

**Addressing Variation in Treatment Decision-Making and Outcomes in
Patients with Locally Advanced and Recurrent Rectal Cancer**

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

Surgical Outcomes Research Centre, Faculty of Medicine & Health

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STATEMENT OF ORIGINALITY

The work presented in this thesis is my own work and, to the best of my knowledge and belief, original except as acknowledged in the text. I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution. No artificial intelligence tool was used in this research or in any part of the preparation of this thesis.

Dr Kilian Brown
28th August 2025

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AUTHORSHIP CONTRIBUTION STATEMENT AND CANDIDATE

DECLARATION

I, Kilian Brown, conducted the research presented in this thesis during my PhD candidature between 2022 to 2025 at the Surgical Outcomes Research Centre, Faculty of Medicine and Health, University of Sydney. I conducted this research under my primary supervisor, Professor Michael Solomon, and secondary supervisors Professor Daniel Steffens and Dr Kheng-Seong Ng. For each study, I contributed intellectually to the study design, obtaining and maintaining ethics and governance approval, conducting recruitment, collecting and managing the data, planning and conducting the data analysis, and writing and revising the manuscripts/chapters. The specific contributions I made to each manuscript/chapter are outlined below.

Chapter 2.1 entitled *'Treatment of locally advanced and recurrent rectal cancer in Australia and New Zealand: recent progress and future challenges'*

The nature of the candidate's contribution to Chapter 1.1 included: study concept and design, manuscript preparation and drafting, final approval of manuscript.

Chapter 2.2 entitled *'The paradox of hope in surgery for advanced gastrointestinal malignancy – how do we define futility?'*

The nature of the candidate's contribution to Chapter 1.2 included: study concept and design, manuscript preparation and drafting, final approval of manuscript.

Chapter 2.3 entitled *'Understanding Quality of Life After Pelvic Exenteration for Patients with Rectal Cancer'*

The nature of the candidate's contribution to Chapter 1.3 included: study concept and design, manuscript preparation and drafting, final approval of manuscript.

Chapter 3.1 entitled *'Development of a risk prediction tool for patients with locally advanced and recurrent rectal cancer undergoing pelvic exenteration: protocol for a mixed-methods study'*

The nature of the candidate's contribution to Chapter 2.1 included: study concept and design, ethics and governance applications, manuscript preparation and drafting, final approval of manuscript.

Chapter 4.1 entitled '*Variation in outcome measurement and reporting in studies of pelvic exenteration for locally advanced and recurrent rectal cancer: a systematic review*'

The nature of the candidate's contribution to Chapter 3.1 included: study concept and design including search strategy, PROSPERO registration, data collection and analysis, manuscript preparation and drafting, final approval of manuscript.

Chapter 4.2 entitled '*The definition of clear resection margins in locally recurrent rectal cancer-time for consensus*'

The nature of the candidate's contribution to Chapter 3.2 included: study concept and design including search strategy, PROSPERO registration, data collection and analysis, manuscript preparation and drafting, final approval of manuscript.

Chapter 5.1 entitled '*A matter of survival - Patients' and carers' perspectives on the decision to undergo pelvic exenteration surgery for locally advanced and recurrent rectal cancer*'

The nature of the candidate's contribution to Chapter 4.1 included: study concept and design, ethics and governance applications, patient recruitment, conducting interviews, data collection and analysis, manuscript preparation and drafting, final approval of manuscript.

Chapter 5.2 entitled '*Life after pelvic exenteration for rectal cancer: the patient and carer perspective on long-term consequences and survivorship*'

The nature of the candidate's contribution to Chapter 4.2 included: study concept and design, ethics and governance applications, patient recruitment, conducting interviews, data collection and analysis, manuscript preparation and drafting, final approval of manuscript.

Chapter 6.1 entitled '*Priority outcomes of pelvic exenteration for rectal cancer: a patient, carer and clinician consensus*'

The nature of the candidate's contribution to Chapter 5.1 included: study concept and design, ethics and governance applications, survey design and piloting, data collection and analysis, manuscript preparation and drafting, final approval of manuscript.

Chapter 7.1 entitled *'Preoperative predictors of consensus-derived priority outcomes of pelvic exenteration for locally recurrent rectal cancer: Results of the mixed-methods EviSurg study'*

The nature of the candidate's contribution to Chapter 5.2 included: study concept and design, ethics and governance applications, data collection, interpretation of analysis, manuscript preparation and drafting, final approval of manuscript.

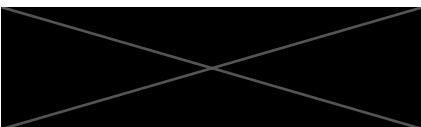
Chapter 8.1 entitled *'Defining Benchmarks for Pelvic Exenteration Surgery: A Multicentre Analysis of Patients with Locally Advanced and Recurrent Rectal Cancer'*

The nature of the candidate's contribution to Chapter 6.1 included: study concept and design, ethics and governance applications, centre recruitment, data collection and analysis, manuscript preparation and drafting, final approval of manuscript.

Chapter 8.2 entitled *'Conventional versus high-complexity total pelvic exenteration for locally advanced and locally recurrent rectal cancer: an international multicentre study'*

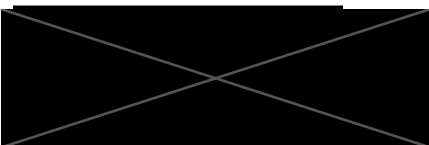
The nature of the candidate's contribution to Chapter 6.2 included: study concept and design, ethics and governance applications, centre recruitment, data collection and analysis, manuscript preparation and drafting (co-first author with Dr Celine Garrett), final approval of manuscript.

I declare that the above attribution statements are correct.



Dr Kilian Brown

As supervisor for the candidature upon which this thesis is based, I confirm that the above attribution statements above are correct.



Professor Michael Solomon

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PUBLICATIONS, PRESENTATIONS AND AWARDS ARISING FROM THIS THESIS

The following scientific publications, conference presentations, awards and scholarships arose directly from this thesis. Additional publications and presentations that relate to this body of work and arose during the candidature, but are not directly relevant to the argument of the thesis, are presented in Appendix I (page 227).

SCIENTIFIC PUBLICATIONS:

Brown KGM, Solomon MJ, Heriot A, Frizelle F. Treatment of locally advanced and recurrent rectal cancer in Australia and New Zealand: recent progress and future challenges. *ANZ Journal of Surgery*. 2023 Oct;93(10):2291-2292. doi: 10.1111/ans.18635.

Brown KGM, Coker DJ, Solomon MJ, Koh CE, Mahon K, Steffens D. The Paradox of Hope in Surgery for Advanced Gastrointestinal Malignancy - How Do We Define Futility? *Ann Surg*. 2024 Oct 23. doi: 10.1097/SLA.0000000000006575. Epub ahead of print.

Brown KGM, Solomon MJ. Understanding Quality of Life After Pelvic Exenteration for Patients with Rectal Cancer. *Ann Surg Oncol*. 2024 Nov;31(12):7668-7670. Epub 2024 Aug 13.

Brown KGM, Solomon M, Ng KS, Sutton P, Koh C, White K, Steffens D; EviSurg Research Group. Development of a risk prediction tool for patients with locally advanced and recurrent rectal cancer undergoing pelvic exenteration: protocol for a mixed-methods study. *BMJ Open*. 2023 30;13(8):e075304.

Brown KGM, Pisaniello J, Ng KS, Solomon MJ, Sutton PA, Hatcher S, Steffens D. Variation in outcome measurement and reporting in studies of pelvic exenteration for locally advanced and recurrent rectal cancer: a systematic review. *Colorectal Disease*. 2024 Feb;26(2):272-2800

Brown KGM, Solomon MJ, Sutton PA, Shin JS, Steffens D. The definition of clear resection margins in locally recurrent rectal cancer-time for consensus. *British Journal of Surgery*. 2024 Jan 3;111(1):znad450. doi: 10.1093/bjs/znad450.

Brown KGM, White K, Solomon MJ, Sutton P, Ng KS, Koh CE, Steffens D. A matter of survival- patients' and carers' perspectives on the decision to undergo pelvic exenteration surgery for locally advanced and recurrent rectal cancer. *Colorectal Disease*. 2024 Dec 10. doi: 10.1111/codi.17259. Epub ahead of print

Brown KGM, White K, Solomon MJ, Sutton P, Ng KS, Steffens D. Life after Pelvic Exenteration for Rectal Cancer: The Patient and Carer Perspective on Long Term Consequences and Survivorship. *Ann Surg*. 2025 Jan 9. doi: 10.1097/SLA.0000000000006625. Epub ahead of print

Brown KGM, Morkaya J, Solomon MJ, Ng KS, White K, Sutton P, Winter DC; EvigSurg Collaborative Group; Steffens D. Priority outcomes of pelvic exenteration for rectal cancer: a patient, carer, and clinician consensus. *Br J Surg*. 2024 Nov 27;111(12):znae298.

Brown KGM, Solomon MJ, Koh CE, Sutton PA, Aguiar S Jr, Bezerra TS, Clouston HW, Desouza A, Dozois EJ, Ersryd AL, Frizelle F, Funder JA, Garcia-Aguilar J, Garfinkle R, Glyn T, Heriot A, Kanemitsu Y, Kong CY, Kristensen HØ, Malakorn S, Mens DM, Nilsson PJ, Palmer GJ, Pappou E, Quinn M, Quyn AJ, Sahakitrungruang C, Saklani A, Solbakken AM, Tiernan JP, Verhoef C, Steffens D. Defining Benchmarks for Pelvic Exenteration Surgery: A Multicentre Analysis of Patients with Locally Advanced and Recurrent Rectal Cancer. *Annals of Surgery*. 2024 May 15. Epub

MANUSCRIPTS UNDER PEER REVIEW:

Brown KGM, Ng KS, Solomon MJ, Vu J, Lo S, Sutton P, EvigSurg Collaborative Group; Steffens D. Preoperative predictors of consensus-derived priority outcomes of pelvic exenteration for locally recurrent rectal cancer: Results of a mixed-methods study. Manuscript under peer review.

Garrett C*, **Brown KGM***, Solomon MJ, Koh CE, Sutton PA, Aguiar S Jr, Bezerra TS, Clouston HW, Desouza A, Dozois EJ, Ersryd AL, Frizelle F, Funder JA, Garcia-Aguilar J, Garfinkle R, Glyn T, Heriot A, Kanemitsu Y, Kong CY, Kristensen HØ, Malakorn S, Mens DM, Nilsson PJ, Palmer GJ, Pappou E, Quinn M, Quyn AJ, Sahakitrungruang C, Saklani A, Solbakken AM, Tiernan JP, Verhoef C, Steffens D. Defining Benchmarks for Pelvic Exenteration Surgery: A Multicentre Analysis of Patients with Locally Advanced and Recurrent Rectal Cancer. Manuscript under peer review.

*Equal contribution

CONFERENCE PRESENTATIONS:

'Defining International Benchmarks for Pelvic Exenteration Surgery'

Association of Coloproctology of Great Britain and Ireland Annual Meeting, 1-3 July 2024, Newport, Wales (invited lecture as the ACPGBI Travelling Fellow)

'Defining International Benchmarks for Pelvic Exenteration Surgery: A Multicentre Analysis of Patients With Locally Advanced and Recurrent Rectal Cancers'

PelvEx Collaborative Annual Meeting, 27-28 June 2024, London, United Kingdom

AWARDS, PRIZES & SCHOLARSHIPS

2022:

Mitchell J Notaras Fellowship in Colorectal Surgery (2022-2025)

Three-year combined clinical/academic training program in colorectal surgery. Competitive scholarship awarded and supervised by Royal Prince Alfred Hospital, the University of Sydney, and the Colorectal Surgical Society of Australia & New Zealand.

2023:

Emerging Perioperative Clinician Researcher Career Development Award

Perioperative Clinical Academic Group, Sydney Health Partners

CSSANZ Foundation Award for Fellow's Research from a Higher Degree

Colorectal Surgical Society of Australia and New Zealand

2024:

Association of Coloproctology of Great Britain and Ireland (ACPGBI) Travelling Fellowship

Expenses paid travel to the Annual Meeting of the ACPGBI, podium presentation and site visits to the Christie Hospital (Manchester) and St Mark's Hospital (London)

Royal Prince Alfred Hospital Medical Officers Association Patron's Prize

For clinical research by a junior medical officer or fellow

THESIS ABSTRACT

Approximately 10% of patients with primary rectal cancer have a T4 tumour at presentation which may locally invade adjacent pelvic organs, bone, neurovascular or other soft tissue structures (T4b tumours). In addition, up to 10% of patients treated for primary rectal cancer may subsequently develop local recurrence in the pelvis. For both patients with locally advanced primary rectal cancer (LARC) and locally recurrent rectal cancer (LRRC), pelvic exenteration surgery, which refers to radical multi-visceral resection for advanced pelvic tumours, represents the only potentially curative treatment option. Refinement of surgical technique, combined with significant developments in perioperative medicine and imaging technology in the last three decades, have translated to dramatic improvements in outcomes for patients undergoing pelvic exenteration for LARC and LRRC. As a result, pelvic exenteration has evolved from a controversial, palliative procedure to the established standard of care for selected patients with LARC and LRRC. In 2025, the goal at exenteration units globally is to build on the highly encouraging results reported in recent decades by identifying and implementing technical, oncological and systems improvements that may contribute to the incremental improvement in patient outcomes. With this in mind, standardisation of this treatment may represent an opportunity to further improve patient outcomes by reducing variation in the way it is delivered both between and within centres. This thesis aimed (i) to address variation in treatment decision-making in patients with LARC and LRRC, and (ii) to establish internationally applicable surgical quality benchmarks for pelvic exenteration surgery.

To address unwarranted variation in treatment decision-making in patients with LARC and LRRC (*Thesis Aim 1*), the most important outcomes of surgery were defined using consensus methods, and preoperative predictors of these outcomes were explored. The ability to preoperatively predict the outcomes of surgery for an individual patient in future may facilitate evidence-based, reproducible treatment decisions. Identification of the 'priority outcomes' of pelvic exenteration

surgery, upon which it would be proposed that treatment decisions should be made, involved a systematic review of all outcomes reported in current exenteration literature (*Chapter 4*), as well as a large, qualitative exploration of patients and carers perspectives on the outcomes of importance after surgery (*Chapter 5*). Using these outcomes identified from the literature and patient/carer interviews, a modified Delphi study of patients, carers and international expert clinicians was designed to gain consensus around the priority outcomes. These priority outcomes, defined as those meeting pre-defined consensus criteria for 'critical importance' among all stakeholder groups, were categorised within four broad domains: survival (overall survival, disease-free survival, local recurrence-free survival), cancer recurrence (distant recurrence), patient-reported outcomes (global quality of life, psychological functioning, physical functioning, mobility) and pathological outcomes (resection margins) (*Chapter 6*). Using a prospectively maintained institutional database of 300 patients with LRRC, multivariate regression models developed to identify preoperative variables that were independent predictors of the three selected priority outcomes: overall survival, quality of life, and R0 resection (*Chapter 7*). Future work will aim to refine, improve and externally validate these predictive models, which will thereafter form the basis of a risk prediction and decision-making tool, which produces a recommendation for or against surgery for an individual patient based on the predicted priority outcomes for that patient.

To establish internationally applicable surgical quality benchmarks for pelvic exenteration surgery (*Thesis Aim 2*), a recently described method of benchmarking surgical outcomes was utilised. A total of 16 expert exenteration centres from 12 countries were recruited, and a multicentre dataset of patients undergoing pelvic exenteration for LARC or LRRC over a five year period was used to define benchmark thresholds for ten key surgical outcomes (*Chapter 8.1*). The same dataset was then used to determine the outcomes of 'high-complexity' exenteration (i.e. those requiring complex bone or neurovascular resections) achieved at these centres (*Chapter 8.2*).

The presented body of work attempted to develop two strategies for the standardisation of pelvic exenteration surgery across expert centres; firstly by facilitating evidence-based and reproducible treatment decision-making by accurate prediction of outcomes of priority to patients, carers and clinicians in the preoperative setting, and secondly by providing a framework for surgical quality improvement. Ultimately it is hoped that the findings of this thesis and planned future work will promote standardisation of this treatment and contribute to improved outcomes for patients with LARC and LRRC.

CHAPTER 1: INTRODUCTION

Colorectal cancer was the fourth most diagnosed cancer in Australia in 2024, with an estimated 15 542 new diagnoses¹. Rectal cancer accounts for approximately one third of all colorectal cancer; translating to around 5,000 new diagnoses per year in Australia. An estimated 10% of patients with rectal cancer have a T4 tumour, which invades beyond the fascia propria of the mesorectum (the 'mesorectal fascia'), and may infiltrate adjacent pelvic organs, bone, neurovascular or other soft tissue structures (T4b)^{2,3}. Total mesorectal excision (TME) surgery is the standard of care for primary rectal cancers which are contained within the fascia propria of the mesorectum^{4,5}. An involved (R1) pathological circumferential resection margin is an important, independent risk factor for local recurrence, reduced disease-free survival and overall survival⁶. Therefore, achieving R0 resection is one of the primary goals of rectal cancer surgery, along with ensuring an intact TME and adequate lymphadenectomy, minimising operative morbidity, and restoration of intestinal continuity, if possible and preferred.

Despite advances in both surgical technique (i.e. TME) and neoadjuvant treatments (including total neoadjuvant treatment more recently), local recurrence after the treatment of rectal cancer remains a significant problem. Reported rates of local recurrence in contemporary literature are between 4-10%⁷⁻¹². The potential for inadvertent increases in local recurrence rates during the experimentation phase of new surgical techniques or neoadjuvant treatments for rectal cancer has been demonstrated, for example during the development of trans-anal TME¹³ and total neoadjuvant treatment¹⁰. Without salvage surgery, locally recurrent rectal cancer (LRR) is almost uniformly fatal, with an expected 5-year survival rate of less than 5%¹⁴⁻¹⁶. Furthermore, the quality of life of patients with unresected pelvic recurrence is poor, due to malignant infiltration of pelvic viscera and neurovascular structures which can cause incontinence, malodorous discharge and intractable pain. As for locally advanced primary (T4) rectal cancer (LARC), clear (R0) resection margins are the most important predictor of long term survival in salvage surgery for LRR¹⁷⁻²⁰.

LARC and LRRC can be considered collectively as tumours that require 'beyond TME' surgery in order to achieve an R0 resection, which, in both cases is critical in minimising the risk of disease recurrence and maximising the chance of long-term survival. LARC infiltrates beyond the mesorectum into adjacent pelvic organs and structures, while LRRC most commonly arises within the extra-TME tissues, i.e. the presacral space or pelvic sidewall. In both instances, radical resection of the tumour and the rectum (or neo-rectum), with en bloc excision of all contiguously involved organs and structures is required to achieve R0 margins.

1.1 Pelvic exenteration surgery for the treatment of rectal cancer

Pelvic exenteration refers to radical multivisceral resection for advanced pelvic tumours. This treatment was originally described in 1948 by Alexander Brunschwig at Memorial Hospital, New York, as a palliative treatment for carcinoma of the cervix, which characteristically persists or recurs locally in the pelvis for prolonged periods without metastasising, and causes significant local symptoms including intestinal and ureteric obstruction, fistulation and pain²¹. Brunschwig pioneered a technique for total evisceration of the pelvis, requiring both faecal and urinary diversion, as the last line treatment for palliation of women with the most extreme and intractable local symptoms. One patient in Brunschwig's original series underwent pelvic exenteration for locally advanced sigmoid carcinoma, while the first exenteration for locally advanced rectal cancer was reported in 1950 by Thompson and Howe in Boston²². In the same year, Brintnall and Flocks reported a series of nine patients who underwent 'pelvic viscerectomy' for rectal (seven patients) or sigmoid carcinoma (two patients), of whom three patients (33%) died in the early postoperative period²³. Other pioneering exenteration surgeons who applied the newly described principles of exenteration to locally invasive rectal cancer with curative intent over the following decade reported

similarly high operative mortality rates²⁴⁻²⁶. These discouraging early outcomes persisted until the 1980s, at which time the expected operative mortality remained 15-20%²⁷⁻²⁹.

Due to the poor outcomes reported in the 20th century, pelvic exenteration for patients with rectal cancer has historically been a controversial treatment amongst the surgical community. Since the 1980s, however, significant improvements in anaesthesia and perioperative medicine, imaging technology (particularly magnetic resonance imaging) and surgical techniques have dramatically improved the safety and oncological efficacy of pelvic exenteration, as well as other major oncological abdominal resections^{30, 31}. The boundaries of resectability have continued to expand, and the historical technical contraindications to surgery, such as involvement of the pelvic sidewall, common or external iliac vessels, sciatic nerve, pubic bone and high sacrum³²⁻³⁸, are no longer applicable at specialised exenteration units, where techniques for the safe resection of major bone and neurovascular have been developed³⁹⁻⁴⁵. In contemporary practice, pelvic exenteration can be performed safely at expert units, with <1% perioperative mortality, acceptable complication rates, encouraging quality of life outcomes, and with the chance of cure in 40-60% of patients⁴⁶⁻⁴⁸. In 2025, pelvic exenteration is well established as the standard of care for appropriately selected patients with LARC and LRRC⁴⁹.

1.2 Variation in treatment decision-making and outcomes

The pioneering phase of exenterative surgery has very much concluded now that the technical aspects are so well developed that the outcomes for patients with LARC and LRRC are dramatically better compared to the 1980s. Now, the priority for the international exenteration community is the ongoing, incremental improvement in patient outcomes in pursuit of excellence. There are a number of current issues which, if addressed, may further improve patient outcomes. These relate to variation in treatment decision-making and treatment outcomes, both within and between centres, as

well as disparity in access to pelvic exenteration services. Variation in treatment decision-making as early as the time of diagnosis of LARC or LRRC, when a patient's local specialist (a colorectal surgeon or oncologist) decides whether or not to refer that patient to an exenteration centre for consideration of surgery. Variation in referral (or not) for consideration of pelvic exenteration for LARC or LRRC is a major contributor to inequity of access to specialised exenteration services. Even after referral, variation in multi-disciplinary team (MDT) decision-making may occur within an exenteration centre, where the recommendation for or against surgery may vary depending on the experience of the individual clinicians present, and may not always be evidence-based or reproducible. Several recent studies have highlighted variation in treatment decision-making and approaches between different exenteration centres, with regard to both the use of neoadjuvant treatment(s) and selection of patients with LARC and LRRC for surgery^{50, 51}. This variation in treatment decision-making likely contributes to the variation in outcomes of patients undergoing surgery for LARC and LRRC both within and between specialist exenteration centres⁵².

Standardisation of evidence-based treatment decision making and rigorous surgical quality improvement may address these issues, and ensure equity of access to potentially curative exenterative surgery for all patients with LARC and LRRC. These concepts form the background and rationale for this thesis.

1.3 Thesis Aims and Overview

With the above concepts in mind, this thesis had two general aims:

- **Thesis Aim 1:** To address unwarranted variation in treatment decision-making in patients with LARC and LRRC
- **Thesis Aim 2:** To establish internationally applicable surgical quality benchmarks for pelvic exenteration surgery

The specific aims of this thesis were:

- To identify the outcomes of pelvic exenteration for LARC and LRRC reported in current literature;
- To gain consensus among local and international multi-disciplinary experts around the most important outcomes following pelvic exenteration and the level of influence each outcome should have on treatment decision-making;
- To define the views of patients with LARC or LRRC and their carers with regard to the most important outcomes following pelvic exenteration and the level of influence each outcome should have on treatment decision-making;
- To identify independent predictors of the identified priority outcomes of pelvic exenteration that are available preoperatively; and
- To define internationally applicable benchmarks for the surgical outcomes of total pelvic exenteration for LARC and LRRC.

The following thesis overview outlines the methodology employed in each chapter to systematically address these aims.

Chapter 2 includes three published articles (including one invited editorial) which provide general background to the thesis and describe the issues relating to variation in treatment decision-making and outcomes in more detail. In *Chapter 2.1*, historical context to the thesis is provided in the form of an overview of how the treatment of LARC and LRRC has evolved in Australia and New Zealand in recent decades, and how variation in treatment decisions and inequities in access to referral to specialist exenteration centres need to be addressed. *Chapter 2.2* discusses the issue of fertility in advanced gastrointestinal surgery, including pelvic exenteration. It sets the scene for how the ability to predict postoperative outcomes in a reliable manner may allow standardisation of

treatment recommendations and potentially prevent futile attempts at resection for patients with LARC and LRRC. *Chapter 2.3* discusses quality of life following pelvic exenteration for LARC and LRRC; specifically how quality of life measurement can and should be incorporated into treatment decision making in an evidence-based, reproducible manner with quality of life as a key outcome underpinning recommendations for or against surgery.

To address *Thesis Aim 1*, the most important outcomes of surgery according to patients, carers and clinicians were defined using consensus methods ('priority outcomes') and preoperative predictors of these outcomes were evaluated. It was hypothesised that the ability to predict the priority outcomes of surgery for an individual patient could facilitate guide evidence-based, reproducible decision-making (i) at the point of referral (to guide the decision to refer), and (ii) at the point of the specialised MDT meeting (to guide the recommendation for or against surgery). The methodology for identifying priority outcomes and their predictive variables involved a mixed methods approach over two phases, which were outlined *a priori* and are presented in a published article included as *Chapter 3*.

Identification of the priority outcomes of pelvic exenteration involved the following steps:

- Identification of the outcomes of pelvic exenteration for LARC and LRRC reported in current literature (which likely reflect those considered important by clinicians). This was approached by designing a comprehensive **systematic review** of contemporary literature. The results of this review are presented in two published articles included as *Chapter 4*.
- Identification of the outcomes of pelvic exenteration for LARC and LRRC that patients and their carers consider important. An **exploratory qualitative research approach** was developed, and **semi-structured interviews** were conducted with patients who had

undergone pelvic exenteration as well as their carers. The results of this qualitative investigation are presented in two published articles included as *Chapter 5*.

