professor Daniel Steffens

X [REDACTION]

A/Professor Cherry Koh

X [REDACTION]

Professor Jane Young

5.2 Ethics Approvals

ADDRESS FOR ALL CORRESPONDENCE
RESEARCH ETHICS AND GOVERNANCE OFFICE
ROYAL PRINCE ALFRED HOSPITAL

TELEPHONE: (02) 9515 6764
EMAIL: SLHD-RPAEthics@health.nsw.gov.au

NSW Health
Sydney Local Health District

28 July 2020

This letter constitutes ethical approval only. You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.

Dear Dr Huang,

Re: Protocol no. X20-0297 and 2020/ETH01751- "Grading complications in Pelvic Exenteration. Limitations of current classification systems"

The Executive of the Ethics Review Committee, at its meeting of 28 July 2020 considered your correspondence of 28 July 2020.

I am pleased to advise that final ethical approval has been granted on the basis of the following:

- The research project meets the requirements of the *National Statement on Ethical Conduct in Human Research*.

This approval includes the following:

- HREA (Version 2, 10 July 2020)
- Protocol (Version 2, 26 July 2020)
- Master Code Sheet (Version 2, 26 July 2020)
- Data Collection Form (Version 2, 28 July 2020)
- Research Data Management Plan (Version 2, 26 July 2020)
- QOL Baseline Questionnaire (Version 8, 20 November 2018)
- PESQI Database Clinical Data Form (Version 4, 14 January 2019)

You are asked to note the following:

On the basis of this ethics approval, authorisation may be sought to conduct this study within any NSW/QLD/VIC/SA/WA/ACT public health organisation and/or within any private organisation which has entered

into an appropriate memorandum of understanding with the Sydney Local Health District, Sydney Local Health Network or the Sydney South West Area Health Service.

The Committee noted that authorisation will be sought to conduct the study at the following sites:

- Royal Prince Alfred Hospital

- This approval is valid for five years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in **July 2021.** If recruitment is ongoing at the conclusion of the four year approval period, a full re-submission will be required. Ethics approval will continue during the re-approval process.

- This human research ethics committee (HREC) has been accredited by the NSW Department of Health as a lead HREC under the model for single ethical and scientific review and is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research* and the *CPMP/ICH Note for Guidance on Good Clinical Practice*.

- You must immediately report anything which might warrant review of ethical approval of the project in the specified format, including unforeseen events that might affect continued ethical acceptability of the project.

- You must notify the HREC of proposed changes to the research protocol or conduct of the research in the specified format.

- You must notify the HREC and other participating sites, giving reasons, if the project is discontinued at a site before the expected date of completion.

- If you or any of your co-investigators are University of Sydney employees or have a conjoint appointment, you are responsible for informing the University's Risk Management Office of this approval, so that you can be appropriately indemnified.

- Where appropriate, the Committee recommends that you consult with your Medical Defence Union to ensure that you are adequately covered for the purposes of conducting this study.

Should you have any queries about the Committee's consideration of your project, please contact me. The Committee's Terms of Reference, Standard Operating Procedures, membership and standard forms are available from the Sydney Local Health District website.

<u>If you are not using REGIS, a copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.</u>

The Ethics Review Committee wishes you every success in your research.

Regards,

pp: [REDACTION]

Patricia Plenge
Executive Officer
Ethics Review Committee (RPAH Zone)

Address for all correspondence
Research Ethics and Governance Office
Royal Prince Alfred Hospital
CAMPERDOWN NSW 2050
Telephone: (02) 9515 6766
Email: SLHD-RPAEthics@health.nsw.gov.au

Health
Sydney
Local Health District

13 September 2019

This letter constitutes ethical approval only. You must NOT commence this research project at ANY site until you have submitted a Site Specific Assessment Form to the Research Governance Officer and received separate authorisation from the Chief Executive or delegate of that site.

Dear Professor Solomon,

Re: X19-0215 & 2019/ETH10689 - Predictors for changes in quality of life in long-term survivors following pelvic exenteration"

The Executive of the Ethics Review Committee, at its meeting of 13 September 2019 considered your correspondence of 10 September 2019. In accordance with the decision made by the Executive of the Ethics Review Committee, at its meeting of 5 June 2019, ethical approval is granted.

- The research project meets the requirements of the National Statement on Ethical Conduct in Human Research.

This approval includes the following:

- HREA (Version 3, 4 September 2019)
- Study Protocol (Version 2, 9 September 2019)
- Data Collection Form (Version 1, 17 August 2019)
- Research Data Management Plan

You are asked to note the following:

On the basis of this ethics approval, authorisation may be sought to conduct this study within any NSW/QLD/VIC/SA/WA/ACT public health organisation and/or within any private organisation which has entered into an appropriate memorandum of understanding with the Sydney Local Health District, Sydney Local Health Network or the Sydney South West Area Health Service.

The Committee noted that authorisation will be sought to conduct the study at the following site:

- Royal Prince Alfred Hospital

- This approval is valid for **five** years, and the Committee requires that you furnish it with annual reports on the study's progress beginning in **September 2020.** If recruitment is ongoing at the conclusion of the four year approval period, a full re-submission will be required. Ethics approval will continue during the re-approval process.

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A copy of this letter must be forwarded to all site investigators for submission to the relevant Research Governance Officer.

The Ethics Review Committee wishes you every success in your research.

Yours sincerely,

[REDACTION]

Patricia Plenge
Executive Officer
Ethics Review Committee (RPAH Zone)

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