- Compiling the outcomes identified from the systematic review of the literature and patient/carer interviews (*Chapters 4 and 5*) as a 'long list' of outcomes. This formed the list of candidate outcomes, which was used to inform the next step of gaining consensus around priority outcomes.
- Development of consensus among international multi-disciplinary experts, patients and carers, around the priority outcomes of pelvic exenteration and the relative influence each outcome should have on treatment decision-making. Using **modified Delphi methodology**, three iterative surveys were distributed to international experts (via the international PelvEx Collaborative), patients and carers, to determine consensus and define the priority outcomes of pelvic exenteration. The results of this study are presented in a published article included as *Chapter 6*.

The second phase was to identify preoperative predictors of the identified priority outcomes. A **retrospective cohort study** was conducted using individual patient data from a prospectively maintained institutional database, where **multivariable regression analysis** was used to identify independent preoperative predictors of the priority outcomes. The results of this study are presented in a manuscript (under peer review) included as *Chapter 7*. The hypothesis was that the ability to accurately predict the priority outcomes of exenterative surgery for an individual patient would facilitate evidence-based decision making. In future post-doctoral work by the candidate, these models will be refined and externally validated, before being used as the basis for a risk prediction and decision-making tool which predicts the priority outcomes for an individual patient and generates an evidence-based recommendation for or against surgery for an individual patient.

Chapter 8 sought to establish internationally applicable surgical outcome quality benchmarks for pelvic exenteration (*Thesis Aim 2*). In this chapter, recently described **surgical benchmarking methodology** was applied to a cohort of patients who underwent pelvic exenteration for LARC and LRRC at 16 centres from 12 countries and five continents. The results of this **international multicentre retrospective cohort study** are presented in two published articles included as *Chapter 8*. The reported benchmark outcomes serve as globally applicable surgical quality standards against which exenteration units can systematically compare their results and, where applicable, implement quality improvement initiatives to improve their own outcomes, hopefully reducing variation in treatment outcomes between centres and ultimately improving outcomes for this group of patients globally.

The line of scientific inquiry outlined above was designed in advance by the candidate under supervision of the supervisory team and for the purposes of this thesis. The candidate was primarily responsible for the conceptual design and conduct of all included studies and manuscripts (including analysis and interpretation). Regarding the novel aspects of this work, priority outcomes of a surgical procedure have not been previously defined and is a novel concept, and required the application of significantly modified existing methodology in order to effectively address the research aim. The qualitative work presented in *Chapter 5* provide unique insights into perspectives of long term survivors of pelvic exenteration and their carers. The multivariate regression analysis in *Chapter 7* demonstrate the difficulty in predicting the important outcomes of exenteration for LRRC using only preoperative information, and the benchmarking analysis in *Chapter 8* is the first study to define internationally applicable benchmarks for this operation. The findings presented in this thesis will inform the candidate's post-doctoral work on standardisation of exenterative surgery, with the ultimate goal of improving treatment outcomes for patients with LARC and LRRC.

It should be noted that the chapters of this thesis are written as individually publishable articles, and therefore some repetition of background information and references across chapters is unavoidable.

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CHAPTER 2: BACKGROUND

CHAPTER OVERVIEW

This chapter provides general background to the thesis in the form of three perspective articles (including one invited editorial). These articles outline current issues relating to variation in treatment decision-making, outcomes and access for patients LARC and LRRC, and collectively this chapter provides historical background and contemporary context to set the scene for the subsequent chapters which address the specific aims of this thesis.

CHAPTER 2.1

Treatment of locally advanced and recurrent rectal cancer in Australia and New Zealand: recent progress and future challenges.

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Treatment of locally advanced and recurrent rectal cancer in Australia and New Zealand: recent progress and future challenges

Centralization of cancer surgical services in Australia and New Zealand remains controversial, though most would agree that patients requiring complex multi-visceral pelvic resection for locally advanced or recurrent rectal cancer should be referred to specialized exenteration centres. Acceptance of pelvic exenteration (PE) by the surgical community was initially slow due to historically poor outcomes reported during the last century, however in contemporary colorectal surgical practice PE is considered the standard of care for patients with both advanced primary and recurrent rectal tumours. In 2023, long term survival after PE compares favourably with hepatectomy for stage IV colorectal cancer,^{1,2} major morbidity rates are equivalent to those of radical oesophagectomy,³ and quality of life outcomes are encouraging.¹

The coordinated evolution of specialist referral PE centres in Australia and New Zealand represents a major success story for complex cancer surgery in our region. Centralized referral to a small number of centres over the last 25 years has facilitated formation of dedicated advanced pelvic oncology multi-disciplinary units with specialized medical, nursing and allied health staff, who have accumulated large experiences and can support these complex patients. Academic collaboration between these centres has facilitated the development of novel surgical techniques which, combined with the results of Australia and New Zealand multi-centre prospective data collection, have advanced this treatment on a global scale.⁴⁻⁶ More recently, PE referral centres have been established with collaboration in states where many patients were previously required to travel interstate for surgery.^{7,8} It seems intuitive that funding for what remains a relatively 'low volume, high cost' procedure should be directed to a small number of well-resourced centres with these capabilities. The centralization of PE in Australia and New Zealand is in stark contrast to the de-centralized nature of services in North America, the United Kingdom and Europe, where (at least historically) the majority of centres managing patients with locally advanced or recurrent rectal cancer had annual operative volumes of less than five patients.⁹⁻¹¹

One of the remaining challenges facing the colorectal community is ensuring equity of access to now well established PE services for all patients with advanced and recurrent rectal cancer in Australia and New Zealand, regardless of geographic location or socioeconomic status. Recently analysed data from one PE centre indicated that geographical location of residence (metropolitan, regional or remote) has no effect on survival, morbidity or quality of life

outcomes following PE (under peer review). While outcomes seem to be comparable for patients who are referred to a specialist centre, it is unknown how many patients are deemed 'unresectable' at a local level prior to referral and for whom a palliative approach is adopted. Another concern, raised by recent Bi-National Colorectal Cancer Audit data, is the number of patients with T4 rectal cancer who undergo more limited resections in some regions with an increased risk of involved margins.¹² In a rapidly evolving field, where tumours that were widely considered incurable less than 10 years ago are now routinely and safely resected with curative intent at PE centres, it is crucial that all patients with locally advanced and recurrent rectal cancer are assessed for suitability for exenterative surgery and afforded the opportunity of potential cure. Of an estimated 5000 new diagnoses of rectal cancer in Australia and New Zealand each year, up to 10% (500 patients) can be expected to develop local recurrence, of which 50% (250 patients) may have disease limited to the pelvis and could be eligible for PE. This estimate greatly exceeds the referral numbers currently seen by Australia and New Zealand PE centres and raises the possibility of inequitable access to referral.

Although routine review of all patients at a specialist PE unit would be ideal, the costs and inconvenience to the patient (particularly long distance travel) and health system remains a significant barrier, this has become easier with development of telemedicine. Another alternative to provide guidance of who to refer, currently under development, is an online risk prediction and surgical decision-making tool designed to be used locally by clinicians at the point of diagnosis (pre-referral to a PE centre) to estimate the survival, functional and economic impacts anticipated after PE for an individual patient. Based on these expected outcomes the tool could then guide the local clinician as to who should be referred to a specialist centre for consideration and assessment of surgery at a specialist referral centre.

PE now represents the standard of care for patients with locally advanced and recurrent rectal cancer, as well as those with advanced primary and recurrent non-rectal pelvic tumours. Close collaboration during the evolution of a small number of specialist tertiary referral PE centres in Australia and New Zealand has given patients in our region access to world class care. Variability in decision making around which patients are referred to these centres can be minimized by development of novel online evidence-based tools for pre-referral patient assessment.

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Author contributions


Kilian G. M. Brown: Conceptualization; writing – original draft. **Michael J. Solomon:** Conceptualization; methodology; supervision; writing – review and editing. **Alexander G. Heriot:** Conceptualization; writing – review and editing. **Frank Frizelle:** Conceptualization; writing – review and editing.


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CHAPTER 2.2

The paradox of hope in surgery for advanced gastrointestinal malignancy – how do we define futility?

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The Paradox of Hope in Surgery for Advanced Gastrointestinal Malignancy

How Do We Define Futility?

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The primary justification for aggressive oncological resection in patients with locally advanced or oligometastatic gastrointestinal malignancies is the reasonable chance of long-term survival. Pelvic exenteration, cytoreductive surgery, hepatic metastasectomy, pancreaticoduodenectomy, and retroperitoneal sarcoma surgery all involve radical, often multivisceral resections. In combination with systemic therapy and/or local ablative techniques, these procedures may offer selected patients the chance of long-term survival and even cure. However, they may also be associated with prolonged recovery, substantial morbidity, and, in some cases, permanent functional sequelae, which significantly impair quality of life. In patients with a disease so extensive that there is no realistic chance of durable disease control or survival, such aggressive surgery may be considered futile.

The issue of futile medical interventions has been discussed previously, primarily in relation to intensive care unit admission and advanced life support,¹ as well as in the context of elderly or comorbid patients being considered for emergency laparotomy.² In recent years, there has been increasing attention given to the concept of futile oncological surgery in patients with advanced gastrointestinal malignancy. Despite significant variation in the definition of what constitutes futility, rates of futile resection appear concerning high in multiple reports of patients undergoing radical surgery for pancreatic cancer (18.9%),³ colorectal liver and peritoneal metastases (12.6% and 25.3%, respectively),^{4,5} locally advanced primary or recurrent rectal cancer (21.4%),⁶ and intrahepatic cholangiocarcinoma.⁷

Patients presenting with advanced gastrointestinal tumors are often young, previously healthy, and highly

motivated to survive, and may be willing to accept any risk, no matter the significance, in the hope of prolonging life. Other oncological treatment options may be limited, and in the absence of any alternative, the multidisciplinary team may turn to the surgeon and ask: “Is surgery an option?”. In many instances, these patients do not fit within the traditional and convenient categories of “resectable” and “unresectable.” Although the broad adoption of multidisciplinary tumor boards has facilitated more rigorous oncological decision-making when evidence is lacking, the focus may shift to a patient “young age” or an aggressive treatment that may represent their “only hope.” Accurate identification of patients who at best will gain nothing other than false hope and at worst be harmed by futile surgery is difficult, and communicating these concepts to a patient and their family is challenging. Bearing in mind the dictum “tumor biology is king and patient selection is queen,” the discussion should be directed not toward what can be resected but what should be.

There is significant variation in how futility is defined in the surgical oncology literature, with many previous studies using the definition of “early” disease recurrence (eg, within a specific time interval from surgery). Even within the same patient population (eg, colorectal peritoneal metastases), the definition of early recurrence varies widely (6, 8, or 12 mo). One issue with defining futility based on time to recurrence is that for some tumors, early recurrence does not always impede long-term survival, especially if this recurrence can be salvaged. A composite endpoint incorporating objective measures, including recurrence and survival, with other subjective but measurable patient-centered outcomes would better define futility. Importantly, the statistical probability of survival or treatment success (referred to as “quantitative futility”) does not consider the anticipated quality of life following the intervention (“qualitative futility”).⁸

There are inherent challenges reconciling the perspectives of the individual and the collective around futile surgery. There is likely to be a difference in what the individual patient facing a terminal disease and their treating clinician consider futile (“individual futility”) and what the broader community would define as futile (“collective futility”), including the economic cost. As a thought experiment, what chance of cure or survival is not considered futile (eg, 1%, 5%, or 30%), at what time point, and by whom—the surgeon, the patient, the multidisciplinary team, society, insurers, or the health care system? This is analogous to the difficulty defining clinical equipoise and what level of uncertainty around treatment options can be

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used as the ethical justification for a randomized trial.⁹ How individual and collective futility should be defined, measured, and incorporated into decision-making needs to be addressed from the perspective of distributive justice within the confines of a finite health care system.

Reliable and reproducible tools to predict futile surgery could be incorporated into surgical decision-making to refine patient selection and ultimately avoid futile surgery. The prediction models and nomograms developed to date have analyzed traditional clinicopathologic factors alone as potential predictors of futility.^{3,4,6,10,11} As understanding of the molecular mechanisms of disease recurrence improves in the era of precision oncology, it is likely that more useful biomarkers will be identified and incorporated into tumor-specific predictive models for futility. Recent advancements in machine learning and artificial intelligence are beginning to show promise in predicting surgical outcomes. These innovative approaches, when applied to established clinicopathologic factors and novel biomarkers, may offer more accurate and personalized predictions of surgical benefit. Such tools would assist the experienced multi-disciplinary team in patient selection for surgery by producing an evidence-based estimate of futility for an individual patient. Predicting futility must also be an iterative concept, as the potential benefit of surgery may be expected to evolve with improvements in systemic treatments and even the potential for new treatments or trials arriving within the predicted period of survival.

These issues have prompted the initiation of a dedicated research program within the Advanced Gastrointestinal Malignancy Surgical Program at the authors' unit; a high-volume academic referral center for pelvic exenteration, cytoreductive surgery, complex hepatobiliary resections, and retroperitoneal sarcoma surgery. Under a co-designed study protocol, rigorous methodology will be used to develop a consensus-based definition of futility among patients, clinicians, and other stakeholders. This is anticipated to be defined as a composite endpoint that incorporates a range of patient-centered outcomes, including survival, recurrence, anticipated complications, and quality of life. Based on this consensus definition, tumor-specific predictive models will be developed with the aim of predicting futile surgery using patient and tumor information available preoperatively. Although treatment decisions must always be individualized, and the output of any model must be interpreted in the context of an individual patient's goals, this work may provide a framework for more reliable and reproducible, evidence-based decision-making and ultimately reduce the incidence of futile oncological surgery.

The integration of advanced predictive tools into clinical practice, however, raises important ethical considerations. While they may enhance decision-making accuracy, there is a risk of over-reliance on technology at the expense of clinical judgment and patient autonomy. Moreover, the use of artificial intelligence in predicting surgical

futility may introduce new forms of bias, potentially exacerbating existing health care disparities. As these technologies evolve, it will be crucial to establish guidelines for their ethical implementation, ensuring that they supplement rather than supplant the human elements of surgical decision-making and patient-centered care.

The reported rates of futile surgery in patients with advanced gastrointestinal malignancy appear alarmingly high. However, there are limitations in interpreting current data. There is an urgent need to develop a consensus definition of futility, which is supported by all stakeholders, including patients and their families. The level of clinical uncertainty (equipose) may relate directly with a dichotomous measure of futility. A continuous or even ranked ordinal measure of futility may be more appropriate. This will help us understand the true incidence of futile surgery and enable us to work toward predicting and avoiding futile interventions, reserving radical surgery for those who may truly stand to benefit.

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CHAPTER 2.3

Understanding quality of life after pelvic exenteration for patients with rectal cancer

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Understanding Quality of Life After Pelvic Exenteration for Patients with Rectal Cancer

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As recently as the 1990s, pelvic exenteration for rectal cancer was associated with substantial morbidity and a perioperative mortality rate of up to 20%, the survival benefit was not well demonstrated, and there was essentially no quality of life (QOL) data. With these poor outcomes, pelvic exenteration has historically not been widely accepted by the surgical community. In 2024, pelvic exenteration is now established as the standard of care for appropriately selected patients with locally advanced primary and recurrent rectal cancer. The pioneering period of the 1990s and 2000s, in which demonstration of safety and oncological feasibility was the priority, is now well behind us. The clinical and academic focus at specialist units around the globe is now on further improvement of the encouraging oncological and QOL outcomes reported in recent decades, as well as minimizing postoperative complications, in pursuit of excellence.

In this issue of the journal, Lin and Haiyang present the outcomes of a 7-year prospective cohort study conducted at a single Chinese center, in which 122 patients underwent exenterative surgery for locally advanced primary or recurrent colorectal cancer. The authors are to be congratulated

for a thorough, prospective assessment of patient-reported outcomes in their practice.¹ The need for up to two permanent ostomies, prolonged recuperation, and time away from family and work, and in some cases the lasting functional consequences, all impair QOL after exenteration, at least in the short term. Lin and Haiyang reported a significant reduction in all QOL domains at 3 months after exenteration compared with preoperative baseline. Although social and emotional well-being scores were slower to improve than physical functioning scores, all QOL domains returned to baseline by 12 months. These findings are consistent with those previously reported in Western populations, including work from our unit where QOL data have been collected prospectively over 15 years for now more than 550 exenteration patients.² Collectively, these data emphasize the prolonged recuperation that can be expected following exenteration, but also that QOL improves by 6 months, and is similar to preoperative baseline by 1 year. It must also be remembered that for patients who do not undergo surgery, the alternative is a gradual deterioration in QOL, likely related to progressive local tumor-related symptoms such as bleeding, malignant fistulae, and intractable pain, such that the QOL trajectory of this group crosses that of patients who undergo exenteration at 9 months.

Until recently, one of the major limitations of reported exenteration QOL data has been the lack of a QOL instrument that adequately captures the wide range of issues encountered by this unique patient cohort. The Functional Assessment of Cancer Therapy—Colorectal questionnaire, Short Form Health Survey, and European Organization for Research and Treatment for Cancer Quality of Life Questionnaire C30 have been the most frequently used tools in the exenteration literature to date.³ Although these instruments

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are valid measures of QOL in generic and colorectal-cancer-specific populations, they do not adequately address the unique and complex issues faced by patients with advanced pelvic malignancy who undergo pelvic exenteration. In 2023, development of a disease-specific outcome measure for patients with locally recurrent rectal cancer was completed and includes nine scales (healthcare services, psychological impact, pain, urostomy-related symptoms, lower limb symptoms, stoma, sexual interest, and urinary symptoms) and three single items.⁴ This LRRC-QoL tool captures the specific issues identified as relevant to patients with locally recurrent rectal cancer and therefore likely has greater utility in both clinical and academic practice than existing, generic colorectal cancer tools.

How predicted QOL for an individual patient can be incorporated into treatment decision-making and patient selection remains to be defined. Justifying the potential morbidity and functional consequences of such radical surgery by selecting patients who will truly benefit is the primary role of an advanced pelvic oncology multidisciplinary team. However, the recommendation for or against exenterative surgery and what constitutes “benefit” for an individual patient has historically been based on anticipated survival alone. Now that prospective patient-reported outcome data are available from exenteration centers, the predicted QOL for an individual patient can and should be incorporated into multidisciplinary decision-making in a reproducible, evidence-based way, and is the subject of ongoing work.⁵

Traditionally, total pelvic exenteration has been considered a standard “off the shelf” operation involving an abdominoperineal excision with en bloc excision of all internal genitourinary viscera. This is now a historical concept, which predates the advent of lateral and posterior compartment bone and neurovascular resections. In contemporary practice, exenterative surgery represents a heterogenous group of procedures in which the extent of resection is anatomically tailored to the extent of local tumor invasion. This bespoke technical approach has led to inconsistent terminology, and without standardized definitions it is difficult to characterize a specific cohort. For example, in Lin and Haiyang’s study, it is noteworthy that 71% did not require urinary reconstruction (which included urinary diversion or ureteric reimplantation), 38% were able to have intestinal continuity restored, only 11 patients underwent sacrectomy (9%), and 75% of the cohort had no history of prior pelvic radiotherapy (only 16% of patients with primary tumors were treated with radiotherapy). This cohort would seem to represent one with mostly primary, central compartment, supra-levator tumors in whom radiotherapy was rarely required. The oncological, morbidity, and quality of life outcomes of this population are expected to differ substantially from

units seeing higher proportions of tumors at the periphery of the pelvis, which require en bloc bone or neurovascular resection. This would include our own experience at Royal Prince Alfred Hospital, where patients are invariably treated with radiotherapy, lateral compartment excision is required in 40% and 55% of primary and recurrent rectal tumors, respectively, and sacrectomy is performed in 40% and 60%, respectively. The Pelvic Exenteration Lexicon overcomes some of these issues by providing a standardized description of the operative components of extended and exenterative pelvic surgery,⁶ and adopting this system may facilitate more meaningful comparison of outcomes between centers in the future.

With the safety and oncological outcomes of pelvic exenteration now well documented, there is increasing focus on understanding postoperative QOL with the aim of improving patient selection and preoperative counseling. Patient-reported outcome measurement should be a mandatory component of prospective data audit at specialist exenteration units, and how these outcomes are most appropriately measured and incorporated into quality improvement requires further investigation.

DISCLOSURE The authors have none to declare.

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CHAPTER 3: METHODOLOGY

CHAPTER OVERVIEW

This chapter outlines the mixed methodological approach utilised to address *Thesis Aim 1: To address unwarranted variation in treatment decision-making in patients with LARC and LRRC.*

This methodology was adapted from that previously described for the development of core outcome sets, and was applied to our specific research question in a novel way: for the identification and preoperative prediction of 'priority outcomes' of pelvic exenteration surgery. The results of this methodology are presented in subsequent *Chapters 4-7.*



CHAPTER 3.1

Development of a risk prediction tool for patients with locally advanced and recurrent rectal cancer undergoing pelvic exenteration: protocol for a mixed-methods study

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BMJ Open Development of a risk prediction tool for patients with locally advanced and recurrent rectal cancer undergoing pelvic exenteration: protocol for a mixed-methods study

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ABSTRACT

Introduction Pelvic exenteration (PE) surgery represents the only potentially curative treatment option for patients with locally advanced or recurrent rectal cancer (LARRC). Given the potential morbidity, whether or not PE should be recommended for an individual patient presents a major decisional conflict. This study aims to identify the outcomes of PE for which there is consensus among patients, carers and clinicians regarding their importance in guiding treatment decision-making, and to develop a risk prediction tool which predicts these outcomes.

Methods and analysis This study will be conducted at a specialist PE centre, and employ a mixed-methods study design, divided into three distinct phases. In phase 1, outcomes of PE will be identified through a comprehensive systematic review of the literature (phase 1a), followed by exploration of the experiences of individuals who have undergone PE for LARRC and their carers (phase 1b, target sample size 10–20 patients and 5–10 carers). In phase 2, a survey of patients, their carers and clinicians will be conducted using Delphi methodology to explore consensus around the outcomes of highest priority and the level of influence each outcome should have on treatment decision-making. In phase 3 a, risk prediction tool will be developed using data from a single PE referral centre (estimated sample size 500 patients) to predict priority outcomes using multivariate modelling, and externally validated using data from an international PE collaboration.

Ethics and dissemination Ethical approval has been granted for phases 1 and 2 (X22-0422 and 2022/ETH02659) and for maintenance of the database used in phase 3 (X13-0283 and HREC/13/RPAH/504). Informed consent will be obtained from participants in phases 1b and 2; a waiver of consent for secondary use of data in phase 3 will be sought. Study results will be submitted for publication in international and/or national peer reviewed journals.

PROSPERO registration number CRD42022351909.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Define priority outcomes of pelvic exenteration according to individuals who have undergone surgery, their carers and clinicians.
- ⇒ Develop a risk prediction tool using prospective individual patient data from a high-volume centre.
- ⇒ External validation using international, multicentre data.
- ⇒ Potential limited generalisability beyond high-volume, specialist centres.

INTRODUCTION

Pelvic exenteration (PE) surgery represents the standard of care for selected patients presenting with locally advanced or recurrent rectal cancer, and the only potentially curative treatment option.¹ This ultraradical surgical procedure involves en bloc resection of all anatomical structures contiguously involved by tumour, and typically requires excision of multiple pelvic viscera as well as pelvic bone and major neurovascular structures, followed by complex reconstruction. Refinement of surgical techniques in recent decades has made increasingly radical ‘higher and wider’ resections in all compartments of the pelvis safe and oncologically feasible.^{2,3} However, such radical surgery may be associated with major morbidity (32%–38%),^{4–6} functional impairment,⁷ at least a temporary reduction in quality of life,⁸ as well as substantial cost to the healthcare system.⁹ Therefore, whether or not radical surgery should be recommended for an individual patient with locally advanced or recurrent rectal cancer presents a major decisional conflict for the team of treating clinicians,

where the consequences of surgery must be weighed against the potential for cure. The paradigm has shifted such that the decision to be made is no longer what can be technically resected, but rather what should be.¹⁰

Currently, the decision-making process around whether curative intent PE surgery is recommended for an individual patient tends to be based on individual clinician and centres' experiences, rather than a reproducible, evidence-based process. This may lead to substantial variation in treatment decision-making within and between PE centres, as has been recently demonstrated by international comparative data,¹¹ as well as variation in which patients with a new diagnosis of locally advanced or recurrent rectal cancer are referred to a PE centre for consideration of potentially curative surgery. Recommendations for or against surgery, and decisions around whether to refer a patient to a PE centre, are often made with survival as the primary outcome of interest, and which other outcomes of surgery (such as anticipated quality of life, functional outcomes and morbidity) are considered important by patients, carers and clinicians and how they should be incorporated into the decision-making process is not well understood.

This study aims to develop a risk prediction tool to predict the outcomes of PE that are considered most important by patients with locally advanced and recurrent rectal cancer, their carers and clinicians. The tool may be used at the time of diagnosis by referring clinicians, as well as those managing patients at a specialist PE centre, to access an evidence-based prediction of the anticipated outcomes of surgery for an individual patient. Development and implementation of this tool will assist clinicians to navigate the decisional conflict

of whether to refer or recommend PE when managing a patient with a new diagnosis of advanced rectal cancer in a reproducible, evidence-based manner.

METHODS AND ANALYSIS

Aims and study design overview

The general aim of this study is to develop and validate a risk prediction tool for patients with locally advanced and recurrent rectal cancer who undergo PE (figure 1). Specifically, this study aims to:

- ▶ Define 'priority outcomes' following PE for locally advanced and recurrent rectal cancer, based on patients, carers and clinicians consensus regarding their importance in guiding treatment decision-making.
- ▶ Develop a risk prediction model which predicts the identified priority outcomes of PE for an individual patient based on information available preoperatively.

This study will employ a mixed-methods study design which will follow recommendations from the established methodology for development of core outcome sets (COS), such as that used for the core outcome research measures in anal cancer study,^{12 13} and be modified for the purposes of addressing the study objectives. COS development methodology has been outlined by the COMET Initiative and uses comprehensive consensus methods, involving patients and clinicians, to develop agreement around a minimum set of outcomes to be reported in all studies and trials for a specific clinical area.¹⁴ While the primary purpose of a COS is to define the minimum outcomes to be used in clinical trials, the purpose of this study is to identify the priority outcomes to be used for clinical decision-making by incorporation into a risk prediction tool, and therefore, the established

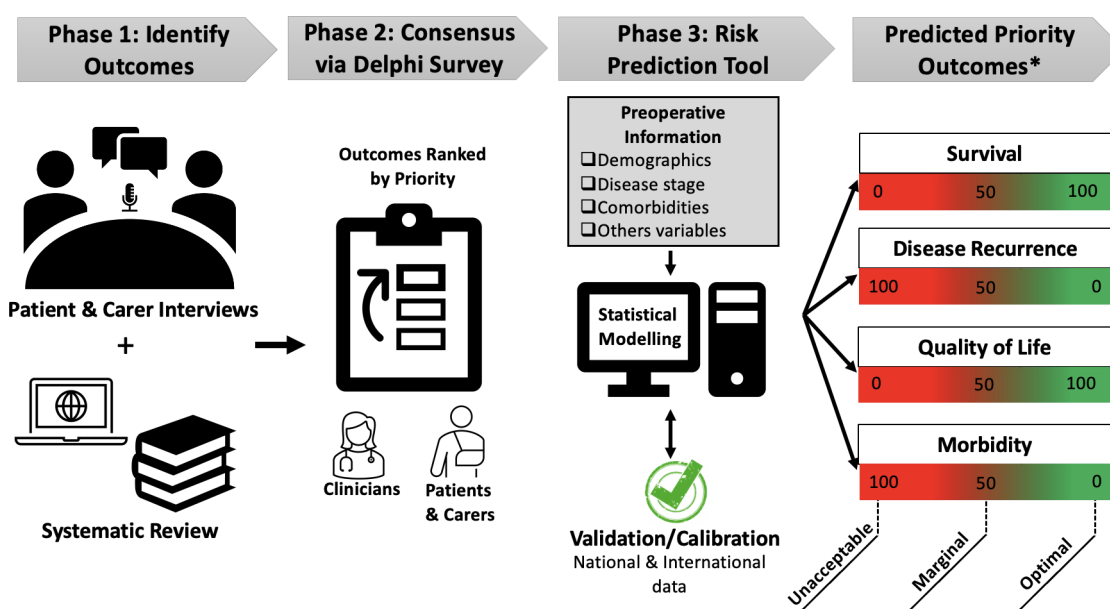


Figure 1 Schematic representation for the development of the pelvic exenteration risk prediction tool. *Hypothesised priority outcomes are listed. Actual outcomes will be identified during phases 1 & 2.

COS methodology will be modified to account for this different objective.

There will be three distinct phases of this study. In phase 1, outcomes of PE will be identified through a comprehensive systematic review of the literature (phase 1a), followed by in depth exploration of experiences of individuals who have undergone PE for locally advanced or recurrent rectal cancer and their carers using qualitative research framework (phase 1b). In phase 2, a survey of individuals who have undergone PE, carers and clinicians will be conducted using the Delphi methodology to explore consensus around the outcomes of highest priority and the level of influence each outcome should have on treatment decision-making. In phase 3, a risk prediction tool will be developed to predict the identified priority outcomes using comprehensive multivariate modelling.

Multidisciplinary advisory committee

This study will be governed by a multidisciplinary advisory committee (MAC), which will comprise of cancer specialists (surgeons, medical and radiation oncologists, senior surgical and cancer nurses, allied health professionals), a health economist, statistician, epidemiologist, health policymaker, guideline and quality measurement developer, information technology professional, patients and carers. The MAC will guide development of the tool and in later phases (beyond those outlined in this protocol) advise on development of a surgical decision-making tool, which produces a recommendation for or against PE surgery based on the risk prediction model developed in this study. The MAC will also develop communication strategies and guide translation to clinical practice with implementation and long-term sustainability plans.

Patient and public involvement

Two consumers have been consulted during the development of the study concept and protocol. Individuals who have undergone PE and their nominated carer/family member will inform the development of PE priority outcomes through in-depth interviews (phase 1). The interviews will explore their experience of PE, the decision-making process and identify priorities and factors that informed the decision. Both are included as participant groups in the Delphi process (phase 2). One or more consumers will be members of the advisory group involved in reviewing the outcomes identified in phase 1 prior to those outcomes being distributed in the subsequent Delphi study.

Phase 1: identifying outcomes of PE

Phase 1a

This phase aims to identify all outcomes of PE for locally advanced or recurrent rectal cancer reported in the published literature. The review will be conducted according to the Cochrane Collaboration guidelines¹⁵ and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.¹⁶

A comprehensive search strategy has been created in conjunction with an experienced medical librarian. The protocol has been published a priori on the PROSPERO registry.¹⁷

MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing & Allied Health Literature (CINAHL) and Scopus were searched from 1990 to 25 April 2023 for combinations of the following medical subject headings and keywords: pelvic exenteration or extended radical resection or multivisceral resection, and rectal neoplasms. The search was limited to studies published from 1990 onward, English language and adult patient. The complete search strategies are available in online supplemental file 1.

Retrospective and prospective cohort studies, cross-sectional studies, qualitative studies and randomised trials reporting outcomes of PE or multivisceral resection as the primary treatment for locally advanced or recurrent adenocarcinoma of the rectum will be included. Studies will be excluded if >10% of the population had non-rectal cancers or underwent less extensive resection and outcomes were not reported separately. Narrative reviews, case reports, case series including <5 patients, conference abstracts and letters will be excluded.

Abstracts will be screened by two reviewers independently and one reviewer will complete the full text screening and data extraction, with all extracted outcomes then reviewed by a multidisciplinary team. Data (all verbatim outcomes and their definitions) will be extracted and entered into an electronic database using a custom-designed data entry form. Outcomes will be merged with similar outcomes using different wording to create 'standardised outcomes' and allocated to a domain, each of which will be reviewed at a multidisciplinary advisory meeting, attended by specialist clinicians and nurses, a surgical outcomes researcher, and two patient advocates.

Phase 1b

In this phase, an exploratory qualitative interpretive design will be used to investigate the perspectives of individuals who have undergone PE and their carers on the important outcomes of surgery for them individually. Individual interviews with people who have undergone PE and their carers will be conducted using opened semistructured interview format to maintain a participant-led dialogue. Two topic frameworks have been developed—for individuals who have undergone PE and for carers (online supplemental file 2). The interviews will aim to identify all outcome following PE which the participant considers important, by exploring the general experience of the individual who underwent PE, which information they did or did not access about PE, alternative treatments at the time of diagnosis, how the patient decided whether or not to undergo PE, how having undergone PE has

Table 1 Purposive sampling criteria to guide recruitment in phase 1b

Characteristics	Target no of participants
Age at surgery	
<50 years	5–8
≥ 50 years	5–8
Sex	
Male	5–8
Female	5–8
Place of residence	
Local (metropolitan Sydney)	6–10
Rural/regional	4–5
Tumour	
Locally advanced primary rectal cancer	5–8
Locally recurrent rectal cancer	5–8
Total sample	10–20

impacted their life, and which factors they would view as most important if counselling someone about undergoing PE.

Participants, recruitment and setting

Individuals who have undergone PE for locally advanced or recurrent rectal cancer at Royal Prince Alfred Hospital, Sydney, Australia, will be identified from a prospectively maintained electronic PE database and invited to participate. The inclusion criteria are outlined below. The final sample size will be determined by iterative analysis for data saturation, with an estimated sample size required for saturation of 10–20 patients and 5–10 carers. A purposive sampling matrix was developed (table 1) to guide recruitment and in order to ensure the participants represent a broad group of individuals with diverse views. Characteristics used for selection will include age at time of surgery, gender, place of residence and tumour type. Carers for individuals who have undergone PE will also be invited to participate. According to participant preference, interviews will take place face to face or via telephone.

Inclusion criteria

- ▶ Adults ≥ 18 years of age.
- ▶ Patients who have undergone PE for locally advanced or locally recurrent rectal cancer.
- ▶ Patients who are more than 6 months post PE surgery.
- ▶ Patients who are fit to participate in an interview (according to their treating clinician).
- ▶ Patients who are able to participate in an interview in English.
- ▶ Patients who have the capacity to provide informed consent.
- ▶ The nominated carer for a participating individual who has undergone PE. This may be a spouse, child or other close relative. Paid carers or those from a support agency will not be included.

Data collection and analysis

Baseline demographic characteristics of participating individuals will be extracted from the existing PE database. Interviews will be audiorecorded, transcribed verbatim and imported into NVivo qualitative analysis software (NVivo V.11, QSR International, Burlington, Massachusetts, USA). Template analysis will be used to analyse the interview content, where outcomes of PE identified in the interview transcripts will be coded using NVivo and themes will be identified. Coded data will be used to generate a list of outcomes of PE which are prioritised by patients and carers.

Participant consent and withdrawal

All participants will complete a consent form after they have read the approved participant information sheet and had time to consider participation, and consent will be confirmed verbally at the start of the interview. Participants will be able to take a break, end the interview or withdraw from the study at any time, without any impact on their relationship with their treating clinician(s) or hospital.

Phase 2: defining priority outcomes by consensus

Outcomes identified from the literature and interviews in phase 1 will be reviewed according to the method described by Fish *et al.*¹² ‘Standardised outcome terms’ will be developed, where outcomes which have the same meaning but are described with different wording are combined. Similar standardised outcomes will then be grouped by domain. Standardised outcome terms and domains for each outcome will be ratified at an MAC subcommittee meeting, attended by cancer specialists, an academic with experience in surgical outcomes, senior PE nursing staff and consumer advocates. Outcomes will be excluded if considered to be of minimal clinical relevance by the MAC subcommittee. The resulting list of standardised outcomes will be used to populate the first of a three round iterative survey process using Delphi methodology.¹⁸

Participants, recruitment and setting

Participants will be recruited from three key participant groups:

- ▶ Clinicians with experience in PE and the management of locally advanced and recurrent rectal cancer (including medical, nursing and allied health staff). Clinicians will be identified via the International PelvEx Collaborative (an international collaborative group made up of specialist surgeons/physicians with experience managing advanced pelvic cancer) and Australia and New Zealand Pelvic Exenteration Multi-Disciplinary teams.
- ▶ Patients who have undergone PE for locally advanced primary or recurrent rectal cancer. Patients will be identified from an existing institutional PE database as for phase 1.

- ▶ Carers for patients who have undergone PE for locally advanced primary or recurrent rectal cancer. Patients who participate will be asked to forward the invitation email to their carers.

Identified potential participants will be initially contacted via email to advise of the upcoming Delphi survey and provide a study information sheet. The first round of the survey will be emailed 5 days after the initial contact, followed by reminders at 10 and 20 days. Following the final reminder, non-responders will be excluded from the study. Late replies will be considered, if within the study time frame. The second and the third rounds of the survey will be emailed to all responders of the survey first round. The same reminder protocol will be used. The survey rounds will be approximately 30 days apart. Snowball sampling will be used where all participants will be invited to forward the first round invitation email to anyone who is eligible to participate.

Data collection and analysis

Survey first round: Participants will indicate whether they are a patient, carer or clinician, which will allow them to access a survey specifically designed for each of these participant groups. The first round of the survey will be divided into two main sections:

- ▶ Section 1 will include demographic information specific to each participant group:
 - Patients: age, gender, tumour type (primary or recurrent rectal), months since surgery.
 - Carers: age, gender, relationship to patient with locally advanced or recurrent rectal cancer.
 - Clinicians: age group, gender, specialty, qualifications, whether a dedicated PE fellowship was undertaken, country of residency, number of years of experience treating locally advanced and recurrent rectal cancer, whether they practice within a dedicated pelvic oncology multidisciplinary team, the number of operations performed annually (in the case of surgeons).
- ▶ Section 2 will present participants with the outcomes identified in the systematic review and interviews, grouped by domains. Participants will be asked to use a 9-point Likert scale to rate the importance of each outcome as limited importance^{1–3}; important but not critical^{4–6} and critically important.^{7–9 14} An open question will be included at the end of the survey to allow participants to list any additional outcomes that they do not feel have been identified or considered in the questionnaire. Each outcome will be described in medical (for clinicians) and lay terms (for patients and carers).

Survey second round: In round 2, a list of all outcomes with a mean score or 4–6 (important but not critical) and 7–9 (critically important) during round 1 will be collated with any additional unique outcomes suggested by participants and redistributed (those scoring 1–3 will be discarded). Participants will be provided with feedback from round 1 in the form of their previous score for each

domain and a mean score from their participant group. Participants will be asked to reflect on the information presented before scoring each outcome again on the 9-point Likert scale.

Consensus around outcomes will be assessed prior to round 3, where consensus status for each outcome will be categorised according to Williamson *et al*¹⁹ as:

1. Consensus in: 70% or more respondents within a participant group rate the outcome as critically important^{7–9} and 15% or fewer rate the outcome as limited importance.^{1–3}
2. Consensus out: 70% or more of respondents within a participant group rate the outcome as limited importance and 15% or fewer rate the outcome as critically important.^{7–9}
3. No consensus: Neither of the above criteria are met.

Survey third round: In this final round, the refined list of ‘consensus in’ outcomes will be included. Participants will be asked to divide 100 points among the ‘consensus in’ outcomes according to the relative level of influence each outcome should have on treatment decision-making. The outcomes will be listed in rank order based on the mean number of points attributed to each. This list will form the provisional list of priority outcomes.

Descriptive statistics will be used to characterise the participants according to participant group. Means and SD will be used to rank the outcomes. The data from all rounds will be displayed in descriptive format, with mean responses, in order of overall ranking of importance.

Participant consent

All invited participants have no obligation to complete the study surveys and can withdraw from the study at any time. Completion of the study survey will be an indication of implied consent.

Phase 3: predicting priority outcomes

This phase aims to develop a risk prediction model, which can be used at the time of diagnosis to predict each priority outcome (identified in phase 2) for individual patients using information available at the time of treatment decision. An MAC subcommittee will review and ratify the provisional list of priority outcomes prior to this phase of the study.

Participants, recruitment and setting

Patients who underwent PE for locally advanced primary or recurrent rectal cancer at Royal Prince Alfred Hospital, Sydney, Australia between 1994 and 2023 will be identified from the authors’ institutional PE database. This database is prospectively maintained and includes extensive preoperative, intraoperative, postoperative, long-term survival and quality of life data. The estimated number of eligible patients is 500.

Preoperative variables

Preoperative variables to be used to calculate patient-specific risk scores for each of the priority outcomes will be selected from the PE database based on demonstrable

predictive value and face validity according to expert opinion. Due to the design of this study, preoperative variables cannot be selected a priori as the priority outcomes to be predicted will not be identified until the end of phase 2. If required, multiple imputation will be used for missing values.

Data collection and analysis

For eligible patients, priority outcome data (eg, survival, quality of life, complication rate) and all potential preoperative risk factors for those outcomes (eg, demographics, comorbidities and tumour factors) will be extracted from the PE database. Using this individual patient data, risk prediction models for each of the priority outcomes of PE will be developed. An experienced biostatistician will be involved in conducting and interpreting these analyses. Two main approaches will be used, including traditional multivariate regression techniques and machine learning approaches. The accuracy of the models will be compared by the computed sensitivity, specificity, negative predictive value, positive predictive value, accuracy and area under the curve. A separate statistical analysis plan will be developed for internal validation and external validation (using Australian wide and international individual patient data via the International PelvEx Collaborative Group).

ETHICS AND DISSEMINATION

Phase 1 involves a systematic review of the literature, semi-structured interviews with patients and their carers, and a Delphi survey study of clinicians, patients and carers. Ethics approval for phase 1 has been granted by the Sydney Local Health District HREC (X22-0422 and 2022/ETH02659). Ethics approval for the Pelvic Exenteration Quality Improvement database, which will be used for the statistical modelling in phase 2, is current (X13-0283 and HREC/13/RPAH/504). Other than the patients/carer interviews and Delphi survey, where the risk to the participant is that of inconvenience or distress, this project is observational and does not involve any therapeutic intervention. Therefore, there are no other potentially ethically adverse consequences. Informed consent will be obtained from participants in phases 1b and 2; a waiver of consent for secondary use of data in phase 3 will be sought prior to commencement of phase 3.

The results of this study will be submitted for publication in scientific journals and for presentation at scientific meetings.

Beyond phase 3, future investigation will focus on development of a surgical decision-making tool which produces a patient-specific recommendation for or against PE, in a reproducible fashion. This recommendation will be based on the predicted priority outcomes for an individual patient according to the risk prediction model developed in the current study. This will involve using consensus methods among experts to

define the threshold values for the predicted priority outcomes at which a recommendation for or against surgery is made.

Study status and planned timeline

Phase 1a: January 2023–September 2023 (manuscript under peer review).

Phase 1b: May 2023–November 2023 (data collection underway).

Phase 2: December 2023–April 2024 (not commenced).

Phase 3: May 2024–December 2024 (not commenced).

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Patient consent for publication Not applicable.

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MEDLINE SEARCH STRATEGY

1. Pelvic Exenteration/
2. (pelvi* and exent*).mp.
3. pelvic clearance.mp.
4. extended resection*.mp.
5. extended radical resection*.mp.
6. (salvage adj2 (surger* or resect* or excis*)).mp.
7. ((multi?visceral or multi?organ) adj2 (surger* or resect* or excis*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Rectal Neoplasms/
10. ((rectal or rectum) adj2 (neoplas* or cancer* or tumour* or tumor* or malignan* or carcinom* or adenocarcinoma* or recurren* or regrowth or mass)).mp.
11. 9 or 10
12. 8 and 11
13. limit 12 to (english language and yr="1990 -Current")

EMBASE SEARCH STRATEGY

1. pelvis exenteration/
2. (pelvi* and exent*).mp.
3. pelvic clearance.mp.
4. extended resection*.mp.
5. extended radical resection*.mp.
6. (salvage adj2 (surger* or resect* or excis*)).mp.
7. ((multi?visceral or multi?organ) adj2 (surger* or resect* or excis*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
9. rectum tumor/
10. exp rectum cancer/
11. rectum carcinoma/
12. ((rectal or rectum) adj2 (neoplas* or cancer* or tumour* or tumor* or malignan* or carcinom* or adenocarcinoma* or recurren* or regrowth or mass)).mp.
13. 9 or 10 or 11 or 12
14. 8 and 13
15. limit 14 to (english language and yr="1990 -Current")

COCHRANE CENTRAL REGISTER OF CONTROLLED TRIALS SEARCH STRATEGY

1. Pelvic Exenteration/
2. (pelvi* and exent*).mp.
3. pelvic clearance.mp.
4. extended resection*.mp.
5. extended radical resection*.mp.
6. (salvage adj2 (surger* or resect* or excis*)).mp.
7. ((multi?visceral or multi?organ) adj2 (surger* or resect* or excis*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Rectal Neoplasms/
10. ((rectal or rectum) adj2 (neoplas* or cancer* or tumour* or tumor* or malignan* or carcinom* or adenocarcinoma* or recurren* or regrowth or mass)).mp.
11. 9 or 10
12. 8 and 11
13. limit 12 to (english language and yr="1990 -Current")

CINAHL SEARCH STRATEGY

S1. (MH "Pelvic Exenteration")

S2. "pelvic exenteration*"

S3. (pelvi* and exent*)

S4. "pelvic clearance"

S5. "extended resection*"

S6. "extended radical resection*"

S7. (Salvage N2 (surger* or resect* or excis*))

S8. ((multi\$visceral or multi\$organ) N2 (surger* or resect* or excis*))

S9. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8

S10. (MH "Rectal Neoplasms+")

S11. ((rectal or rectum) N2 (neoplas* or cancer* or tumour* or tumor* or malignan* or carcinom* or adenocarcinoma* or recurren* or regrowth or mass))

S12. S10 OR S11

S13. S9 AND S12

S14. S9 AND S12 **Limiters** - Published Date: 19900101-20221231

S15. S9 AND S12 **Narrow by Language:** - english

SCOPUS SEARCH STRATEGY

(TITLE-ABS-KEY ((pelvi* AND exent*) OR "pelvic clearance" OR "extended* resection*") OR TITLE-ABS-KEY (salvage W/2 (surger* OR resect* OR excis*)) OR TITLE-ABS-KEY (((multi?visceral OR multi?organ) W/2 (surger* OR resect* OR excis*))))

AND

TITLE-ABS-KEY (((rectal OR rectum) W/2 (neoplas* OR cancer* OR tumour* OR tumor* OR malignan* OR carcinom* OR adenocarcinoma* OR recurren* OR regrowth OR mass))))

AND

(LIMIT-TO (PUBYEAR , 1990 - 2022))

AND

(LIMIT-TO (LANGUAGE , "English"))

SEMI-STRUCTURED INTERVIEW TOPIC GUIDE (CARERS)

Topic Guide

Topic 1 - General experience

- Initial open-ended questions regarding their general experience caring for someone with locally advanced or recurrent rectal cancer pelvic exenteration surgery
- *'Could you tell me about your experience caring after someone with [locally advanced or recurrent] rectal cancer?'*
- *'Could you tell me what it has been like to care for someone requiring major cancer surgery?'*

Topic 2 - Diagnosis

- *'Could you tell me about how you first found out your loved one had [locally advanced or recurrent] rectal cancer?'*
- *'What were your first thoughts when you heard the words "rectal cancer"? Had you ever heard of it before?'*
- Enquire about what were they most interested to learn more about when their loved one was first diagnosed - which were the post-surgical outcomes they were most interested to know about?

Topic 3 - Treatment

- Enquire how they and their loved one decided whether to undergo pelvic exenteration surgery, how involved was the carer or spouse in the decision-making process?
- Ask which information they asked for and how it impacted their decision making
- Ask about the impact surgery has/had on their loved one and their relationship, specifically prompt for physical and psychological impacts. Were these consequences expected or unexpected?
- Ask what is the most significant way that surgery has affected the carer or spouse and their relationship with their loved one? Prompt for both positive and negative impacts of surgery
- If they had to help their loved one make the decision about undergoing surgery again, which would be the most important factors to be aware of and consider?
- Ask unambiguously which outcomes of pelvic exenteration surgery are the most important when deciding whether to have surgery, and how each outcome would influence this decision

Conclusion

- Final open ended question: *'Is there anything else that we haven't addressed that you think is important for patients with locally advanced or recurrent rectal cancer and their carers to be aware of or consider when deciding about whether to undergo surgery?'*

SEMI-STRUCTURED INTERVIEW TOPIC GUIDE (PATIENTS)

Topic Guide

Topic 1 - General experience

- Initial open-ended questions regarding their general experience having locally advanced or recurrent rectal cancer and pelvic exenteration surgery
- *'Could you tell me about your diagnosis and treatment journey with [locally advanced or recurrent] rectal cancer?'*
- *'Could you tell me about the surgery you underwent to treat your tumour?'*

Topic 2 - Diagnosis

- *'How did you first come to be diagnosed with [locally advanced or recurrent] rectal cancer?'*
- Enquire about what were they most interested to learn more about when first diagnosed - which were the post-surgical outcomes they were most interested to know about?

Topic 3 - Treatment

- Enquire how they decided whether to undergo pelvic exenteration surgery and any other treatment options
- Ask which information they asked for and how it impacted their decision making
- Ask about the impact surgery has/had on the participant, specifically ask about physical and psychological impacts. Were these consequences expected or unexpected?
- Ask what is the most significant way that surgery has affected the patient? Prompt for both positive and negative impacts of surgery
- If they had to make the decision about undergoing surgery again, which would be the most important factors to be aware of and consider?
- Ask unambiguously which outcomes of pelvic exenteration surgery are the most important when deciding whether to have surgery, and how each outcome would influence this decision

Conclusion

- Final open ended question: *'Is there anything else that we haven't addressed that you think is important for patients with locally advanced or recurrent rectal cancer to be aware of or consider when deciding about whether to undergo surgery?'*

CHAPTER 4: IDENTIFYING THE OUTCOMES OF EXENTERATION CONSIDERED IMPORTANT BY CLINICIANS

CHAPTER OVERVIEW

Chapter 4 addresses *Thesis Aim 1*: to address unwarranted variation in treatment decision-making in patients with LARC and LRRC. *Chapter 4.1* presents the results of a comprehensive systematic review of pelvic exenteration literature, where all outcomes of exenteration reported in all studies published after 1990 were manually extracted, collated, and categorised. *Chapter 4.2* provides further information specifically relating to resection margin status reporting in this current literature. The studies within this chapter are the first to rigorously assess the quality of outcome reporting in pelvic exenteration surgery. Collectively, this chapter serves to identify all outcomes reported in current exenteration literature, which were then catalogued and carried forward as candidate priority outcomes, and included in the Delphi study presented in *Chapter 6*. The findings also highlight the variation in outcome reporting and lack of standardised definitions in current literature.

CHAPTER 4.1

Variation in outcome measurement and reporting in studies of pelvic exenteration for locally advanced and recurrent rectal cancer: a systematic review

Chapter 4.1 is published as:

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SYSTEMATIC REVIEW

Variation in outcome measurement and reporting in studies of pelvic exenteration for locally advanced and recurrent rectal cancer: a systematic review

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Abstract

Aim: There is increasing research interest in pelvic exenteration for locally advanced and recurrent rectal cancer. Heterogeneity in outcome reporting can prevent meaningful interpretation and valid synthesis of pooled data and meta-analyses. The aim of this study was to assess homogeneity in outcome measures in the current pelvic exenteration literature.

Method: MEDLINE, Embase, CENTRAL, CINAHL and Scopus databases were searched from 1990 to 25 April 2023 to identify studies reporting outcomes of pelvic exenteration for locally advanced or recurrent rectal cancer. All reported outcomes were extracted, merged with those of similar meaning and assigned a domain.

Results: Of 4137 abstracts screened, 156 studies met the inclusion criteria. A total of 2765 outcomes were reported, of which 17% were accompanied by a definition. There were 1157 unique outcomes, merged into 84 standardized outcomes and assigned one of seven domains. The most reported domains were complications (147 studies, 94%), survival (127, 81%) and surgical outcomes (123, 79%). Resection margins were reported in 122 studies (78%): the definition of a clear resection margin was not provided in 45 studies (37%), it was unclear in 11 studies (9%) and not specified beyond microscopically 'clear' or 'negative' in 31 (28%). Measurements of 2, 1, 0.5 mm and any healthy tissue were all used to define R0 margins.

Conclusion: There is significant heterogeneity in outcome measurement and reporting in the current pelvic exenteration literature, raising concerns about the validity of comparative or collaborative studies between centres and meta-analyses. Coordinated international collaboration is required to define core outcome sets and benchmarks.

KEYWORDS

pelvic exenteration, recurrent rectal cancer, surgical outcomes

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INTRODUCTION

With the improved long-term survival and quality of life outcomes after exenterative surgery for locally advanced and recurrent rectal cancer now well documented, there is increasing clinical and academic interest in this ultra-radical surgery [1–3]. The increasing number of centres with experience in pelvic exenteration has facilitated international collaborative studies [4–6] and meta-analyses [7, 8] that aim to provide adequate volumes of data to answer questions about a procedure that remains relatively uncommon even at specialist referral units. Heterogeneity in outcome reporting can prevent meaningful synthesis of pooled data and valid comparison of outcomes between centres and across time periods. This is particularly important when the results of such analyses are used to define benchmark standards [9, 10] or safety parameters for newly established centres or when adopting new (e.g. minimally invasive) approaches [11].

Anecdotally, there is significant variation concerning which outcomes are reported and how they are defined in the pelvic exenteration literature. Furthermore, whether currently reported outcomes are consistent with those supported by and considered most important to patients and their carers is unknown. This systematic review was conducted to assess whether there is heterogeneity in outcome measurement and reporting in studies of pelvic exenteration or multivisceral resection for locally advanced and recurrent rectal cancer. The findings of this study will inform a future Delphi study to define the outcomes of pelvic exenteration that are considered the highest priority for patients, carers and clinicians when making treatment decisions.

METHOD

The protocol for this systematic review was developed in accordance with the Cochrane Handbook for Systematic Reviews of Interventions and registered a priori on the International Prospective Register of Systematic Reviews (PROSPERO registration CRD42022351909) [12]. The systematic review is reported according to PRISMA guidelines [13].

Search strategy

The search strategy was developed in close consultation with a medical librarian. The following medical subject headings (MeSH) and keywords were combined: pelvic exenteration or extended radical resection or multivisceral resection, and rectal neoplasms. MEDLINE, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), Cumulative Index to Nursing and Allied Health Literature (CINAHL) and Scopus were searched from 1990 to 25 April 2023. The search was limited to studies published from 1990 onward to include only current exenterative literature and avoid historical reports which often do not reflect modern practice or

What does this paper add to the literature?

There is increasing clinical and research interest in pelvic exenteration for locally advanced and recurrent rectal cancer. This study demonstrates that there is significant heterogeneity in outcome measurement and reporting in the current pelvic exenteration literature, raising concerns about the validity of comparative or collaborative studies between centres and meta-analyses.

outcomes. English language and adult patient limits were applied to the search. The complete search strategies are detailed in [Figure S1](#).

Eligibility criteria

Retrospective and prospective cohort studies, cross-sectional studies, qualitative studies and randomized trials reporting outcomes of pelvic exenteration or multivisceral resection as the primary treatment for locally advanced or recurrent adenocarcinoma of the rectum were included. Studies that included adjuvant treatment modalities in addition to pelvic exenteration or multivisceral resection (such as radiotherapy, immunotherapy and chemotherapy) were included, and where a single institution published multiple studies with accumulating patient cohorts, all studies were included in order to ensure all reported outcomes were identified. The following exclusion criteria were applied: >10% of the study population had nonrectal cancers or underwent less extensive resection (i.e. proctectomy only) and outcomes were not reported separately, narrative reviews, case reports, case series including fewer than five patients, conference abstracts and letters.

As previously described by Fish et al. [14], outcomes identified in qualitative studies and those listed as objectives in systematic reviews were included in the list of potential priority outcomes for inclusion in the subsequent Delphi study, but were excluded from the descriptive analysis presented in the current study.

Data extraction

Systematic review management software (Covidence, Melbourne, Australia) was used during screening and full text assessment. Two reviewers (KB, JP) independently screened all abstracts according to the eligibility criteria and disagreements were resolved by discussion with a third, senior reviewer (DS). One reviewer (KB) completed the full text screening and data extraction, with all extracted outcomes then reviewed by a multidisciplinary team (see details below). Data were extracted and entered into an electronic Microsoft Access database using a custom-designed data entry form. Study title, year, design, sample size and included tumour type (primary or recurrent rectal cancer) were collected. Studies which extracted and analysed

data from a prospective database were categorized as prospective studies. In studies which included nonrectal cancers and/or single organ resection, the recorded sample size included only rectal cancer patients undergoing multivisceral resections. Verbatim outcomes and their definitions were extracted from the study manuscript. An outcome was defined if there was an accompanying description of how the outcome was measured or recorded, or if a citation for a tool or grading system was provided. Individual items of patient-reported outcome tools that were reported were extracted as outcomes, as were aggregate and composite scores. Only histopathological characteristics which were potentially altered by the surgery or neoadjuvant treatment (such as tumour regression or margin status) were considered outcomes, while others (i.e. depth of invasion, nodal status, tumour size, etc.) were not.

Cataloguing of outcomes

Outcomes were catalogued according to methods previously described by Fish and colleagues [14]. Initially a single reviewer (KB) reviewed each verbatim outcome, which were merged with other outcomes capturing the same or similar concepts but with different wording to create 'standardized outcomes'. For example, time to bowel movement, time to flatus and time to normal diet were merged as a standardized outcome called 'return of bowel function'. Each standardized outcome was reviewed at a multidisciplinary advisory meeting, attended by specialist surgeons, an experienced surgical outcomes researcher, a pelvic exenteration nurse specialist and two patient advocates. At the meeting, all verbatim and standardized

outcomes were reviewed and ratified, and disagreement was resolved by discussion. Standardized outcomes were allocated to one of seven domains: surgical outcomes, pathological outcomes, cancer recurrence, survival, patient-reported outcomes and function, complications, other. These domains were based on those proposed by the Core Outcome Measures in Effectiveness Trials Initiative but modified for applicability to pelvic exenteration patients for the purposes of this study [15].

RESULTS

The search identified 4137 records. After removing duplicates and applying the eligibility criteria after abstract and full text review (Figure 1), there were 166 studies which met the inclusion criteria (Table 1). Of these studies, 111 (67%) were published after 2009, 92 (55%) were retrospective observational studies and most originated from Europe and Central Asia, East Asia or North America. Details and references for each included study are provided in Table S1. Outcomes from nine systematic reviews and one qualitative study were extracted for use in the subsequent Delphi study but were not included in the analysis presented here. The remaining 156 studies included 23 931 patients (median 53, range 5–2472), although this number may include the same patients multiple times given that studies from the same centre with accumulating cohorts were included.

A total of 2765 outcomes were extracted verbatim from the included studies, of which 1157 were unique. The median number of outcomes reported per study was 17 (range 1–54) and a definition

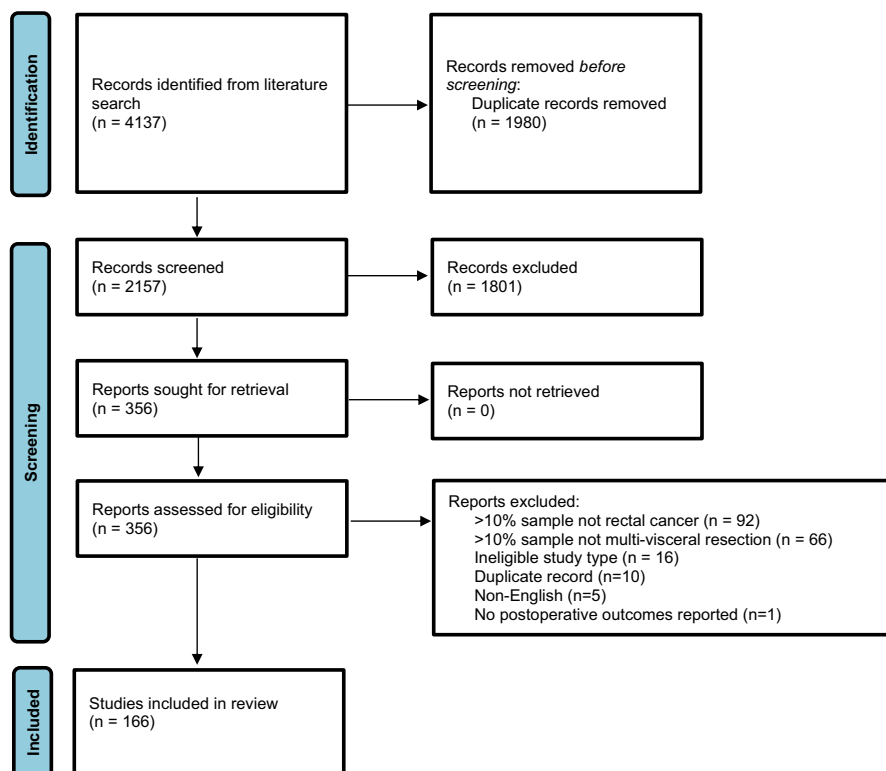


FIGURE 1 Preferred Reporting Items for Systematic Reviews (PRISMA) diagram summarizing the search and study selection process.

TABLE 1 Characteristics of included studies (N=166).

Characteristic	N (%)
Publication year	
1990–1999	20 (12)
2000–2009	35 (21)
2010–2019	67 (40)
2020–2023	44 (27)
Region	
Europe and Central Asia	52 (31)
East Asia	34 (20)
North America	31 (19)
Australasia and Pacific	21 (13)
South Asia	12 (7)
International multicentre	11 (7)
Latin America	4 (2)
Africa	1 (1)
Study design	
Retrospective observational	92 (55)
Prospective observational	56 (34)
Administrative database/registry	7 (4)
Systematic review	9 (5)
Qualitative study	1 (1)
Cross-sectional study	1 (1)
Tumour type	
Locally advanced rectal cancer	64 (39)
Locally recurrent rectal cancer	37 (22)
Both	65 (39)

was provided for 17% of outcomes. Outcomes reported in studies published before the year 2000 were less likely to be accompanied by a definition (5% vs. 19%, $p < 0.001$, chi-square test), as were studies which included fewer than 100 patients (14% vs. 23%, $p < 0.001$). The unique outcomes terms were merged into 84 standardized outcomes and allocated to one of seven domains: surgical outcomes, pathological outcomes, cancer recurrence, survival, patient-reported and functional outcomes, complications, other (Table 2). The most reported domains were complications (147 studies, 94%), survival (127, 81%) and surgical outcomes (123, 79%). Patient-reported or functional outcomes were reported in 40 studies (26%). All 84 standardized outcomes, their frequency of reporting and proportion that were defined are included in Table 3.

Surgical and pathological outcomes

The most reported surgical/perioperative outcomes were length of hospital stay (99 studies, 63%), for which there were 18 unique terms, and operative time (81 studies, 52%), for which there were 21 unique terms. Three unique terms relating to nutritional status were reported in two studies (subjective global assessment, body

mass index, hand grip strength), all of which were defined. Discharge destination was only reported in two studies.

Resection margin (status or distance) was the most reported pathological outcome, reported in 122 studies (78%). In these studies, the definition of what constituted a clear resection margin was not defined (45 studies, 37%), was unclear from the provided definition (11, 9%) or was not further specified beyond microscopically 'clear' or 'negative' (31, 28%). Where a reproducible distance was provided as a definition, there was significant variation between studies and included 2, 1 and 0.5 mm and any healthy intervening tissue between the tumour and the margin (Table 4).

Cancer recurrence and survival

Cancer recurrence was reported in 97 studies (62%) as one or more of the following standardized outcomes: local recurrence (reported in 56% of studies), distant recurrence (40%) or overall disease recurrence (27%). Local recurrence comprised 24 unique terms (including local relapse, local control, local failure, local pelvic re-recurrence, loco-regional recurrence, pelvic recurrence and regional recurrence) and only 18% of outcomes were defined. In the survival domain, the most reported outcome was overall survival (118 studies, 76%). Disease-free and disease-specific survival were reported in 40% and 21% of studies, respectively.

Patient-reported and functional outcomes

Patient-reported and functional outcomes were reported in 26% of studies. The most reported outcome in this domain was urinary function (17 studies, 11%) and psychological and emotional functioning (14, 9%). There were low rates of reporting of physical functioning (8%), sexual function (5%), mobility (4%) and social functioning (6%). Patient-reported stoma-related problems were only individually reported in one study (although they were included in aggregate/composite instrument scores in others). Use of a tool or instrument was reported for 52% of outcomes in this domain, those most commonly used being the FACT-C and SF-36 (Figure 2).

Complications

The most reported outcomes relating to complications of surgery were perioperative mortality (108 studies, 69%) and total/overall postoperative complications (106, 68%). Radiological and surgical reintervention were reported in 28% and 4%, respectively. Complication severity was reported in 44% of studies, and 62% of these outcomes were accompanied by a definition, most commonly Clavien–Dindo. Regarding specific systems, gastrointestinal (65%), urinary (48%) and wound-related complications (37%) were the most commonly reported. Ileus and intestinal obstruction were both reported in 24% of studies, and urinary leaks were reported in

TABLE 2 Number of studies and outcomes according to allocated domain (N=156 studies).

Outcome domain	Studies, n (%)	Verbatim outcomes	Unique outcomes	Standardized outcomes
Surgical	123 (79)	351	111	11
Pathological	122 (78)	187	90	3
Cancer recurrence	97 (62)	230	84	3
Survival	127 (81)	329	95	9
Patient-reported outcomes and functioning	40 (26)	196	138	17
Complications				
Overall/nonspecific	146 (94)	504	190	11
Infection	108 (69)	255	82	1
Gastrointestinal	101 (65)	214	80	5
Urinary	75 (48)	146	96	3
Wound	58 (37)	89	58	8
Respiratory	45 (29)	58	19	1
Cardiac	33 (21)	41	17	1
Miscellaneous	33 (21)	38	26	2
Vascular	29 (19)	44	16	3
Renal/metabolic	23 (15)	25	13	1
Neurological	23 (15)	29	19	2
Ostomy	20 (13)	27	19	1
Other	2 (1)	2	2	2
Total	156	2765	1157	84

37%. Ostomy-related complications were reported in 13% and those relating to the empty pelvis syndrome were reported in 13%.

None of the included studies reported outcomes relating to treatment cost.

DISCUSSION

The results of this systematic review demonstrate that the number of studies reporting outcomes of pelvic exenteration or multivisceral resection for patients with locally advanced or recurrent rectal cancer is increasing, with 67% reported in or after 2010, yet there is significant heterogeneity in the outcome measurement and reporting in the current literature. For example, resection margins are the most important predictor of long-term survival and quality of life after pelvic exenteration for locally recurrent rectal cancer and are widely considered the 'holy grail' of these procedures. Although resection margin status was found to be commonly reported (in 78% of publications), there was no definition provided in 37% of these studies. Where a definition was provided, it was either unclear or poorly defined beyond 'microscopically clear' in most studies. Furthermore, 2, 1, 0.5 mm and 'any intervening healthy tissue' have all been used to define a clear margin in various studies (Table 4). Similarly, there were 18 unique terms used to describe local recurrence and only 18% of outcomes were accompanied by a definition. These issues raise concerns about the validity of comparative or collaborative studies between centres as well as meta-analyses.

Pelvic exenteration has only relatively recently evolved from a poorly accepted palliative treatment for gynaecological malignancy into an accepted treatment for locally advanced and recurrent rectal cancer, and it is only in the last decade that it has become established as the standard of care [16]. It is therefore anticipated that most studies published to date have been retrospective reports focused on perioperative safety and demonstrating survival benefit, and it is also not surprising that there is significant variation in outcome definitions for what is an inherently heterogeneous procedure. However, as interest in exenterative pelvic surgery increases and new centres are established, consistent outcome definitions are essential to ensure meaningful synthesis of data to guide future refinement of surgical technique, (neo)adjuvant treatments and service configuration. This is particularly important if the results of pooled collaborative data are to be used to define surgical performance benchmarks for these procedures [9, 11]. Furthermore, whether the outcomes of interest to patients and their carers are being adequately addressed in the literature is unclear, and it is worth noting that patient-reported or functional outcomes were only included in 26% of studies and there were no reported outcomes relating to economic cost of treatment or health service utilization.

Fortunately, solutions to the above issues are under way. The PelvEx collaborative will continue to play an important role in coordinating collaboration between pelvic exenteration centres globally and facilitating consensus processes around outcome reporting. Recently, the United Kingdom Pelvic Exenteration Network developed a consensus lexicon to classify the operative components of

TABLE 3 Standardized outcomes categorized according to domain.

Outcome domain	Standardized outcome term	No. of studies reporting	Frequency of definition	Unique outcomes
Surgical outcomes	Length of hospital stay	99 (63)	5%	18
	Operative time	81 (52)	2%	21
	Blood loss	70 (45)	1%	11
	Blood transfusion	31 (20)	6%	18
	Length of ICU stay	16 (10)	0%	12
	Return of bowel function	9 (6)	0%	15
	Conversion to open surgery	8 (5)	25%	4
	Discharge destination	3 (2)	0%	3
	Permanent stoma rate	3 (2)	0%	3
	Analgesia use	2 (1)	0%	3
	Nutritional status	2 (1)	100%	3
Pathological	Resection margins	122 (78)	58%	64
	Pathological tumour response	18 (12)	41%	12
	Lymph node yield	16 (10)	0%	12
	Quality of mesorectum	2 (1)	0%	2
Cancer recurrence	Local recurrence	87 (56)	18%	24
	Distant recurrence	63 (40)	5%	31
	Disease recurrence	42 (27)	4%	29
Survival	Overall survival	118 (76)	29%	17
	Disease-free survival	63 (40)	26%	21
	Disease-specific survival	33 (21)	24%	34
	Survival with disease	15 (10)	1%	11
	Local recurrence-free survival	14 (9)	42%	6
	Metastases-free survival	2 (1)	0%	2
	Complication-free survival	1 (1)	0%	1
	Hernia-free survival	1 (1)	0%	1
	Progression-free survival	1 (1)	0%	2
	Patient-reported outcomes and functioning	Urinary function	17 (11)	4%
Psychological and emotional functioning		14 (9)	61%	18
Physical functioning		12 (8)	87%	5
Pain		10 (6)	40%	12
Colorectal-specific QOL		9 (6)	82%	5
Global QOL		8 (5)	100%	9
Sexual function		8 (5)	41%	15
Long-term bowel function		7 (4)	44%	13
Mobility		6 (4)	0%	9
Social functioning		6 (4)	89%	4
Role function		5 (3)	63%	6
Energy/vitality		4 (3)	50%	5
Lower limb function		4 (3)	0%	12
Sleep		3 (2)	67%	2
Appetite and weight		2 (1)	100%	2
Prostate-specific QOL		1 (1)	100%	2
Stoma-related problems	1 (1)	100%	1	

(Continues)

TABLE 3 (Continued)

Outcome domain	Standardized outcome term	No. of studies reporting	Frequency of definition	Unique outcomes
Complications				
General	Perioperative mortality	108 (69)	16%	33
	Postoperative complications	106 (68)	25%	37
	Complication severity	69 (44)	62%	43
	Surgical reintervention	43 (28)	0%	31
	Haemorrhage	36 (23)	0%	19
	Hospital readmission	22 (14)	4%	8
	Late or long-term complications	11 (7)	55%	6
	Radiological reintervention	7 (4)	0%	5
	Unplanned ICU admission	6 (4)	0%	3
	Cause of postoperative mortality	5 (3)	0%	2
	Intraoperative complication rate	4 (3)	0%	3
Wound	Perineal wound dehiscence	14 (9)	0%	8
	Perineal flap loss or dehiscence	13 (8)	0%	14
	Abdominal wall hernia	7 (4)	0%	5
	Perineal hernia	4 (3)	0%	1
	Abdominal wound dehiscence	3 (2)	0%	3
	Wound dehiscence, nonspecified	18 (12)	0%	10
	Nonspecific abdominal wound complication	15 (10)	0%	9
	Nonspecific perineal wound complication	8 (5)	20%	8
Gastrointestinal	Anastomotic leak, gastrointestinal	51 (33)	16%	26
	Ileus	38 (24)	11%	6
	Intestinal obstruction	38 (24)	0%	10
	Gastrointestinal injury/perforation	10 (6)	0%	8
	Other gastrointestinal complications	51 (33)	0%	30
Urinary	Anastomotic leak, urinary	57 (37)	4%	47
	Ureteric stricture	15 (10)	0%	13
	Other urological complications	43 (28)	8%	36
Vascular	Venous thromboembolism	26 (17)	0%	9
	Limb ischaemia	6 (4)	0%	5
	Other vascular/haematological complications	3 (2)	0%	2
Neurological	Nerve injury	5 (3)	0%	6
	Other neurological complications	18 (12)	0%	13
Infection	Infection-related complication	108 (69)	2%	82
Respiratory	Respiratory complications	45 (29)	7%	19
Cardiac	Cardiac complications	33 (21)	0%	17
Renal/metabolic	Renal complications	23 (15)	0%	13
Ostomy	Ostomy complications	20 (13)	0%	19
Miscellaneous	Miscellaneous complications	26 (17)	7%	18
	Empty pelvis syndrome	7 (4)	45%	8
Other	Relief of tumour related symptoms	1 (1)	0%	1
	Symptoms of recurrent disease	1 (1)	0%	1

Abbreviations: ICU, intensive care unit; QOL, Quality of life.

extended pelvic resections and pelvic exenteration, implementation of which will facilitate more meaningful data synthesis [17]. The authors of the current study are coordinating an international study including highly experienced pelvic exenteration centres from Europe, the United Kingdom, Australia and New Zealand, Asia, North America and South America, which aims to define benchmark outcomes for pelvic exenteration using rigorous definitions and established benchmarking methodology [18]. Collectively, these efforts should improve the standard of outcome measurement and reporting and the quality of data in the pelvic exenteration literature.

One of the potential limitations of this systematic review is use of broad inclusion criteria whereby studies of any multivisceral pelvic resection (i.e. *en bloc* resection of any adjacent organ in addition to the rectum) were included. Therefore, some outcomes which only apply to patients undergoing less extensive resections were included, such as urinary function in those with bladder-sparing procedures. This was intentional to ensure that all outcomes reported in the current literature for any extended radical and exenterative pelvic resection were identified to inform a planned Delphi study, which aims to achieve consensus around the outcomes of highest priority to patients, carers and clinicians after pelvic exenteration. Another potential limitation is the criteria used to determine whether an outcome was recorded as defined or undefined. Some outcomes (such

as intraoperative blood loss or length of hospital stay) might be considered to convey an implied definition; however, these outcomes were considered undefined unless a description of the outcome or how it was measured was provided. This method is likely to have contributed to the low proportion of outcomes which were considered to have been defined.

The results of this study highlight the variation in outcome reporting and definitions in current pelvic exenteration literature for patients with locally advanced or recurrent rectal cancer. Resection margins are widely considered the 'holy grail' of pelvic exenteration surgery but were only defined in 37% of studies, and the majority of these definitions were unclear or poorly defined. Potential solutions to these issues include coordinated international collaboration to rigorously define core outcome sets and surgical performance standards (benchmarks). The results of this study will also inform future development of a list of 'priority outcomes' which is supported by patients, carers and clinicians.

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CONFLICT OF INTEREST STATEMENT

None declared.

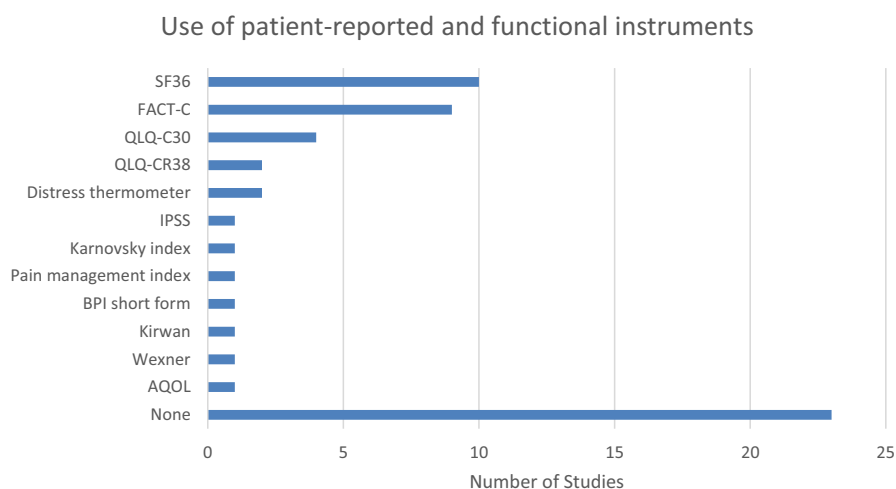
DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

TABLE 4 Definitions provided in studies which reported resection margins (N=122).

Definition	No. of studies (%)
2 mm from tumour	2 (2)
1 mm from tumour	29 (24)
0.5 mm from tumour	1 (1)
>0mm from tumour/any intervening healthy tissue	3 (2)
Clear or negative, but not otherwise specified	31 (28)
Unclear from provided definition	11 (9)
No definition provided	45 (37)

FIGURE 2 Patient-reported and functional outcome tools or instruments used in studies reporting outcomes in this domain (N=40). AQOL, Assessment of Quality of Life; BPI, Brief Pain Inventory; FACT-C, Functional Assessment of Cancer Therapy-Colorectal; IPSS, International Prostate Symptom Score; QLQ-C30, Quality of Life Questionnaire Core 30; Quality of Life Questionnaire, Colorectal Cancer Module; SF36, 36-Item Short Form Survey.



ETHICS STATEMENT

Ethical approval was not sought for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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The following tables and figures are included as supplementary information to Chapter 4.1.

Supplementary table 1. Details of individual included studies.

First Author	Year Published	Country	Sample Size	Tumours	Design
Steffens(1)	2023	Australia	981	Mixed	Prospective cohort
Palma(2)	2023	Australia	329	Mixed	Prospective cohort
Kazi(3)	2023	India	285	Mixed	Prospective cohort
Tang(4)	2023	China	144	LARC	Retrospective cohort
Huang(5)	2022	Australia	271	Mixed	Prospective cohort
Aiba(6)	2022	Japan	73	Mixed	Retrospective cohort
Das(7)	2022	India	12	LARC	Retrospective cohort
Pandit(8)	2022	Nepal	7	LARC	Retrospective cohort
de Nes(9)	2022	Netherlands	406	LARC	Admin data/registry
Jaganmurugan(10)	2022	India	5	LARC	Retrospective cohort
Kazi(11)	2022	India	171	Mixed	Retrospective cohort
Komori(12)	2022	Japan	20	Mixed	Retrospective cohort
Kazi(13)	2022	India	124	LARC	Prospective cohort
Gould(14)	2022	United Kingdom	2864	Mixed	Systematic review
Fahy(15)	2022	Ireland	3188	LARC	Systematic review
Denys(16)	2022	Australia	878	Mixed	Systematic review
Kazi(17)	2021	India	158	LARC	Retrospective cohort
Khan(18)	2021	United Kingdom	104	Mixed	Retrospective cohort
van Rees(19)	2021	Netherlands	227	Mixed	Retrospective cohort
Alahmadi(20)	2021	Australia	710	Mixed	Prospective cohort
Kumar(21)	2021	India	100	LARC	Prospective cohort
de Nes(22)	2021	Netherlands	936	LARC	Admin data/registry
Kazi(23)	2021	India	100	Mixed	Prospective cohort

Larach(24)	2021	Australia	11	LARC	Prospective cohort
Piozzi(25)	2021	South Korea	137	LARC	Prospective cohort
Tashiro(26)	2021	Japan	11	LARC	Retrospective cohort
Nonaka(27)	2021	Japan	6	Mixed	Retrospective cohort
Dijkstra(28)	2021	Netherlands	61	LRRC	Retrospective cohort
Culcu(29)	2021	Turkey	17	LRRC	Retrospective cohort
Konstantinidis(30)	2020	United States	1367	LARC	Admin data/registry
Tuech(31)	2020	France	16	Mixed	Prospective cohort
Zhang(32)	2020	China	6	LARC	Retrospective cohort
Denost(33)	2020	International multi-centre	154	Mixed	Prospective cohort
Smith(34)	2020	Australia	8	LARC	Retrospective cohort
Oke(35)	2020	South Africa	43	Mixed	Retrospective cohort
Hagemans(36)	2020	Netherlands	259	Mixed	Prospective cohort
Kong(37)	2020	Australia	452	Mixed	Prospective cohort
Belli(38)	2020	Italy	152	LRRC	Prospective cohort
Ahmadi(39)	2020	Australia	71	Mixed	Retrospective cohort
Pokharkar(40)	2020	India	7	LARC	Prospective cohort
Koh(41)	2020	Australia	210	LRRC	Prospective cohort
Kelly(42)	2020	International multi-centre	128	LARC	Retrospective cohort
PelvEx Collaborative(43)	2020	International multi-centre	1147	Mixed	Retrospective cohort
Commins(44)	2020	Australia	8	LARC	Retrospective cohort
PelvEx Collaborative(45)	2019	International multi-centre	2472	Mixed	Retrospective cohort
Liccardo(46)	2019	United Kingdom	220	Mixed	Retrospective cohort
PelvEx Collaborative(47)	2019	International multi-centre	1291	LARC	Retrospective cohort
Dimitrijevic(48)	2019	Serbia	106	LARC	Prospective cohort
Steffens(49)	2018	Australia	319	Mixed	Prospective cohort
Pellino(50)	2018	Spain	82	LARC	Admin data/registry

Mehta(51)	2018	United Kingdom	10	Mixed	Retrospective cohort
Hagemans(52)	2018	Netherlands	126	Mixed	Prospective cohort
Verma(53)	2018	India	61	LARC	Prospective cohort
Crolla(54)	2018	Netherlands	28	LARC	Prospective cohort
Pokharkar(55)	2018	International multi-centre	10	LARC	Prospective cohort
Mariathasan(56)	2018	Norway	224	LARC	Prospective cohort
Thiptanakit(57)	2018	Thailand	53	Mixed	Retrospective cohort
Bird(58)	2018	Australia	98	LRRC	Prospective cohort
Garcia-Granero(59)	2018	Spain	56	Mixed	Retrospective cohort
Dinaux(60)	2018	United States	29	LARC	Retrospective cohort
PelvEx Collaborative(61)	2018	International multi-centre	1184	LRRC	Retrospective cohort
Platt(62)	2018	United Kingdom	1016	Mixed	Systematic review
Hino(63)	2017	Japan	31	LARC	Prospective cohort
Dosokey(64)	2017	United States	36	LARC	Retrospective cohort
Georgiou(65)	2017	United Kingdom	41	Mixed	Prospective cohort
Brown(66)	2017	Australia	62	LRRC	Retrospective cohort
Denost(67)	2017	International multi-centre	101	LARC	Prospective cohort
Choy(68)	2017	Australia	117	LRRC	Prospective cohort
Rausa(69)	2017	United Kingdom	382	Mixed	Systematic review
Sasikumar(70)	2017	United Kingdom	220	LRRC	Systematic review
Simillis(71)	2017	United Kingdom	1326	Mixed	Systematic review
Quyn(72)	2016	Australia	104	LARC	Prospective cohort
Shin(73)	2016	United States	36	LARC	Prospective cohort
Radwan(74)	2016	United Kingdom	120	LARC	Retrospective cohort
Harris(75)	2016	International multi-centre	533	LRRC	Prospective cohort
Radwan(76)	2016	United Kingdom	65	LARC	Prospective cohort

Espinosa-de-Los-Monteros(77)	2016	Mexico	10	LARC	Retrospective cohort
Pai(78)	2016	India	54	LARC	Prospective cohort
Radwan(79)	2015	United Kingdom	56	LARC	Prospective cohort
Moghadamyeghaneh(80)	2015	United States	303	LARC	Admin data/registry
Radwan(81)	2015	United Kingdom	174	LARC	Prospective cohort
Orsini(82)	2015	Netherlands	128	LARC	Cross-sectional study
Crawshaw(83)	2015	United States	61	Mixed	Prospective cohort
Ghouti(84)	2015	France	27	LRRC	Retrospective cohort
Uehara(85)	2015	Japan	35	LRRC	Prospective cohort
Kusters(86)	2015	International multi-centre	95	LARC	Retrospective cohort
Carballo(87)	2015	Spain	34	Mixed	Retrospective cohort
Manas(88)	2015	Spain	30	LARC	Retrospective cohort
Selvaggi(89)	2015	Italy	150	LRRC	Prospective cohort
Xin(90)	2014	Singapore	13	Mixed	Prospective cohort
Davidge(91)	2014	Canada	177	Mixed	Prospective cohort
Colibaseanu(92)	2014	United States	30	LRRC	Retrospective cohort
Bhangu(93)	2014	United Kingdom	100	Mixed	Prospective cohort
Beaton(94)	2014	Australia	31	Mixed	Retrospective cohort
Thaysen(95)	2014	Denmark	122	Mixed	Prospective cohort
Khaled(96)	2014	Canada	19	LRRC	Prospective cohort
Speicher(97)	2014	United States	226	LARC	Admin data/registry
Milne(98)	2013	Australia	49	LRRC	Prospective cohort
Beaton(99)	2013	Australia	88	Mixed	Prospective cohort
Colibaseanu(100)	2013	United States	47	LRRC	Retrospective cohort
Mohan(101)	2013	United Kingdom	1575	Mixed	Systematic review
Yang(102)	2013	Australia	1049	Mixed	Systematic review

Smith(103)	2012	United States	124	LARC	Retrospective cohort
Nielsen(104)	2012	Denmark	90	Mixed	Prospective cohort
Kang(105)	2012	South Korea	54	LARC	Prospective cohort
Hsu(106)	2011	Taiwan	23	Mixed	Retrospective cohort
Domes(107)	2011	Canada	28	Mixed	Retrospective cohort
Harris(108)	2011	United Kingdom	42	LARC	Prospective cohort
Chen(109)	2011	China	278	LARC	Retrospective cohort
Saito(110)	2010	Japan	20	LARC	Retrospective cohort
Austin(111)	2010	Australia	37	Mixed	Retrospective cohort
Lohsiriwat(112)	2008	Thailand	10	LARC	Prospective cohort
Heriot(113)	2008	International multi-centre	160	LRRC	Prospective cohort
Derici(114)	2008	Turkey	57	LARC	Retrospective cohort
Saito(115)	2007	Japan	11	Mixed	Retrospective cohort
Uehara(116)	2007	Japan	48	LRRC	Retrospective cohort
Szynglarewicz(117)	2007	Poland	21	LARC	Retrospective cohort
Gannon(118)	2007	United States	72	Mixed	Retrospective cohort
Vermaas(119)	2007	Netherlands	35	Mixed	Retrospective cohort
Akasu(120)	2007	Japan	44	LRRC	Retrospective cohort
Govindarajan(121)	2006	United States	1741	LARC	Admin data/registry
Melton(122)	2006	United States	29	LRRC	Retrospective cohort
Bannura(123)	2006	Chile	30	LARC	Retrospective cohort
Stocchi(124)	2006	United States	82	LRRC	Prospective cohort
Szynglarewicz(125)	2006	Poland	21	LARC	Retrospective cohort
Wright(126)	2006	Canada	10	Mixed	Qualitative study
Takeuchi(127)	2005	Japan	15	Mixed	Retrospective cohort
Moriya(128)	2004	Japan	57	LRRC	Retrospective cohort
Oledzki(129)	2004	Poland	19	LARC	Prospective cohort

Kakuda(130)	2003	United States	22	LRRC	Retrospective cohort
Gohl(131)	2003	Germany	113	LARC	Retrospective cohort
Ike(132)	2003	Japan	45	LRRC	Retrospective cohort
Saito(133)	2003	Japan	43	LRRC	Retrospective cohort
Ike(134)	2003	Japan	71	LARC	Retrospective cohort
Hahnloser(135)	2003	United States	304	LRRC	Retrospective cohort
Vitelli(136)	2003	Italy	26	Mixed	Retrospective cohort
Jimenez(137)	2003	United States	55	Mixed	Retrospective cohort
Wiig(138)	2003	Norway	6	Mixed	Prospective cohort
Esnaola(139)	2002	United States	29	LRRC	Prospective cohort
Yamada(140)	2002	Japan	64	Mixed	Retrospective cohort
Wiig(141)	2002	Norway	47	Mixed	Prospective cohort
Lehnert(142)	2002	Germany	62	LARC	Retrospective cohort
Sanfilippo(143)	2001	United States	45	LARC	Retrospective cohort
Yamamoto(144)	2001	Japan	5	Mixed	Retrospective cohort
Onodera(145)	2000	Japan	51	LRRC	Retrospective cohort
Law(146)	2000	Hong Kong	24	Mixed	Retrospective cohort
Sokmen(147)	1999	Turkey	20	LARC	Retrospective cohort
Russo(148)	1999	United States	47	Mixed	Retrospective cohort
Adachi(149)	1999	Japan	9	LRRC	Retrospective cohort
Zacherl(150)	1999	Austria	12	LRRC	Retrospective cohort
Verschueren(151)	1998	Netherlands	11	LARC	Retrospective cohort
Maetani(152)	1998	Japan	59	LRRC	Retrospective cohort
Saito(153)	1998	Japan	36	LRRC	Retrospective cohort
Meterissian(154)	1997	United States	40	Mixed	Retrospective cohort
Luna-Perez(155)	1996	Mexico	49	LARC	Retrospective cohort
Shirouzu(156)	1996	Japan	26	Mixed	Retrospective cohort

Luna-Perez(157)	1995	Mexico	18	LARC	Retrospective cohort
Yeh(158)	1995	United States	9	LRRC	Retrospective cohort
Liu(159)	1994	China	31	Mixed	Retrospective cohort
Wanebo(160)	1994	United States	53	LRRC	Retrospective cohort
Estes(161)	1993	United States	16	LRRC	Retrospective cohort
Yeung(162)	1993	United States	50	Mixed	Retrospective cohort
Wanebo(163)	1992	United States	47	Mixed	Retrospective cohort
Maetani(164)	1992	Japan	35	LRRC	Retrospective cohort
Hafner(165)	1992	United States	75	Mixed	Retrospective cohort
Buhre(166)	1991	Netherlands	20	LARC	Retrospective cohort

LARC - locally advanced rectal cancer; LRRC - locally recurrent rectal cancer

Supplementary Figure 1. Search strategy

Medline

1. Pelvic Exenteration/
2. (pelvi* and exent*).mp.
3. pelvic clearance.mp.
4. extended resection*.mp.
5. extended radical resection*.mp.
6. (salvage adj2 (surger* or resect* or excis*)).mp.
7. ((multi?visceral or multi?organ) adj2 (surger* or resect* or excis*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Rectal Neoplasms/
10. ((rectal or rectum) adj2 (neoplas* or cancer* or tumour* or tumor* or malignan* or carcinom* or adenocarcinoma* or recurren* or regrowth or mass)).mp.
11. 9 or 10
12. 8 and 11
13. limit 12 to (english language and yr="1990 -Current")

Embase

1. pelvis exenteration/
2. (pelvi* and exent*).mp.
3. pelvic clearance.mp.
4. extended resection*.mp.
5. extended radical resection*.mp.
6. (salvage adj2 (surger* or resect* or excis*)).mp.
7. ((multi?visceral or multi?organ) adj2 (surger* or resect* or excis*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
9. rectum tumor/
10. exp rectum cancer/
11. rectum carcinoma/
12. ((rectal or rectum) adj2 (neoplas* or cancer* or tumour* or tumor* or malignan* or carcinom* or adenocarcinoma* or recurren* or regrowth or mass)).mp.
13. 9 or 10 or 11 or 12
14. 8 and 13
15. limit 14 to (english language and yr="1990 -Current")

Cochrane central register of controlled trials

1. Pelvic Exenteration/
2. (pelvi* and exent*).mp.
3. pelvic clearance.mp.
4. extended resection*.mp.
5. extended radical resection*.mp.
6. (salvage adj2 (surger* or resect* or excis*)).mp.
7. ((multi?visceral or multi?organ) adj2 (surger* or resect* or excis*)).mp.
8. 1 or 2 or 3 or 4 or 5 or 6 or 7
9. Rectal Neoplasms/

10. ((rectal or rectum) adj2 (neoplas* or cancer* or tumour* or tumor* or malignan* or carcinom* or adenocarcinoma* or recurren* or regrowth or mass)).mp.
 11. 9 or 10
 12. 8 and 11
 13. limit 12 to (english language and yr="1990 -Current")

CINAHL

- S1. (MH "Pelvic Exenteration")
 S2. "pelvic exenteration*"
 S3. (pelvi* and exent*)
 S4. "pelvic clearance"
 S5. "extended resection*"
 S6. "extended radical resection*"
 S7. (Salvage N2 (surger* or resect* or excis*))
 S8. ((multi\$visceral or multi\$organ) N2 (surger* or resect* or excis*))
 S9. S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
 S10. (MH "Rectal Neoplasms+")
 S11. ((rectal or rectum) N2 (neoplas* or cancer* or tumour* or tumor* or malignan* or carcinom* or adenocarcinoma* or recurren* or regrowth or mass))
 S12. S10 OR S11
 S13. S9 AND S12
 S14. S9 AND S12 **Limiters** - Published Date: 19900101-20221231
 S15. S9 AND S12 **Narrow by Language:** - english

Scopus

(TITLE-ABS-KEY ((pelvi* AND exent*) OR "pelvic clearance" OR "extended* resection*") OR TITLE-ABS-KEY (salvage W/2 (surger* OR resect* OR excis*)) OR TITLE-ABS-KEY (((multi?visceral OR multi?organ) W/2 (surger* OR resect* OR excis*))))

AND

TITLE-ABS-KEY (((rectal OR rectum) W/2 (neoplas* OR cancer* OR tumour* OR tumor* OR malignan* OR carcinom* OR adenocarcinoma* OR recurren* OR regrowth OR mass))))

AND

(LIMIT-TO (PUBYEAR , 1990 - 2022))

AND

(LIMIT-TO (LANGUAGE , "English"))

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CHAPTER 4.2




The definition of clear resection margins in locally recurrent rectal cancer -

Time for consensus

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The definition of clear resection margins in locally recurrent rectal cancer—time for consensus

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The primary justification for the potential morbidity and functional consequences associated with pelvic exenteration surgery is the reasonable chance of cure. Today, it is widely accepted that a clear (R0) resection margin is the most important predictor of long-term survival in patients undergoing surgery for locally recurrent rectal cancer (LRRc), and also that it is associated with improved quality of life and morbidity^{1–3}. On this basis, achieving R0 resection has become the ultimate goal or ‘holy grail’ for exenteration surgeons, as well as an important audit metric to assess and compare surgical performance⁴. Specialized exenteration centres now routinely offer more extensive resections, such as complex bone (for example, high sacrectomy) and neurovascular resections, in order to achieve R0 resection.

Despite its accepted importance, the definition of R0 resection for LRRc and how it is recorded varies between centres. In a recent systematic review by the authors, 156 studies of pelvic exenteration for locally advanced primary or LRRc were identified between 1990 and 2023, in which resection margin status was reported in 122 studies (78%)⁵. In the majority of these studies resection margin status was undefined or poorly defined (71%). When a definition was provided, there was substantial variation in the distance (between the tumour and inked margin) used to differentiate R0 and R1 resection. Further analysis from the same review is provided in [Table 1](#), which summarizes the definition of R0 resection described in the 73 studies which included patients with LRRc. Similar findings are demonstrated, with cut-off distances of >0 mm, 0.5 mm and 1 mm used to define R0 in different studies. Similar issues with variation in margin status definitions for primary colorectal cancer have recently been highlighted in an international survey of multi-disciplinary team members, where more than one-third of respondents used a definition for R1 margin other than cancer cells within 1 mm⁶. Such variation questions the ability to reliably compare data between centres⁷ and to pool data in collaborative studies^{1,8} and meta-analyses^{9,10}.

The most common minimum distance used to define R0 resection in LRRc is 1 mm, which has been extrapolated from primary rectal cancer literature and is based on the definition of

Table 1 Definitions provided in studies reporting resection margins following multi-visceral resection for locally recurrent rectal cancer (n = 73)

Definition	Number of studies (%)
1 mm from tumour	10 (14)
0.5 mm from tumour	1 (1)
>0 mm from tumour/any intervening healthy tissue	2 (3)
Clear or negative margin, not otherwise specified	27 (37)
Complete removal of or no residual pelvic disease, not otherwise specified	3 (4)
Unclear from provided definition	2 (3)
Other	4 (5)
No definition provided	24 (33)

the circumferential resection margin after total mesorectal excision (TME)^{11,12}. However, the rationale for applying this definition to LRRc is questionable given the anatomy, biology, and surgery is expected to fundamentally differ from that of primary tumours, where exenterative surgery involves resection beyond the traditional TME plane and the margins, by definition, are outside the mesorectal fascia. Previously published data from the authors’ unit demonstrated that while any clear margin (defined by evidence of normal tissue between the tumour and the closest inked resection margin) was associated with improved survival in LRRc, any wider margin did not convey an additional survival benefit¹³. By contrast, two previous studies have found an overall survival benefit associated with margins >2 mm¹⁴ and >1 mm¹⁵, which may be at least in part due to substantially smaller sample sizes, differences in patient selection, use of frozen sections, and radiotherapy (both neoadjuvant and intraoperative) between centres.

The pathological processing and assessment of LRRc exenteration specimens is challenging due to the inherently heterogeneous nature of the disease and resections, and variation in institutional pathological practices may affect the reproducibility of resection margin measurement and reporting¹⁶. The majority of locally recurrent tumours are extra-luminal and therefore the ‘standard’

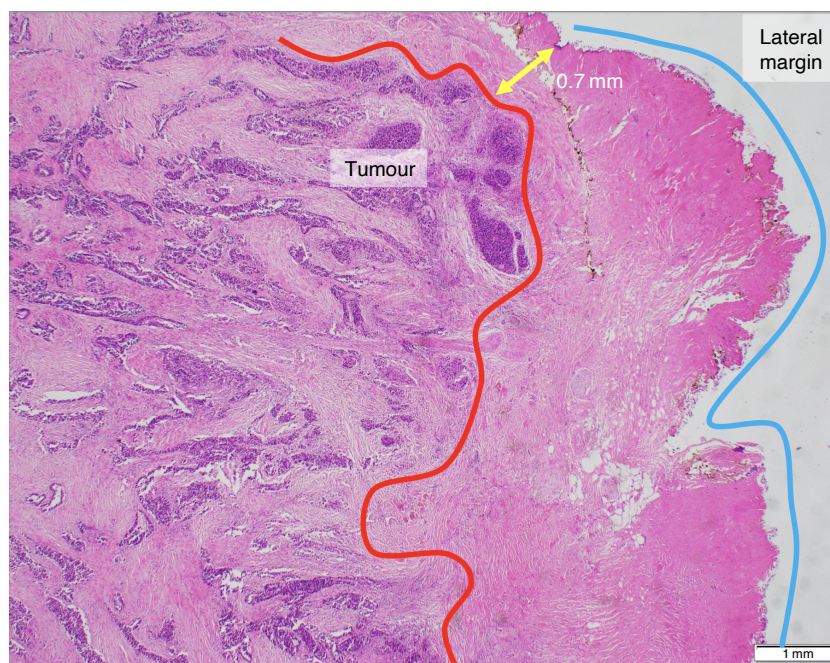


Fig. 1 Histopathological slide assessing the left lateral resection margin in a patient who underwent total pelvic exenteration with abdominolithotomy sacrectomy for locally recurrent rectal cancer

The closest distance between the tumour (red line) and resection margin (blue line) is measured (0.7 mm, yellow line). This margin was recorded as R0 based on the authors' proposed definition of 'any normal tissue', although would be recorded as R1 if a 1 mm cut-off definition was used.

proximal, distal, and circumferential margins of a primary rectal cancer specimen are not applicable. Rather, the organs, neurovascular and bony structures that are involved by the tumour and therefore resected vary from patient to patient, producing a unique specimen requiring complex assessment of bone and soft tissue margins in three dimensions (Fig. 1). Issues with specimen orientation, variation in specimen handling (such as thickness of serial sections and methods for assessment of bony margins) and use of frozen sections all may influence measurement of the resection margin. The authors believe that recording any intervening normal tissue present at the margin is likely to be more reliable and reproducible (reduced inter-observer variability) than using a specified distance as a cut-off.

It is the authors' opinion that 'evidence of normal tissue between the cancer and the closest inked resection margin' is the most meaningful and reliable definition of R0 resection for LRRC (Fig. 1). However, we note this position is not without controversy, and development of consensus-based, international recommendations, similar to the recently proposed 'pelvic exenteration lexicon'¹⁷, are needed in order to standardize margin status definitions and reporting for LRRC. It is critical that the exenteration community ensures that the 'holy grail' of this procedure is both reliable and reproducible to allow meaningful synthesis of data and valid comparative assessment of performance.

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Data availability

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CHAPTER 5: EXPLORING THE OUTCOMES OF EXENTERATION CONSIDERED IMPORTANT BY PATIENTS AND CARERS

CHAPTER OVERVIEW

Chapter 5 addresses *Thesis Aim 1*: to address unwarranted variation in treatment decision-making in patients with LARC and LRRC. It follows on sequentially from *Chapter 4*, which identified outcomes of pelvic exenteration previously reported in the literature (i.e. considered important by clinicians), and uses a qualitative approach to allow in-depth exploration of patient and carer perspectives as to the important outcomes of surgery on which treatment decisions should be made. The findings are presented as two manuscripts relating to patient/carer decision-making (*Chapter 5.1*) and survivorship issues (*Chapter 5.2*).

CHAPTER 5.1

A matter of survival - Patients' and carers' perspectives on the decision to undergo pelvic exenteration surgery for locally advanced and recurrent rectal cancer

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ORIGINAL ARTICLE

A matter of survival—patients' and carers' perspectives on the decision to undergo pelvic exenteration surgery for locally advanced and recurrent rectal cancer

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Abstract

Aim: Pelvic exenteration is the only potentially curative treatment for patients with locally advanced or recurrent rectal cancer. This study aimed to investigate how patients decide to undergo such radical surgery.

Method: This qualitative study employed an exploratory interpretive design informed by hermeneutic philosophy. During semi-structured interviews, individuals who had undergone pelvic exenteration at a specialised centre and their carers were asked to reflect on the decision-making process around surgery.

Results: Thirty-eight interviews were conducted with 39 participants (34 patients and five carers). Four themes were identified. *There really wasn't a choice*—participants indicated that long-term survival was their absolute priority, with many feeling that there was no alternative. Only one participant expressed decision regret due to the consequences of surgery. *Grappling with the magnitude of surgery*—despite extensive preoperative education and counselling, the enormity of the surgery and recovery experience was incomprehensible to participants until they were 'in it', with many surprised by a slow and protracted recovery. *A spectrum of psychological states and support needs*—participants reflected on their psychological state prior to surgery, identifying family or professional pre-surgery counselling as sources of support. *Understanding life after surgery*—although most participants were willing to accept anything in order to survive, many identified the impact on bodily functions, body image and overall quality of life as important.

Conclusions: Long-term survival was the principal factor influencing the decision to undergo pelvic exenteration. Individualised preoperative counselling may improve patient preparedness for the consequences of surgery.

KEYWORDS

pelvic exenteration, recurrent rectal cancer, surgical outcomes

INTRODUCTION

Whether or not an individual with locally advanced or recurrent rectal cancer should undergo pelvic exenteration surgery presents a major

decision for the patient, their family and their treating clinicians. Such radical surgery, although potentially curative in 40%–60% of selected patients, may be associated with significant postoperative complications, as well as at least temporary but often permanent changes to

quality of life and functioning [1]. Shared decision making in this setting requires an understanding of the consequences of potentially curative surgery, which must be weighed against the anticipated outcome of a palliative, non-surgical approach. In the latter situation, anticipated 5-year survival is less than 5% for locally recurrent rectal cancer and a gradual deterioration in quality of life is expected, probably due to progressive local tumour-related symptoms such as bleeding, malignant fistulas, intractable pain and intestinal obstruction [2,3].

In recent decades, the majority of the exenteration literature has focused on refining surgical techniques, associated morbidity and survival outcomes, which has determined the technical indications and contraindications of surgery [4]. These indications primarily inform a clinician's decision making about whether surgery should be offered to an individual patient. However, at the authors' centre more than 10% of patients offered potentially curative exenteration do not proceed with surgery, most often due to patient preference [5]. Ultimately, the decision to undergo this radical treatment is made by an individual patient in the context of their own treatment priorities and preferences. How patients and their carers' approach this difficult decision, which information they do or do not access, and the post-surgical outcomes they are most interested in have not been thoroughly investigated [6]. This qualitative study aimed to explore how individuals with locally advanced or recurrent rectal cancer and their carers perceive and negotiate this difficult decision-making process.

METHOD

This qualitative study employed an exploratory interpretive design informed by hermeneutic philosophy. The study is one component of a broader research programme at the authors' centre for which the protocol has been published a priori [7], and was developed by a multidisciplinary advisory committee comprising cancer specialists, senior cancer nurses, allied health professionals, experienced qualitative and quantitative researchers, patients and carers. This study was reported in line with the Standards for Reporting Qualitative Research [8].

Participants and recruitment

Adult patients who underwent pelvic exenteration for locally advanced primary or recurrent rectal cancer at Royal Prince Alfred Hospital, Sydney, Australia, between 2015 and June 2022 were identified from a prospectively maintained electronic database. Patients recorded as deceased and those who underwent surgery less than 12 months from the time of invitation were excluded, such that most participants were expected to have recovered from surgery. Subsequent recruitment of patients was guided by purposive sampling to ensure a diverse range of views were captured, based on age, sex, place of residence (metropolitan, rural/regional or interstate) and tumour type (locally advanced primary or recurrent rectal cancer). Approximately 80 patients were identified based on these characteristics and were invited to participate to ensure a minimum of 20 available participants (assuming a minimum 20%

What does this paper add to the literature?

Whether or not an individual with locally advanced or recurrent rectal cancer should undergo pelvic exenteration surgery presents a major decision for the patient, their family and their treating clinicians. This study provides a detailed exploration of the lived experiences of 34 patients and five carers facing this decision.

response rate). The final number of participants was determined by iterative analysis for data saturation, where no further interviews were conducted after three consecutive interviews in which no new concepts were identified. Patients were invited to participate by a mailed invitation letter. Those interested in participating contacted the research team by phone or mail and an interview time was scheduled. At the conclusion of each interview, participating patients were asked if their carer would also consider participating. All participants provided a written consent form.

Data collection

Opened semi-structured interviews were conducted using previously published topic frameworks [7], which aimed to explore the patient's or carer's general experience with the decision-making process, which information they did or did not access, alternative treatment options considered at the time of diagnosis, and on what basis they decided to undergo surgery. Interviews were iterative, that is, concepts identified in earlier interviews were used to inform discussion in subsequent interviews. Interviews were conducted by a single researcher (KGMB), a surgeon with experience managing patients undergoing pelvic exenteration who was completing a period of full-time research. Prior to commencing the interview, it was emphasised that the researcher was not involved in the clinical care of the participant. Although participants were given the option of either an in-person or telephone interview, all preferred to conduct the interview via telephone. Interviews were audio-recorded and transcribed verbatim.

Data analysis

Thematic analysis of interview transcriptions was performed to identify similarities and differences in participant experiences of the decision-making process around pelvic exenteration. Transcribed interviews were coded by a single researcher (KGMB) using NVivo software (NVivo 11, QSR International, Burlington, MA, USA). All codes (including verbatim source data) were then reviewed by a second, experienced qualitative researcher (KW). Employing principles outlined by Braun and Clarke, codes representing similar concepts were then grouped into major and minor themes and revised iteratively during in-depth discussion between the two researchers, which included review of the raw data associated with a code [9].

Ethical approval for this study was granted by the Royal Prince Alfred Hospital Human Research Ethics Committee.

RESULTS

Of 245 eligible patients, 83 were invited to participate based on the previously described purposive sampling matrix [7]. Thirty-four patients (41%) and five carers responded and participated in this study. For one patient and their carer, a joint interview was conducted at their request, while all remaining participants were interviewed individually (total 38 interviews). Demographic and tumour characteristics for participating patients are summarised in Table 1. The median interview duration was 32 min (range 12–57). Four major themes were identified (Figure 1) and are outlined below. Additional illustrative quotes are presented in Table 2.

There really wasn't a choice

The majority of participants indicated that long-term survival was their absolute priority and ultimately the basis on which they decided to undergo surgery. While most acknowledged that their treating specialists discussed alternative (i.e., palliative) treatment options, participants felt that they did not have a choice or that there was no alternative, because their only chance of surviving was to undergo surgery. For this reason, most patients and carers did not recall the decision to undergo surgery as a difficult one, despite it being confronting. Only one patient felt they were not presented with other treatment options.

There really wasn't a choice. Dr [name] described the percentages of having [surgery] against not having it... and said the ultimate decision is yours... go away, think about it, and come back.... And we just looked

TABLE 1 Characteristics of participating patients (N=34).

Characteristics	N (%)
Age at time of surgery, median (range)	62 (36–82)
Sex	
Male	20 (59)
Female	14 (41)
Geographical location of residence	
Metropolitan	12 (35)
Rural/regional	14 (41)
Interstate metropolitan	6 (18)
Interstate rural/regional	2 (6)
Tumour type	
Locally advanced primary rectal cancer	17 (50)
Locally recurrent rectal cancer	17 (50)

at him and said, well, there's really no decision to be made. The surgery has to be done.

The participants identified specific reasons that survival was their ultimate priority. Participants with young children commonly expressed the desire to see their children grow up or to be able to continue to care for them. Wanting to be alive to meet grandchildren was also commonly identified as a reason to undergo surgery in the hope of long-term survival.

I didn't have a choice... I was 36 with two young kids. I had lost my mum to cancer as well. So, I didn't have that support system. It was... me and my husband, and that's it. And I didn't have a choice. Because if I didn't do it, I was gonna die.

This theme was also identified by carers, who generally identified prolonging their loved one's life as the main reason for supporting the decision to undergo surgery.

I just wanted, maybe for selfish reasons, to be with him for longer than 18 months.

Notably, two participants reflected that if they were older and their children were adults ('if I felt like I'd finished my life') then they would have given more consideration to not undergoing surgery. Participants, both patients and carers, recalled a feeling of desperation, commonly because they had been initially informed that they had incurable cancer, prior to referral for consideration of surgery.

We went in there almost hat in hand, you know, sort of saying can you help us? So we would have taken anything.

Only one participant expressed decision regret. While this patient acknowledged they were cancer free, the changes to their physical function and body image led them to regret the decision to undergo surgery.

Grappling with the magnitude of surgery

Despite extensive preoperative education and counselling, the enormity of the surgery and recovery experience was incomprehensible to participants until they were 'in it', with many surprised by a slow and protracted recovery.

I got a real shock at how physically unable I was afterwards... just simple things like rolling over and getting up were really difficult... I don't know if I was naive, or I didn't ask those questions, or I wasn't educated. But I was really shocked.... I'm a pretty independent person.

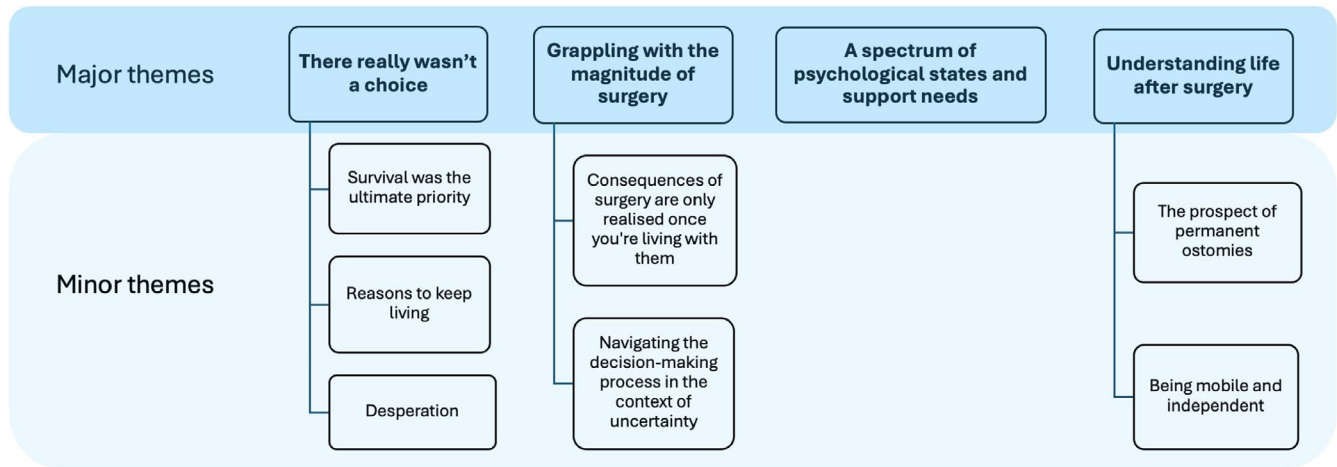


FIGURE 1 Major and minor themes.

Participants expressed that they approached the operation too casually, noting in retrospect that they would not or could not accept the magnitude of the operation. Some identified this refusal to accept their situation as a mechanism of coping with the prospect of such radical treatment, and in some cases was thought to have amplified the psychological impact of surgery.

While everything had been explained thoroughly to you... and I did ask lots of questions... I was hoping that it wasn't as bad as it obviously was.... I hid the dangers in my subconscious. And I sort of thought that I was going in for an appendix operation.... The enormity of it... I just couldn't accept.... And the more I think about that, and the more I feel I was a bit of a fool because I knew it, but I just ignored it.

Many patients and their carers identified the consequences of surgery (such as chronic pain) which, despite being informed about, could only truly be comprehended once they were living with them. This inability to truly understand some of the possible outcomes of surgery made it difficult for patients and carers to envisage the recovery and life after exenteration surgery and therefore make an informed decision.

Participants described being overwhelmed by the amount of preoperative information they were presented with and needed to comprehend. Many recalled that they did not know which questions to ask. The amount of time that patients and carers had to make the decision, that is, between referral and undergoing surgery, was perceived to be short and contributed to the difficulty of their decision making. Most were not aware of the nature of exenterative surgery prior to consultation with an exenteration surgeon and it often had not been discussed in any detail by their referring clinicians.

To be honest, I didn't know what to ask. You know, it was so quick. A lot of my questions came afterwards. Because it was just so overwhelming.

Many participants had difficulty grappling with the uncertainty associated with exenteration surgery, with respect to the extent of resection required (i.e., exactly which organs they would 'lose' and if they would require one or two permanent ostomies), anticipated postoperative function (e.g., genitourinary function and mobility) and what life after surgery looked like.

We were really looking at a bit of an unknown surgery. We really weren't quite sure what it was going to be. Whether I'd need the flap, whether my bladder would be impacted, what organs they were going to have to remove.

A spectrum of psychological states and support needs

Participants reflected on their psychological state during the preoperative counselling and decision-making phase, and recalled a range of different mindsets at this time. Many highlighted the importance of a pragmatic and positive outlook. Others were nervous about their diagnosis and the short-term risks of such major surgery. Participants who had previously undergone major abdominal surgery (i.e., those with locally recurrent rectal cancer) tended to be less concerned about the short-term recovery from surgery itself.

I didn't see getting cancer as a disaster. It wasn't a disaster in my life. It didn't define me. And that's a psychological approach. That's a perspective... okay, I've got this, let's get it sorted and then get on with life.

The extent to which participants involved their carers, family and friends in the decision-making process varied. Many attended consultations with their spouse, involved them in discussions about surgery and identified them as a major source of support. Others found professional preoperative counselling services valuable, while some made the decision alone. The COVID-19 pandemic was commonly identified as having a negative impact on preoperative consultations, by

**TABLE 2** Additional quotes demonstrating the identified themes.

Major theme 1: <i>There really wasn't a choice</i>	<p>'I just didn't want to die.'</p> <p>'It's not really a question to have the operation or not, to be honest. It's just a step that needs to be taken. That's the way I look at it: do you want to live or not? It's in our genes to just try and survive. It's just what you do.'</p> <p>'The fact that it was gonna extend my life was the ultimate reason I decided to go ahead.'</p> <p>'I'd rather have the surgery than sit there and watch the cancer eventually grow over time and die from it.... I wanted to live.'</p> <p>'It basically boiled down to having a chance of living or not having a chance at living. It was pretty black and white that if I didn't have anything done, I was going to die... fairly quickly. So, it was like a black and white decision really.'</p>
Minor theme: <i>Survival was the ultimate priority</i>	<p>'To be quite honest. It was never an option to me. The operation, with all its brutality and everything, was the opportunity to continue to enjoy life, be it on a limited scale. Or to leave my loved ones... And I didn't want to do that.'</p> <p>'I had no choice. It was either the cancer was going to keep growing... or have the operation. So, I've got children, who are adults now. And I'm hoping to be around 1 day for the grandchildren.'</p> <p>'My kids are now 22 and 24. They haven't obviously yet had children of their own.... I want to see them have kids, and I want to get old and do all those fun things, of course. So, it was really a no brainer.'</p> <p>'I wasn't old and I've got five kids, youngest one has just turned 14, so you know, would the decision have been different if I was 70? Maybe.'</p>
Minor theme: <i>Reasons to keep living</i>	<p>'I had chemo and radiation therapy. That didn't work. And they said, "Look, there's nothing really we can do now". They gave me 18 months' lifespan.'</p> <p>'[My husband] had 4 months of chemo... and then he was told that they could only offer him palliative care... we'd already got the shock when we were told it was palliative care or nothing. So, we needed to pick ourselves up off the floor.' (carer)</p>
Minor theme: <i>Desperation</i>	<p>'Most of the time (after previous operations) I was back to normal within 2 weeks. And I thought it was going to be the same and I didn't realise how severe the surgery was, and it literally did depress me that I was taking so long to recover.'</p> <p>'I didn't really concept when he said 6 to 12 months (recovery). I thought "oh yeah" but he was right. I just thought "I'll be fine". Maybe in 6 weeks, maybe 3 months. Yeah, it took me 9 months.'</p> <p>'I have quite a high bed. And I couldn't actually get on it. So, I had to have steps next to my bed to get into bed. And from being an active person, to having to climb on steps to get to bed, it was pretty disheartening.'</p> <p>'It took months before I could walk. When I first came home from hospital, the local physio... he got me going on Canadian crutches. Before that I was wheelchair bound.... Then I was able to get to the stage where I could walk with one of them. And I got rid of that one too. So I can walk without them.'</p> <p>'It's a very, very long journey. There's a lot of ups and downs obviously, infections, and rehospitalisation you can't really forecast... it is a possibility that it can happen... it's not an in and out treatment, that's for sure. It's a long way to go. And the operation itself is the easy part I think.'</p> <p>'Looking back, I probably wasn't aware of what was going to happen as much as I thought. I think the operation had a bigger impact on me and my health than I imagined.'</p>
Minor theme: <i>Consequences of surgery are only realised once you're living with them</i>	<p>'You're never going to be the same after such radical surgery. I don't think you at the time understand what that really means.'</p> <p>'People say "oh you'll have nerve damage, you'll have chronic pain", but it doesn't mean anything to you. Because you haven't experienced chronic pain.'</p>
Minor theme: <i>Navigating the decision-making process in the context of uncertainty</i>	<p>'I just didn't realise that he (the patient) was going to be in the ongoing pain that he's in.' (carer)</p> <p>'You got to work out what your life's gonna be like afterwards. And, yeah, you can't really work that out.'</p> <p>'The one thing that I did ask him was, what would I be able to have (the stoma) reversed? ... He said if it's on the right hand side, I can reverse it, but on the left hand side, no. So as soon as (I woke up from surgery) I put my hand down to feel where the bag was, and it was on the right hand side.'</p>
Major theme 3: <i>A spectrum of psychological states and support needs</i>	<p>'My mental state is very strong and I'm a very resilient person. I, I get frustrated with people that aren't.'</p>

(Continues)

TABLE 2 (Continued)

	'Having a strong mental perspective, and good psychological approach. I think it's really important.'
	'Because of the previous surgeries that I'd had, I had no real fear of the surgery. I was confident in my own mind that whatever surgery was done, I could handle.'
	'I'd already been through the peritonectomy. I knew the magnitude of what the operation was. And I just thought, well, I've been through it once. I can do it again.'
	'I must admit, after the diagnosis, the second time around, I was very angry. Because I'd done all the right things. I'd been for the check-ups, I hadn't missed anything. And I thought it was going to be okay. I was angry.'
	'My husband's dad's wife has the same thing. She has her rectum removed. And she's 60 odd. So she's been living with it for about 20 years. So she was a good reference point for me because she's had exactly the same thing. So that was good having someone who's gone through it to talk to as well.'
	'It was not talk it over with your family and agonise over it. It was all left to me to make the decision because it was me.'
	'My husband wouldn't understand what these things are. I'm sort of, you know, listening to it, and digesting it, and then come back with questions. And then I tell him what each of the steps are.'
	'I said it's entirely up to you (patient), it's your body and I said I'd be behind him. 100%, whatever you decide to do, and that's when he decided to have it.' (carer)
Major theme 4: <i>Understanding life after surgery</i>	'I was more interested in how I would come out of it. Was I going to be able to walk since he was going to take away a lot of my... nerves, pelvic floor etc. So quality of life ... is it going to be all worth it?'
	'That was the thing I was honing in on, was the quality of life after the surgery, and what that would be like.'
<i>Minor theme: the prospect of permanent ostomies</i>	'To be honest, all I wanted to know is if [surgeon] thought he could operate and get it out. As far as it went with stoma and change of life, whatever had to be removed. I was willing to deal with... I thought, yeah, my life will change a lot. And I wouldn't be able to do a lot. But again, at that stage of making that decision, it didn't bother me. It really didn't. That was a second problem to me.'
	'The stomas and that didn't really bother me. You know, that's just par for the course. I had my colostomy put in beforehand, which was a good move, because it got me used to it, then when the other one went on it was basically a piece of cake.'
	'I just thought, if I have to have this stoma, I'm gonna lock myself away and not go out and become a hermit. It's just the unknown of... are people gonna know it's there, it's gonna leak everywhere, how could I work with it? That was the biggest fear I had.'
	'I've never known anybody with a stoma bag. So, to me, I'm thinking wow, how do you cope with that? I went through the pre-admissions and saw the stoma nurse and it's all extremely daunting.'
<i>Minor theme: Being mobile and independent</i>	'Whether or not I would walk again... they did say that there was a chance that I might not walk, depending if I had severe nerve damage.'
	'My only concern throughout the whole thing was walking differently. I can walk around without the walking stick. Just saves me tripping over or whatever. I do use it, but I can walk without it. That was the biggest, the biggest killer for me.'
	'I can remember him saying to me that the worst case scenario is you might not be able to walk. And then we will teach you how to walk.'
	'He showed me a video of a guy that was able to walk afterwards with his sciatic nerve cut. He showed me what that looked like, and it didn't seem that bad.'
	'I thought, I hope I'll still be able to look after myself.'
	'As long as I was still going to be able to look after myself, and wasn't going to be in a nursing home or anything like that.'
	'I don't like being dependent.... I didn't want to end up becoming dependent and a burden to the family.'

preventing attendance of carers or other family members or because tele-consultations were required.

Understanding life after surgery

Although most of the participants were willing to accept anything in order to survive, many identified the anticipated impact of surgery on bodily functions, body image and their ability to participate in society as important information during preoperative discussions and counselling.

I didn't think to ask the questions about what's the actual quality of life. Even if I'd known... if I could go back in time from today... with the full knowledge of what it entails, it wouldn't change my decision, but it probably would have been useful.

The prospect of requiring one or more permanent stomas was a major concern for some patients and carers but not others. Some patients identified the need for permanent stoma/s as a major source of distress and something which was considered carefully during the decision-making process. Others did not consider the need for

stoma/s a significant issue, particularly those with an existing or temporary ostomy which had been subsequently reversed.

They said the bad news is you're going to have a permanent colostomy bag. And I said, oh I already knew that... that's the last of my worries... I've had an ileostomy, so a colostomy is going to be so much easier.... No, let's go back to these tumours... I'm much more interested in that than a colostomy bag.

Many participants considered the ability to be mobile and independent after surgery a highly important consideration. The effect that complete or partial sciatic nerve or sacral nerve root resection was expected to have on lower limb function and mobility, as well as the need for rehabilitation, was identified as important preoperative information. Two participants recalled being shown videos of a person walking after a complete sciatic nerve resection and found this a helpful addition to verbal information. Being able to live independently after surgery was also a priority for many patients.

My questions were really around what was my quality of life gonna be afterwards, because I'd heard some horror stories... some people that really were house-bound or mobility was a huge issue.

Tumour-related symptoms (most commonly pain or incontinence) were identified by several patients as contributing to their decision to undergo surgery. Some indicated that these symptoms became worse after neoadjuvant treatments and relief from these symptoms was an important goal for many.

DISCUSSION AND CONCLUSIONS

Individuals with locally advanced or recurrent rectal cancer who are offered pelvic exenteration surgery face a major decision. This study employed a qualitative, interpretive design to provide a detailed exploration of the lived experiences of 34 patients and five carers facing this decision and who ultimately decided to undergo surgery. The key finding was that despite the potential complications and prolonged recovery associated with surgery, patients and carers felt they had no choice, because it was their only chance of long-term survival, and (at a minimum of 12 months after surgery) they were content with their decision. Participants found it difficult to comprehend the enormity of surgery, and, despite extensive preoperative consultation and counselling, many were surprised by a slow and protracted recovery. Although survival was invariably seen as the priority, many identified the impact of surgery on bodily functions, body image and overall quality of life as important information to ensure patient preparedness before surgery.

The findings of this study demonstrate that despite routine, extensive preoperative education and counselling, many patients struggle to comprehend the magnitude of the recovery from surgery. This is likely to be at least partly due to variation in the needs of patients

both with respect to the amount of information and psychological support required and the outcomes of interest. For example, patients with locally recurrent rectal cancer who had previously undergone complete or partial proctectomy were to some degree psychologically 'more prepared' for major pelvic surgery, and similarly were more likely to be comfortable managing stomas, whereas ostomy-naïve patients were more concerned or in some cases distressed about the prospect of permanent ostomies. These findings support the concept of individualised preoperative counselling, in both format and content, according to an individual patient's preferences and priorities which should be established early during the process of shared decision making. Currently, preoperative counselling at the authors' unit includes a minimum of one joint consultation with the treating exenteration surgeon and nurse consultant (but often more depending on patient preference and clinical need). Patients are then given contact details of the nurse consultant to allow follow-up questions and discussion after the patient has had time to reflect on the decision. Prior to surgery, patients attend a dedicated pelvic exenteration pre-admission outpatient clinic, which involves individual consultations with an anaesthetist, stomal therapist, physiotherapist, psychologist, dietitian and pain specialist (in selected cases).

In 2006 Wright and colleagues conducted semi-structured interviews with 10 patients who underwent multi-visceral resection for locally advanced primary or recurrent rectal cancer and reported similar findings to the current study [10]. In their study, participants felt that they had limited treatment options, consistent with the feelings of desperation and of not having a choice identified in the current study. Wright and colleagues also found that the morbidity of surgery was unanticipated by participants, who reported the need for a more realistic view of the consequences of surgery. As in the current study, participants noted that this information would not have changed their decision about undergoing surgery but may have improved their preparedness and thereby reduced the psychological impact of such radical treatment. Qualitative studies of women treated with pelvic exenteration for advanced gynaecological cancers have similarly found that patients feel they have little choice when presented with pelvic exenteration as the only potentially curative treatment option and are unprepared for the functional and emotional consequences of surgery despite being informed preoperatively [11,12].

Future investigation should focus on improving preoperative education, which may facilitate better patient understanding of the magnitude and consequences of surgery and ultimately ensure patients are fully informed when faced with a decision involving such radical treatment. Individualising preoperative education and counselling based on patient preferences and priorities may be facilitated by development of patient decision aids, of which there is one currently being developed [13]. The results of the current study will be used to inform the development of a risk-prediction tool at the authors' unit, which generates an individualised, reproducible and evidence-based recommendation for or against surgery and can be used at the point of diagnosis to guide decision making [7].

The strengths of the current study include a large sample size for what remains a relatively uncommon procedure. The exploratory

interpretive design permitted in-depth exploration of the views and experiences of both patients who have undergone exenterative surgery as well as their carers, the nuances of which are unlikely to be captured in generic quality of life tools. Limitations of the study include the selected nature of the patient population (i.e., those who underwent pelvic exenteration and survived), which precludes any comment about the experience of those who decline or are not suitable for surgery. Initial coding was performed by a single researcher due to the large volume of data; however, during data analysis, all codes (including the verbatim source data) and themes were reviewed in depth with an experienced qualitative researcher.

In conclusion, this study demonstrated that a chance of survival is the ultimate priority for most patients who undergo pelvic exenteration for locally advanced or recurrent rectal cancer. Despite extensive education and counselling, many patients remain surprised at the physical and psychological insult of surgery. An individualised approach to pre-operative counselling, with consideration given to a particular patient's priorities and information needs, may improve preparedness for the prolonged recovery that lies ahead of this group of patients.

AUTHOR CONTRIBUTIONS

Kilian G. M. Brown: Conceptualization; methodology; data curation; writing – original draft; formal analysis. **Kate White:** Conceptualization; methodology; formal analysis; writing – review and editing; supervision; data curation. **Michael J. Solomon:** Conceptualization; supervision; writing – review and editing. **Paul Sutton:** Conceptualization; methodology; writing – review and editing. **Kheng-Seong Ng:** Conceptualization; methodology; writing – review and editing. **Cherry E. Koh:** Methodology; writing – review and editing. **Daniel Steffens:** Conceptualization; supervision; resources; project administration; methodology; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical approval for this study was granted by the Royal Prince Alfred Hospital Human Research Ethics Committee (Approval no. X22-0422)

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CHAPTER 5.2

Life after pelvic exenteration for rectal cancer: the patient and carer perspective on long term consequences and survivorship

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Running head: Pelvic exenteration survivorship

ABSTRACT

Objective: To explore the perspectives and experiences of patients and carers living with the long-term consequences of pelvic exenteration.

Summary background data: Pelvic exenteration is accepted as the standard of care for selected patients with locally advanced or recurrent rectal cancer. With contemporary 5-year survival reported at 40-60%, the number of long-term survivors is expected to increase. The long-term consequences of such radical surgery for patients and their survivorship needs are not well understood.

Methods: This was an exploratory, qualitative study conducted at a high-volume pelvic exenteration centre. Semi-structured interviews were conducted with survivors of pelvic exenteration surgery for locally advanced or recurrent rectal cancer and their carers.

Purposive sampling was used to ensure a diverse cohort. Data were thematically analysed.

Results: Three major themes were identified: 1. *The consequences of surgery are the price you pay for survival*: the majority of participants accepted the sequelae of surgery as the cost of survival. 2. *Our lives are changed forever*: Adjusting to changes in body appearance and function was an ongoing challenge. Chronic pain, stomas, altered bowel function and mobility issues impacted work and social life. 3. *The good days and bad days as a survivor*: While several participants reported a more positive approach to life, many were living with a pervasive fear of recurrence and/or dying, and the ripple effect on family and friends was significant.

Conclusions: Although survivors of pelvic exenteration accept the long-term consequences of surgery as the price of survival, these are significant, and improved access to support services in the community may better equip survivors to manage these challenges.

INTRODUCTION

The anticipated 5-year overall survival following pelvic exenteration for the treatment of locally advanced and recurrent rectal cancer may be as high as 65% and 45%, respectively (1, 2). Survival outcomes for this group of patients continue to improve as more radical techniques have been developed to allow safe and oncologically complete resection of more extensive tumours at the pelvic periphery (3, 4). These progressively more favourable oncologic results, combined with encouraging quality of life outcomes, have prompted increased interest in exenterative surgery globally. Existing referral centres have reported increasing case volumes (4-6), while new centres are being established (7, 8). Given the improved oncological outcomes and clear increase in pelvic exenteration activity globally, it is expected that the number of long-term survivors after pelvic exenteration for locally advanced and recurrent rectal cancer will increase.

The short-term surgical outcomes, including the risk of complications associated with such radical treatment, as well as long term survival, have been extensively documented in the literature (9, 10). However, patient and carer perspectives on life after pelvic exenteration and survivorship issues have not been well described. Despite an increasing focus on quality of life after exenteration surgery, most studies employ quantitative methodology to measure patient-reported quality of life scores (11). Although useful for analysing quality of life trajectories for cohorts of patients (12, 13), patient-reported outcome measures typically include closed questions or scores in pre-determined domains, and are generally designed and validated for use in broader colorectal cancer cohorts, where many items may not be relevant to pelvic exenteration patients. These quantitative techniques may not adequately capture the complex and broad range of issues faced by exenteration survivors in the long

term and their carers (14). Therefore, the aim of this qualitative study was to conduct an in-depth exploration of the experiences of patients and carers with the long-term consequences of pelvic exenteration surgery.

METHODS

Study design

An exploratory interpretive qualitative research approach was employed to examine the perspective and experience of individuals who had previously undergone pelvic exenteration for rectal cancer, as well as their carers. This study was one component of a broader research program which aimed to develop a risk prediction tool to assist treatment decision-making in patients with locally advanced or recurrent rectal cancer. The protocol for this group of studies was developed by an experienced multi-disciplinary clinical research team (including physicians, senior surgical nurses, allied health professionals, quantitative and qualitative researchers, and patient representatives) (15). This study was reported in accordance with the Consolidated Criteria for Reporting Qualitative Research Publications Guidelines (16). Ethical approval for this study was granted by the Royal Prince Alfred Hospital Human Research Ethics Committee (protocol no. X22-0422).

Participants

Individuals who underwent pelvic exenteration surgery for the treatment of locally advanced or recurrent rectal cancer at a single academic referral centre were eligible for inclusion. Pelvic exenteration was defined as en bloc resection of a minimum of three pelvic compartments and/or bone or lateral neurovascular resection. Potential participants were identified from a prospective institutional pelvic exenteration database. Those who underwent surgery less than six months prior to recruitment, were treated with palliative intent, or did

not speak English, were excluded. Purposive sampling, where patients were identified based on age, sex, metropolitan or regional residence, and primary vs. recurrent rectal cancer, was used to ensure a broad range of perspectives were captured. The purposive sampling matrix used for this study has been previously reported (15). Eligible patients were sent an invitation to participate and study information sheet, and those who did not respond were contacted by phone two weeks after the letter of invitation was sent. Participating patients completed a written consent form and were asked to consider inviting their carer (defined as a spouse, child or close relative) to participate. Data saturation was considered achieved when no new concepts arose in three consecutive interviews, which determined the final sample size.

Data collection

Demographics and information relating to surgical treatment were extracted from a prospectively maintained institutional database. Major nerve resection referred to en bloc excision of the sciatic or femoral nerves, lumbosacral trunk or high sacral nerve roots (S1 or 2). Semi-structured interviews with open ended questions and prompts guided the participants' to reflect on their experience, to go beyond description, and outline their subjective perspectives. Only participants who were at least six months post-surgery were included to ensure they had mostly recuperated from surgery. Interviews were conducted during June and July 2023 by a single researcher (KGMB), a surgeon with experience caring for patients undergoing pelvic exenteration and who was trained in qualitative methods and supervised by an experienced qualitative researcher (KW). The interview topic guides (supplementary information, Supplemental Digital Content 1, <http://links.lww.com/SLA/F374>) were developed by the previously described multi-disciplinary research team, and included open-ended questions about the physical and psychological consequences of surgery, the impact on daily life and whether they were

expected or unexpected. An iterative approach to the interviews was used, where findings from previous interviews were used to guide subsequent interview discussions. Interviews were audio-recorded, transcribed verbatim, de-identified and imported into NVivo software (NVivo 11, QSR International, Burlington, MA, USA).

Data analysis

Data were thematically analysed, where the data were explored inductively without any pre-determined structure or framework. This involved initial line-by-line open coding of all transcripts by a single researcher to identify emerging patterns and concepts (KGMB). Two researchers (KGMB, KW) then considered all verbatim text within each initial code, and during in-depth discussion, refined the preliminary codes and grouped them into broader themes. Themes that were identified were then reviewed at the raw data level to ensure participant perspectives were accurately reflected by the description of each theme. Proposed themes were then reviewed by the research team including illustrative quotes. Participants did not review transcriptions or study findings.

RESULTS

Of 83 patients who were invited, 34 patients (41%) and five carers participated in this study. For one patient and their carer, a joint interview was conducted at their request, while all remaining participants were interviewed individually (total 38 interviews). Demographic and tumour characteristics for participating patients are summarised in Table 1. The median time between surgery and interview was 32 months (range 6-91), and the median interview duration was 32 minutes (range 12-57). Analysis of participants interview transcripts identified three main themes, and 11 minor themes (Figure 1, Supplementary Table 1, Supplemental Digital Content 2, <http://links.lww.com/SLA/F375>).

The consequences of surgery are the price you pay for survival

Participants viewed the physical and mental consequences of surgery as the cost of survival. The magnitude and significance of the chronic sequelae of surgery differed between patients. While some considered these sequelae to be a small price to pay for survival, others regarded them to be more significant. Regardless of the ramifications of surgery on their life, the vast majority of patients still considered surgery worthwhile.

"It's been a struggle, but it's better than being dead. I got to meet my grandkids." (patient 16)

"Ultimately, I'm still alive because of the operation, and I just have to live with the side effects." (patient 3)

Only one patient expressed regret about the decision to undergo pelvic exenteration due to the changes to his life and lifestyle, despite being cancer free and the perceived oncological success of the procedure. Many other patients also remarked about changes to their body, their life/lifestyle, and relationships (described below), but for these patients it was considered the price of surviving and they did not express regret.

Our lives are changed forever

Patients and carers described the way in which their lives were changed by surgery. For some, life returned to 'normal' following their recovery, without any physical restrictions or lasting psychological impact. Many participants, however, described permanent physical

changes to their body and psychological consequences which impacted their day to day life, including their ability to work, travel and connect with others.

"Once we came home, I thought that our life would go back to normal. But it hasn't.

He's still in a lot of pain, pain all the time. And he can't walk very well. So, when he walks, he walks with a limp. We don't travel anywhere." (Carer 2)

My body will never be the same again

Adjusting to changes in body appearance and function, was an ongoing challenge for many patients. Such issues identified by patients included scars, living with stomas, and changes to their body contours. Mobility was limited for some patients by lower limb weakness, including those with a permanent foot drop. Some patients experienced long term perineal wound complications (i.e. developed chronic sinuses) which required prolonged periods of wound care in the community and disrupted their day to day activities.

"I've got physical reminders of (cancer). My kids also have a physical reminder of that. They will see my scars, they see my bag, they see me having a bad day and needing to lay down." (patient 23)

Patients felt that the physical changes to their body affected the way they were seen and treated by friends and family, or society more broadly, and this led to a sense of embarrassment or shame for some.

Living with pain

Prolonged pain was identified as a significant challenge during the months following surgery. Although many patients were free of pain at the time of interview, some experienced ongoing pain in the longer term. Difficulty sitting for prolonged periods was commonly identified and limited the ability to travel distances (particularly by car), work (due to difficult sitting at a desk) and engage in social activities (such as attend dinner parties, restaurants or bars). A small number of patients experienced severe, chronic pain requiring complex analgesic regimes, causing major disability, and from which they felt there was 'no escape'.

"People say "you'll have nerve damage, you'll have chronic pain", but it doesn't mean anything to you, because you haven't experienced chronic pain." (patient 29)

My stoma is not going away

The extent to which having one or more permanent ostomies impacted participants' lives varied. Some patients did not consider their stoma/s to have had a negative impact or restrict them in any way, and many were open with family, friends and their community having a stoma.

"Managing the stoma is really easy. That's never been an issue. I don't even think about it. And my partner says to me, I don't even realise you've got it there. Like, it's just such a not an issue for me" (patient 21)

For other patients, having one or more stomas had a major impact on their life. Appliance leakage was identified as a daily problem for many patients, which restricted their ability or willingness to leave the house and attend social events. For many, the ability to manage their bags and avoid leaks improved with time, although two patients relied on their spouse to

change their stoma bags. Noises from the colostomy was an ongoing source of social anxiety or embarrassment for many.

"It was a very, very difficult period of time in learning to change bags. I remember lying in bed and waking up in a pile of urine...I'd rolled over and...the bag must have been full. But I'd sit there and I'd cry." (patient 24)

For patients without a colostomy or urostomy, changes to their bowel and urinary habits (frequency and/or incontinence) were commonly reported. Erratic bowel habits influenced social behaviours, due to patients' need to be constantly aware of the nearest toilet as well as needing to modify their diet.

"There are times when I go out with friends. And I'll say "no, I don't think I'll have anything to eat". Because I don't want to go into the toilet and sit there for half an hour." (patient 28)

Some patients who had not required a cystectomy reported needing to always wear urinary incontinence pads, which, for some, effected their ability to complete tasks at work and travel, particularly long distances.

"I've got to always wear a female incontinence pad in case I have a tip over. I can't stop it because of half of my pelvic floor muscles being cut...So I can't stop it, it'll just pour out" (patient 21)

Loss of intimacy

Participants described how surgery had affected their sex life and ability to be intimate with others. Some male patients described their inability to gain an erection, while some female patients reported a lack of sensation. While many patients anticipated and felt they were well prepared for the change in sexual function, others still held hope that this might improve with time.

"There's nerve damage there, and so intimacy is just not really a thing anymore"
(patient 21)

The good days and bad days as a survivor

Although patients expressed they were grateful to be alive, many described the ups and downs of day to day life after pelvic exenteration, characterised by a change in outlook, living with uncertainty, a lack of support services and the impact on family and friends.

"You have good days, you have bad days. Some mornings, you lie in bed and you think, "oh, shit, this is me and I'm not really happy with it", then other mornings you bounce out (of bed)" (patient 7)

A change in outlook

A number of the patients reflected that having cancer and requiring such extensive surgery had changed their perspective on life. Many described a more positive approach to life as a survivor, commonly expressing a feeling of gratitude or being lucky. Several patients emphasised the importance of not letting their cancer consume their life or define them. One patient felt that becoming 'too embedded' in the cancer survivor community could prevent people moving on with their lives.

"I've met people who make surgery a problem. It defines them. And I think in myself, I doesn't define me, It's not who I am. It's not what I want to do. I have other things that I can get on with in life and enjoy, and those are the things that identify me" (patient 4)

Living with uncertainty and fear of dying

Many participants reported living with a pervasive fear of recurrence or dying. Surveillance investigations and follow up appointments were identified as common sources of anxiety, to the point where some patients felt their life revolved around blood tests and scan results and limited their ability to enjoy life.

"It could come back at any time. And that always plays on my mind" (patient 26)

Lack of support and services

Patients identified the support and counselling provided by medical and allied health members of the multi-disciplinary exenteration team as critical during the preoperative period and during their recovery in hospital. Many, however, felt that this support ended abruptly following discharge from hospital. This created a feeling of isolation and helplessness for some, who felt they did not know how or where to access help, particularly given their unique circumstances and care requirements. Some patients reflected that local medical services (e.g. hospitals or individual practitioners) were not familiar with pelvic exenteration surgery and were unable to provide the required care. This was a particular problem for patients living in rural areas, who reported having limited access to services (particularly stomal therapists) locally, and were required to travel long distances at their own expense to access such

services. Patients living interstate felt there was a lack of specialized support available after they were transferred to their local referral centres for recuperation and long term follow up.

"I felt quite alone, quite deserted." (patient 18)

"I came back to Adelaide...all of the support from RPA was gone. I didn't have the psychologists. I didn't have the nutritionists, dieticians, physio...All of those things. The support was gone." (Patient 23)

Ripple effect on family and friends

Patients and carers reflected on the impact that surgery had on their own relationships, as well as their broader family and friends. Carers (all of whom were the spouse of a patient) described the way in which their role had changed in the relationship, from one of a spouse to that of a carer, characterised by the need to provide both physical and psychological support, such as assistance with dressing and managing stoma appliances. Carers did not express resentment or regret about this change in their role, although it was generally not anticipated.

"You've got a partner that needs 24/7 support and help and love. And that's what I give him. And I'm fine with that. That's okay." (carer 1)

DISCUSSION

This qualitative study provided an in-depth exploration of the patient and carer perspective on life after pelvic exenteration surgery for locally advanced or recurrent rectal cancer. Despite the detailed accounts of significant and life altering sequelae of surgery, these were accepted by participants as the cost of surviving and, for many, were considered a small price to pay

for being alive. Most significant for participants were the permanent changes to their lives that resulted from surgery, including physical changes to their body and body image, such as stomas and scars, which served as daily reminders of their cancer and impacted their ability to work, travel, and connect with others. Participants reflected on the good days and bad days as a survivor, with some living with a pervasive fear of recurrence or dying. Although there were strong common themes identified, the individual survivorship experience was wide and varied among participants.

This study illustrates the long-term consequences of exenteration surgery that survivors of this radical treatment live with, well beyond the immediate recuperation from surgery and the associated short term morbidity. Although some of the experiences identified in this study may be shared with patients who undergo surgery for other major cancers, it is clear that the simultaneous impact that exenteration has on multiple systems (urinary, gastrointestinal, sexual, neurological) creates a uniquely complex set of daily challenges. For many patients, the management of multiple permanent stomas distinguishes this experience from most other cancer surgeries. While some aspects of these identified themes and survivorship issues (such as difficulties managing stoma/s) may be considered expected side effects to a clinician with experience managing patients who have undergone pelvic exenteration, it is the lived experience of patients and carers, and their perspectives, which contextualises how these clinical side effects meaningfully impact people's lives.

The findings of the current study expand upon those reported by two smaller qualitative studies. Wright and colleagues reported findings from semi-structured interviews with 10 patients who underwent extended resection for locally advanced primary or recurrent rectal cancer (17). Participants in that study were grateful to be alive, despite the side effects of

surgery which were reported as impacting their mobility, activities of daily living, and sexual function. This finding was consistent with one of the major themes identified in the current study ('The consequences of surgery are the price you pay for survival'). Additionally, Wright and colleagues described the issue of recurrence as a source of patient anxiety, which was also identified in the current study. The authors' group also previously contributed to qualitative work, which utilised focus groups with patients with locally recurrent rectal cancer during the development of a patient-reported outcome measurement tool (18). A range of symptoms and side effects were identified, including pain, gastrointestinal and urological symptoms, and the impact these had on sexual function, body image, self-confidence, daily activities, and plans for the future. Importantly, both of these previous studies had relatively short follow up periods; a median of 11 months (Wright et al) (17) and up to 24 months (Harji et al)(18), compared to a median follow up of 32 months (and up to 7 years) in the current study, which permitted the assessment of longer term survivorship issues. A qualitative investigation of chronic pain management and long-term analgesia in patients undergoing surgery for locally recurrent rectal cancer has recently been reported by our group (19).

As the number of new exenteration programs increases globally and existing centres see increasing numbers of referrals (4-8), it is expected that the number of locally advanced primary and recurrent rectal cancer survivors living with the lasting effects of this radical surgery will increase. In this context it is important that specialised referral centres are appropriately funded and equipped to address survivorship issues and provide ongoing supportive care. While some of these needs are similar to a broader colorectal cancer population (20), many chronic issues identified in this study are unique to pelvic exenteration patients, including dealing with two permanent ostomies, issues related to perineal wounds

and empty pelvis syndrome, and mobility problems related to lower limb neurological deficits (21-23). Importantly, the delivery of such a highly complex surgical service is typically provided by a single quaternary referral centre for a given state or region, and in some instances for an entire country. Therefore, it may not be feasible for that centre to manage all survivors in the long term, particularly for rural, regional or interstate patients. For example, at the authors centre, many such patients return to their referring colorectal surgeon or oncologist for surveillance, with those results communicated to the exenteration centre. An open line of communication between local clinicians responsible for regular follow up and the specialised exenteration unit is crucial. This includes, in particular, the ability to discuss unique management issues and/or reinstitute referral for re-review with not only surgeons, but nursing and allied health professionals with specialty expertise in managing patients after pelvic exenteration. Educational resources and ongoing remote support streamlined from the specialised centre in a hub and spoke type model may better meet patients' needs. In addition, it is likely that prehabilitation, rehabilitation and survivorship care will be increasingly provided virtually in the future (or a hybrid model), which may be both more cost effective and more convenient for patients than traditional face to face clinical care (24).

The strengths of this study included use of an inductive, qualitative approach which facilitated detailed and in-depth exploration of participants' lived experiences, a relatively large sample size for what is still an uncommon operation, and use of purposive sampling to ensure a broad range of perspectives were captured. The fact that participants were treated at a single centre may limit the generalisability of the findings.

Although survivors of pelvic exenteration accept the long-term consequences of surgery as the price of survival, these sequelae are significant and life altering for many. Improved access to support services in the community may better equip survivors and clinicians to manage these challenges. The optimal way to deliver such services is likely a 'hub and spoke' model where local referring specialists who, in many instances, manage the follow up of this patient group, are educated and empowered to address their patients' ongoing supportive care needs. This requires a proactive, collaborative approach with the specialised exenteration unit.

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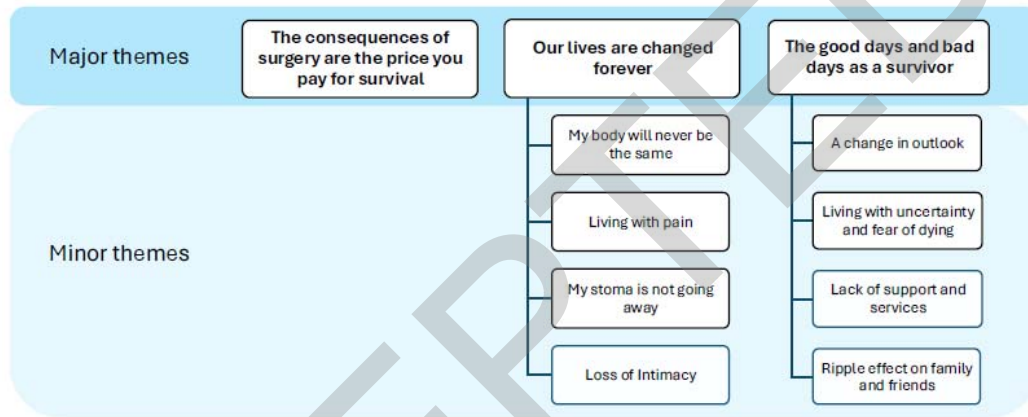
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ACCEPTED

Figure 1. Major and minor themes identified during in depth interviews with patients following pelvic exenteration and carers



ACCEPTED

Table 1. Characteristics of participating patients (N=34)

Characteristics	N (%)
Age at time of surgery, median (range)	62 (36-82)
Sex	
Male	20 (59)
Female	14 (41)
Geographical location of residence	
Metropolitan	12 (35)
Rural/regional	14 (41)
Interstate metropolitan	6 (18)
Interstate rural/regional	2 (6)
Tumour type	
Locally advanced primary rectal cancer	17 (50)
Locally recurrent rectal cancer	17 (50)
Operation details	
Stoma	
Permanent colostomy	17 (50)
Temporary ileostomy	7 (21)
Ileal conduit	17 (50)
Myocutaneous flap perineal reconstruction	5 (15)
Major nerve resection	11 (32)
Sacrectomy	20 (59)
Postoperative details	
Length of hospital stay, days, median (range)	22 (7-107)
Length of intensive care unit stay	3 (1-20)
Return to operating theatre	8 (24)
Return to intensive care unit	1 (3)

The following tables and figures are included as supplementary information to Chapter 5.2.

Supplementary Table 1. Additional quotes demonstrating the identified themes

Major theme 1: *The consequences of surgery are the price you pay for survival*

"Does it affect you in terms of what you can wear? Or what you can do? Or it's just something you're conscious of? A little bit. But that's a small price to pay." (Patient 12)

"It's something you've just got to do...I'm here, I'm not dead." (Patient 5)

"Initially, I said no to (surgery). But thinking back, Dr. X was right. I'm still alive, and I still get to see the grandkids and that sort of thing, so I'm happy with that." (Patient 34)

"At no stage have I felt sorry for myself or for us. As far as I'm concerned, I got a positive result from a difficult situation and I'm better off now than I would have been without" (Patient 2)

"In retrospect, I can say I would have preferred not to have had the surgery. I know it's been completely successful, I'm cancer free now. But I just would have preferred not to have had it. Before that, I was feeling the healthiest I had for years". (patient 20)

Major theme 2: *Our lives are changed forever*

"I can do everything. I'm just not the same person I used to be" (Patient 34)

"It's not just psychological...it's your whole life changed. The way that you dress is different, the way that you walk is different, the way that you sit is different" (Patient 20)

"I think mentally is one of the big things that people have to be on board with...they have to be ready for what's going to happen...there's a big, big change in their life" (Patient 9)

"I had to sell me farm and that just changed everything. It just turned everything upside down. What I was planning to do and what me aims were, were just completely scratched and gone" (Patient 19)

"I spend a lot of time on my own at home. So that makes me feel down. Depressed, I mean...I'm normally around a lot of people, especially when I was at work. So, life has changed a lot in that sense." (Patient 9)

"For me, it's a little bit of a surprise because...they sort of said, you know, you pretty much will have the life you had... And I don't think that's the case" (Carer 5)

Minor theme: My body will never be the same

"You look different, you walk different. You go to the toilet different. There's all these different things. I don't know how the rest of the world looks at me now." (Patient 7)

"Body image is important. I live on a beach, the whole ability to just cut your grass with just a pair of shorts and be down the beach every day." (Patient 20)

"You're never going to be the same after such radical surgery. I don't think you at the time understand what that really means" (Patient 25)

"You do feel like a bit of a circus freak sometimes" (Patient 20)

"Where the flap is...it's not my body, if that makes sense. So, it kind of chafes...like it rubs a little bit because it's sort of not sitting where it should be sitting" (Patient 23)

"Nothing ever feels the same after you've had a full proctectomy me and also pelvic exenteration...nothing will ever feel the same I don't think" (Patient 15)

"I love to go and lay in the sun and stuff. I don't as much now. How would I go with my costume on? I don't know. I'm a bit ashamed of it. But it's just part of me. It's not something that can go away" (Patient 26)

"Your body is changed forever" (Patient 20)

Minor theme: Living with pain

"You can't do a long drive anymore, because it's just impossible to sit" (Patient 20)

"You've always got pain. You're always aware of it, but it's background. So, every time I sit down, it's a bit sore, which I just put in the background." (Patient 29)

"I still get a lot of pain around the groin. Even if I do get out and exercise a lot, like start walking around, without aids. I almost can't sleep that night because it's painful." (Patient 9)

"From the operation, the muscles are out of whack on one side and it pinches sciatic nerve. and it feels like you broke your toe. But it's actually a nerve." (Patient 29)

"He has an air cushion. If we go out to dinner. He takes it with him because it makes him a bit more comfortable" (Carer 2)

"Nerve pain is a particularly unkind pain" (Patient 15)

"I've still got considerable pain. To be honest, I'm taking painkillers like lollies at the moment" (Patient 18)

Minor theme: My stoma is not going away

"For the first 12 months I had a lot of trouble with pancaking, leakages, bags bursting off my stomach" (Patient 2)

"When you do get a bag on... the crisis you go through with the leakage and the malfunction of the bag and the pancaking and...bloody everything" (Patient 1)

"I think that having any sort of incontinence would be more of a much more of a nuisance than having the bags, or having to wear some form of nappy. I mean, this is a fairly clean operation, I can just change my bags, and it's all done" (Patient 4)

"The management of the bags in terms of the physical appliance took me a very long time to get on top of right. I'm pretty much sorted that out now, very rarely have a bag failure, they will last quite a few days" (Patient 25)

"The biggest issue I find that with the bags and my present situation is that I can only get dressed in certain clothes. I can't put a pair of trousers on with a belt. I can't tuck me shirt into me trousers, like if I have to get dressed in a suit or something to go out.... my dress is normally a pair of tracksuit pants and a flannel shirt, which is left open at the front and it covers the two bags...there's been times when I couldn't push myself to go to a funeral...I wouldn't go to a funeral dressed the way I am...to go out to a nice restaurant or something like that, I feel uncomfortable being dressed as I am." (Patient 2)

"I thought, well I'm not going to let life pass me by. Just because I look a little bit different. And if people want to know, I tell them. I'm not embarrassed by all this sort of stuff, it's all out in the open so people are more accepting" (Patient 7)

"Traveling is more difficult...every time I get on a plane, man, I gotta use that toilet because bags fill up on their own. You can't control that...you're always conscious of the bags, because the urine one, they have a tendency to leak if you put pressure on the wrong way, and that's a shocker. So traveling is not as easy, even if it's a road trip for three hours" (Patient 29)

"I was always in business, a pretty smart dresser. I always made sure my shirt was tucked in and me trousers were at the right height and all that silly bloody shit that we go on with...now where you got to wear your shirt out, because your trousers cut off the flow to the stomas...and so on. So it's just that vanity part...once you get your head around that...And still, to this day, I haven't got my head around it." (Patient 8)

"If you sit in a meeting for more than an hour, you have to apologize for the noises that your stomach makes, and people look at you and you have to explain and you get to the point where it doesn't bother you anymore" (Patient 20)

"Because of the incontinence I can't drive too far. I used to drive down to see my family. But now if I've got to drive anywhere, I've got to stop maybe half or three quarters of an hour into the trip to change the pad" (Patient 3)

Minor theme: Loss of intimacy

"Intercourse isn't great for us. It's because I don't have a lot of sensation. So, it's a non-event for me really. And I always end up with a UTI afterwards. So it's, that's probably the only thing that sort of really slowed down" (Patient 23)

"In all honesty, the whole sex thing... it's gone. But my wife and I, we discussed that. For anyone that's got an active sex life, that is an issue. A big issue" (Patient 4)

"It's not a normal sex life" (Patient 3)

"The sexual side of things, I know that my prostate was all part of it, but I was told that things may improve and nothing has." (Patient 9)

Major theme 3: *The good days and bad days as a survivor*

"Psychologically, you have good days and bad days, but that was gonna happen when I had cancer. Anyway...that's just life" (Patient 23)

"My quality of life isn't what it was before. But I've still got a quality of life. There's still quality there. And I'm not like a vegetable, I can get up and do things. And I can contribute" (Patient 33)

"I try to stay upbeat and look to the positive rather than negative" (Patient 32)

"You just got to learn to accept your new self, I guess. That's what I've sort of done. I've accepted the way it is" (Patient 7)

"The positive is I'm still here and when I'm not sick I'm living life to the fullest" (Patient 33)

Minor theme: A change in outlook

"As weird as this is, I'm actually glad of my diagnosis because I was stuck in a rut, and I wasn't doing the things I loved and I was focusing way too much on work. And it's made me change how I am." (Patient 14)

"It's different...in a good way, because well, how lucky am I to be here? So, you do appreciate things a lot more" (Patient 15)

"I just try and look at it as how lucky am I that I've just been given a second chance of life." (Patient 33)

"I'm enjoying myself at the moment, that's all I can do. Just trying to put as much as I can into a day" (Patient 19)

"I just sort of think well, you've got to just sort of get on with it and sort of make the best of it" (Patient 22)

"I just feel grateful all the time" (Patient 12)

"I feel probably the best health that I've been in for a long time, because I'm always conscious now of my health. I think that, you know, that's a good thing" (Patient 31)

Minor theme: Living with uncertainty and fear of dying

"I live with a bit of fear, but I think that's just living with cancer. I think that's going to be a lifelong journey of coping with that fear...is it going to come back?" (Patient 23)

"Every little niggle you think, is that something?" (Patient 15)

"It's really, really stressful. And I try not to let it show...it's until you hear those words: Everything's fine." (Patient 33)

"You start looking for signs of other cancers. And that is a real mind game because you read stuff online, (about) metastasising to livers and lungs and all that sort of gear. And that

is scary. But you can't live like that, you've just got to keep on going through your CTs"
(Patient 7)

Minor theme: Lack of support and services

"After that 20 week hospitalisation, the only real contact I had was with my local GP and the community nurse, who was attending to the wound daily at that stage. And I felt quite alone, quite deserted." (Patient 18)

" I think it would be great if whether it was an outpatient service that you went in, and you saw the...physio and a dietitian...some sort of tailored, every three months for the first year or something? Because otherwise you're just left out there on your own." (Patient 20)

"Going home to a country area after two weeks. There's the nurses that called in...but they really didn't understand anything about stomas." (Patient 4)

"Being in Western Australia, away from Dr. X and the team is a little bit of an issue. It would be better if I lived five minutes away from the hospital. I'm sure it would be better."
(Patient 30)

Minor theme: Ripple effect of family and friends

"I was quite teary some days when X was in Sydney and I just thought, can we cope when we come home" (Carer 3)

"I just didn't realise that he was going to be in the ongoing pain that he's in... the amount of drugs that he's on. Sometimes I look at him, tell him something and then he forgets" (Carer 2)

"It was more what it done to my family, my wife was coming in almost every day...she stayed in Sydney for 10 weeks. What it done to her was more of a concern to me" (Patient 9)

" But he can't do anything...if anything happened to me, he would have to go into care"
(Carer 2)

"I didn't realize that I would have to change his urostomy bag. Which is fine. But there was nothing said about you may have to." (Carer 3)

"When we got home (my husband) had to make sure my wounds were clean and stuff, because I couldn't reach them or see them...how confronting that can be" (Patient 23)

CHAPTER 6: DEFINING PRIORITY OUTCOMES OF EXENTERATION

CHAPTER OVERVIEW

Chapter 6 addresses *Thesis Aim 1*: to address unwarranted variation in treatment decision-making in patients with LARC and LRRC. This chapter builds on the findings presented in *Chapters 4 and 5*, which reported the outcomes of pelvic exenteration for LARC and LRRC that are considered important by patients, carers and clinicians. These outcomes were then collated and distributed via iterative surveys, using a modified Delphi method, to patients, carers and international expert clinicians, to gain consensus as to the priority outcomes, i.e. those that are most critically important and based on which treatment decisions should be made. The results of this Delphi study are presented in *Chapter 6.1*.

CHAPTER 6.1




Priority outcomes of pelvic exenteration for rectal cancer: a patient, carer and clinician consensus

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Priority outcomes of pelvic exenteration for rectal cancer: a patient, carer, and clinician consensus

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Members of the EviSurg Collaborative Group are co-authors of this study and are listed under the heading Collaborators.

Introduction

Pelvic exenteration is the standard of care, and only potentially curative treatment option, for selected patients with locally advanced or recurrent rectal cancer. This complex procedure involves surgical resection of all anatomical structures involved by the tumour and typically requires the removal of multiple pelvic viscera, as well as major pelvic bone, blood vessels, and nerves, generally followed by complex reconstruction of these systems. Although potentially curative, such radical surgery may be associated with major morbidity (up to 60%), functional impairments, and reduction in quality of life^{1,2}. Therefore, whether or not pelvic exenteration should be recommended for an individual patient is a major and often difficult decision. The consequences of surgery must be weighed against the potential for cure, with consideration given to a patient's individual treatment goals and priorities.

Currently, decision-making around whether to recommend pelvic exenteration is based on individual surgeon or team experiences and does not follow an evidence-based approach. These decisions have traditionally been made with anticipated survival benefit as the main outcome of interest, with relative neglect of quality-of-life and functional outcomes. Furthermore, the views of patients, carers, and clinicians regarding which outcomes are most important and should guide decision-making have not been previously determined. It is also clear from recent comparative studies that there are dramatic differences in practices between specialist exenteration centres with respect to both patient selection and treatment approach^{3,4}. This unwarranted variation in treatment decision-making may be, at least in part, due to lack of a standardized, reproducible, evidence-based approach to decision-making in this group of patients.

The aim of this study was to identify the pelvic exenteration outcomes that are considered most important by patients with locally advanced or recurrent rectal cancer, their carers, and treating clinicians. This will inform the development of an evidence-based surgical decision-making tool that can be used at the time of diagnosis to predict a range of individual patient outcomes (beyond survival alone).

Methods

This study was coordinated by the Surgical Outcomes Research Centre (SOuRCe) in conjunction with the Institute of Academic Surgery (IAS) at Royal Prince Alfred Hospital, Sydney, New South Wales, Australia. The study involved two phases. First, a longlist of outcomes of pelvic exenteration was generated by systematically reviewing the literature⁵ and conducting in-depth interviews with patients who had undergone exenteration surgery and their carers⁶. Second, longlisted outcomes were reviewed by a multidisciplinary committee and used to populate a three-round Delphi survey of patients, carers, and clinicians to identify the outcomes of highest priority to these stakeholder groups. The study protocol was published a priori⁷ and was reported according to the Conducting and REporting of DELphi Studies (CREDES) recommendations⁸. Ethical approval for this study was granted by the Royal Prince Alfred Hospital Human Research Ethics Committee (X22-0422 and 2022/ETH02659).

Phase one: outcomes longlist

A systematic review of the contemporary literature (published between 1990 and 2023) was conducted to identify all reported outcomes of extended or exenterative multivisceral resections

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for locally advanced primary or recurrent rectal cancer⁵. Semi-structured interviews were then conducted to explore the experiences of patients who had undergone pelvic exenteration and their carers in depth, with a focus on the outcomes of surgery that they considered important⁶. Outcomes identified by the systematic review and interviews were then combined to generate a longlist. The longlist was reviewed by a multidisciplinary committee that included specialist surgeons, an experienced surgical outcomes researcher, a pelvic exenteration nurse specialist, and two patient advocates. During this review process, outcomes addressing the same or similar concepts were combined as 'standardized outcomes'. Standardized outcomes were excluded when they were considered to be of minimal clinical relevance by the committee. Standardized outcomes were assigned a domain and a lay definition, and were used to populate the first round of the Delphi survey. Domains were based on those proposed by the Core Outcome Measures in Effectiveness Trials Initiative, but modified for applicability to pelvic exenteration patients for the purposes of this study⁹.

Phase two: Delphi survey

The Delphi process involved three iterative surveys, which were distributed using the online software known as Research Electronic Data Capture (REDCap), with reminders sent at 10 and 20 days for each round. Participants were recruited from three stakeholder groups:

- Clinicians with experience in pelvic exenteration for locally advanced and recurrent rectal cancer. An invitation to participate was distributed to members of the PelvEx Collaborative (an international collaborative of clinicians with experience managing advanced pelvic tumours), Australia and New Zealand pelvic exenteration multidisciplinary teams and to corresponding authors of publications identified in the systematic review described above⁵. Although the first-round invitation was sent to approximately 350 clinicians, participants were encouraged to forward the first-round invitation e-mail to their local networks, including multidisciplinary teams, and therefore the total number of invited clinicians is unknown.
- Patients who had undergone pelvic exenteration for locally advanced primary or recurrent rectal cancer. A total of 50 patients who had indicated an interest in participating in the second phase during the semi-structured interviews conducted in the first phase (see above) were invited to participate.
- Carers for patients who had undergone pelvic exenteration for locally advanced primary or recurrent rectal cancer. Patients who participated were invited to forward the invitation e-mail to their carers.

First-round survey

The first-round survey was piloted on a patient representative, an experienced qualitative researcher, and two clinicians, and was then revised before distribution. The first section of the survey captured participant demographic information, including type of rectal cancer (primary or recurrent) and time since exenteration surgery (for patients), and information about specialty training and level of experience managing exenteration patients (for clinicians). The second section of the survey included a list of standardized outcomes identified during the first phase, with associated lay definitions. Participants rated the importance of each outcome using a nine-point Likert scale (limited importance, 1–3; important, but not critical, 4–6; and critically important, 7–9).

A final open question allowed participants to list additional outcomes using free text.

Second-round survey

Outcomes with a mean score of one to three during the first round were discarded, whereas those scoring four to nine (important, but not critical, or critically important), and any additional unique outcomes suggested by participants, were included in the second-round survey. For each outcome, participants were provided with their score for the first round, as well as the mean score from their stakeholder group, and were asked to reflect on this information before scoring each outcome using the same nine-point Likert scale. Before the third round, each outcome was assessed for consensus according to criteria proposed by Williamson *et al.*¹⁰, which were defined a priori⁷:

- Consensus in: 70% or more of respondents within a participant group rate the outcome as critically important (7–9) and 15% or fewer rate the outcome as of limited importance (1–3).
- Consensus out: 70% or more of respondents within a participant group rate the outcome as of limited importance and 15% or fewer rate the outcome as critically important (7–9).
- No consensus: neither of the above criteria are met.

Third-round survey

Outcomes meeting 'consensus in' criteria within all stakeholder groups during the second round were used to populate the third-round survey. Participants were asked to give each outcome a score between 0 (less important) and 100 (more important) to indicate its relative importance in relation to the other listed outcomes.

Statistical analysis

Demographic information and survey results are summarized using descriptive statistics. During the third-round survey, outcomes were ranked from one to nine for each stakeholder group according to the median score (of importance) attributed by participants within that group (where the outcome with the highest median score was assigned a rank of '1' and the outcome with the lowest median score was assigned a rank of '9'). For each outcome, the ranks provided by stakeholder groups were summed to give a combined rank for the entire cohort, where the lowest value represented the most important outcome. This approach was adopted to ensure the final priority outcomes were equally representative of the three stakeholder groups, despite uneven numbers of participants within these groups.

Results

Phase one: outcomes longlist

Results of the systematic review and interviews with patients and their carers have been previously reported⁵. In brief, 2765 outcomes were identified from the literature (1157 after exclusion of duplicates) and combined with 46 outcomes extracted from transcripts of interviews with 34 patients and 5 carers. During the multidisciplinary committee evaluation process duplicates were removed before outcomes were reviewed, merged, and piloted. At the conclusion of this process, there were 70 standardized outcomes that were carried forward to the Delphi process and used to populate the first-round survey.

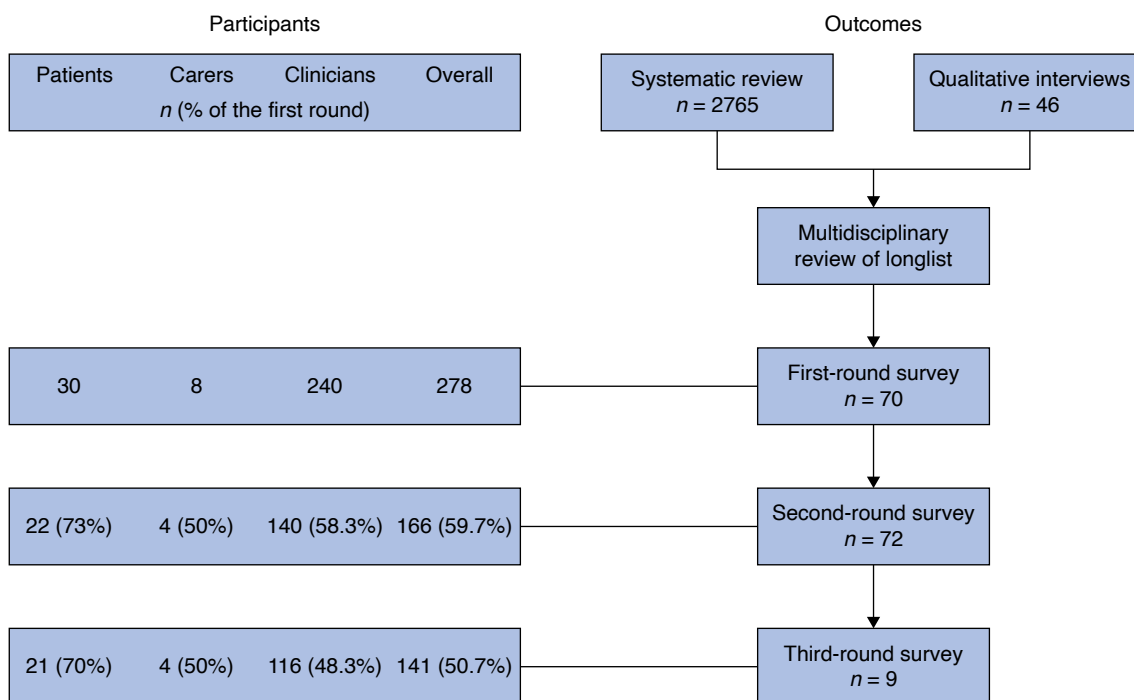


Fig. 1 Flow chart outlining the numbers of participants and outcomes included in each round of the Delphi survey

Phase two: Delphi survey

A total of 278 participants (30 patients, 8 carers, and 240 clinicians) responded to the invitation to participate and completed the first round of the survey, of which 166 (59.7%) completed the second round of the survey and 141 (50.7%) completed the third round of the survey (Fig. 1). Demographic information of the participating patients and carers who completed all three rounds of the Delphi survey are presented in Table 1 and the demographic information of the participating clinicians who completed all three rounds of the Delphi survey are presented in Table 2. In total, 11 (52%) and 10 (48%) patients had locally advanced primary and locally recurrent rectal cancer respectively and the median time since exenteration surgery was 36 (interquartile range 24–50) months. All four carers were spouses of patients who had undergone exenteration and all were female. The majority of clinicians were surgeons (78%); however, there was a range of multidisciplinary experts, including oncologists, nurses, radiologists, and dietitians.

First-round survey

The mean score according to each stakeholder group for the 70 outcomes during the first round (and their lay definitions) is presented in Table S1. The participants suggested 46 additional outcomes in response to the open text question of the first round, from which 2 unique outcomes were identified and included in the second round ('decisional regret' and 'cost of treatment'). Because all outcomes had a mean score of 4–9, with no outcomes meeting the predefined criterion for exclusion after the first round (mean score of 1–3), 72 outcomes were carried forward to the second round.

Second-round survey

The consensus status for the 72 outcomes included in the second round are included in Table S2. There were nine outcomes that met

Table 1 Demographic information of the participating patients and carers who completed all three rounds of the Delphi survey (n = 25)

Characteristic	Value
Patients (n = 21)	
Age (years)	
30–50	3 (14)
51–70	13 (62)
>70	5 (24)
Sex	
Male	10 (48)
Female	11 (52)
Type of tumour	
Locally advanced primary rectal cancer	11 (52)
Locally recurrent rectal cancer	10 (48)
Time since exenteration surgery (months), median (interquartile range)	36 (24–50)
Carers (n = 4)	
Age (years)	
30–50	0
51–70	2 (50)
>70	2 (50)
Sex	
Male	0
Female	4 (100)
Relationship to patient who underwent exenteration	
Spouse	4 (100)
Immediate family	0
Other	0

Values are n (%) unless otherwise indicated.

'consensus in' criteria among all stakeholder groups (patients, carers, and clinicians) and were therefore considered the final priority outcomes.

Third-round survey

The nine priority outcomes were distributed in the third round and scores of relative importance attributed to these outcomes

Table 2 Demographic information of the participating clinicians who completed all three rounds of the Delphi survey (n = 116)

Characteristic	Value
Age (years)	
<31	3 (2.6)
31–50	66 (56.9)
51–70	47 (40.5)
Sex	
Male	84 (72.4)
Female	32 (27.6)
Profession	
Surgeon	91 (78.4)
Nurse	7 (6.0)
Radiation oncologist	4 (3.4)
Anaesthetist	4 (3.4)
Medical oncologist	3 (2.6)
Dietitian	3 (2.6)
Radiologist	2 (1.7)
Nuclear medicine specialist	1 (0.8)
Administrator	1 (0.8)
Region	
Europe and Central Asia	57 (49.1)
Australasia and Pacific	31 (26.7)
North America	20 (17.2)
East Asia	3 (2.6)
Latin America	3 (2.6)
South Asia	2 (1.7)
Dedicated exenteration training (surgeons only)	
Yes	58 (50.0)
No	28 (24.1)
Not applicable	30 (25.9)
Experience treating advanced and recurrent rectal cancer (years)	
<5	29 (25.0)
5–10	29 (25.0)
11–20	38 (32.8)
>20	20 (17.2)
Access to dedicated pelvic oncology MDT meeting	
Yes	106 (91.4)
No	10 (8.6)
Annual centre pelvic exenteration case volume, median (interquartile range)	30 (18–50)

Values are n (%) unless otherwise indicated. MDT, multidisciplinary team.

by each stakeholder group are presented in [Table 3](#). The outcomes of highest importance to patients were ‘overall survival’ (median score = 90.0), ‘disease-free survival’ (median score = 89.0), ‘mobility’ (median score = 88.0), and ‘resection margins’ (median score = 88.0). The outcomes of highest importance to carers were ‘distant recurrence’ (median score = 94.5), ‘resection margins’ (median score = 92.5), and ‘local recurrence-free survival’ (median score = 91.0). The outcomes of highest importance to clinicians were ‘resection margins’ (median score = 90.0), ‘overall survival’ (median score = 85.0), ‘local recurrence-free survival’ (median score = 85.0), and ‘global quality of life’ (median score = 85.0). Patient responses demonstrated less discrimination in importance between outcomes (median score range 83.0–90.0) compared with carers (77.5–94.5) and clinicians (70.0–90.0). When the ranks of individual stakeholder groups were combined, the outcomes of highest importance to the overall cohort were ‘resection margins’, ‘local recurrence-free survival’, and ‘overall survival’.

Discussion

This study identifies nine outcomes of pelvic exenteration surgery that are considered of highest priority by patients, carers, and clinicians. These nine ‘priority outcomes’ cover four broad

domains: survival (overall survival, disease-free survival, and local recurrence-free survival), cancer recurrence (distant recurrence), patient-reported outcomes and functioning (psychological functioning, physical functioning, global quality of life, and mobility) and pathological outcomes (resection margins). Priority outcomes were considered critically important by 70% or more of participants in each stakeholder group and were selected after a comprehensive review of 1157 unique outcomes reported in the contemporary literature (published between 1990 and 2023) and 46 additional outcomes from patient and carer interviews. Importantly, the rigorous consensus methodology used to identify the high-priority outcomes in this study ensured that patients, carers, and clinicians were equally represented.

When scored and ranked by participants according to relative importance, ‘resection margins’, ‘local recurrence-free survival’, and ‘overall survival’ were considered the most important outcomes of exenteration surgery for locally advanced primary and recurrent rectal cancer. Importantly, this rank order may be less discriminatory than it appears because all nine outcomes were, by definition, already considered critically important and were scored highly in the third-round survey, particularly by patients, with little discrimination as to the relative importance of outcomes. Therefore, it is difficult to draw conclusions about differences in priorities between stakeholder groups. Nonetheless, the finding that ‘resection margins’ was ranked highest overall by participants in this study is noteworthy. R0 resection is strongly associated with improved overall survival^{11,12}, disease-free survival¹³, and local recurrence-free survival¹⁴, as well as lower patient-reported long-term pain scores¹⁵ and quality of life¹⁶. On this basis, achieving clear resection margins has become the ‘holy grail’ of exenterative surgery and it is likely that patients and their carers are counselled extensively by their treating clinicians about the importance of pathology margin status. However, resection margins remain only a surrogate marker for the more clinically meaningful outcomes identified in this study: survival, disease recurrence, and quality of life.

The priority outcomes identified in this study will form the outcomes of interest of a risk prediction tool being developed for patients with locally advanced primary or recurrent rectal cancer⁷. Developed using prospectively collected data from Royal Prince Alfred Hospital, a high-volume exenteration centre, this tool aims to predict the priority outcomes of exenteration surgery for individual patients based on preoperative information (such as demographic and disease characteristics). The goal of the risk prediction tool is to support reproducible, evidence-based decision-making for patients with locally advanced and recurrent rectal cancer, by quantifying the predicted outcomes of surgery for individual patients. Importantly, unlike many risk prediction tools and nomograms, which generally predict survival as the single outcome of interest^{17,18}, the outcomes identified in this study and included in the proposed risk prediction tool address a range of outcome domains considered critically important by patients and carers, as well as clinicians. Although treatment decision-making must always be individualized, with consideration given to a specific patient’s goals and priorities, the ability to predict the priority outcomes identified in this study may serve as a framework for decision-making. The broader goal is to address the issue of unwarranted variation in treatment decision-making both at the time of diagnosis (that is whether an individual patient should be referred to a specialist exenteration centre) and by

Table 3 Final priority outcomes of pelvic exenteration, which met ‘consensus in’ criteria among patient, carer, and clinician stakeholder groups

Priority outcome	Lay description	Patients (n = 21)		Carers (n = 4)		Clinicians (n = 116)		Combined rank
		Median	Rank	Median	Rank	Median	Rank	
Survival								
Overall survival	The length of time until death from any cause (including cancer and non-cancer causes)	90.0	1	77.5	9	85.0	2	3
Disease-free survival	The length of time a person lives without cancer coming back	89.0	2	88.5	5	80.0	5	4
Local recurrence-free survival	The length of time a person lives without cancer coming back in the pelvis	86.0	6	91.0	3	85.0	2	2
Cancer recurrence								
Distant recurrence	The cancer coming back elsewhere in the body, other than the pelvis	83.0	9	94.5	1	70.0	8	8
Patient-reported outcomes and functioning								
Psychological functioning	Ability to think, reason, remember, and make decisions, as well as experience and cope with emotions, including fear of the cancer coming back	84.0	8	80.5	8	76.0	7	9
Physical functioning	Ability to perform daily activities, such as walking, climbing stairs, and carrying out self-care tasks	87.0	5	88.0	6	80.0	5	5
Global quality of life	Overall well-being, including physical health, emotional well-being, social relationships, and life satisfaction	85.0	7	81.5	7	85.0	2	5
Mobility	Being able to walk or get around	88.0	3	90.5	4	70.0	9	5
Pathological outcomes								
Resection margins	Surgical removal of the entire tumour in one piece, with clear margins	88.0	3	92.5	2	90.0	1	1

The median score of relative importance and corresponding rank for each stakeholder group is presented, as well as the combined rank.

exenteration multidisciplinary teams (that is whether an individual patient should be offered surgery).

A possible secondary application of the priority outcomes is to direct future research, including selection of endpoints and outcomes in database and trial design. The priority outcomes identified in this study address four domains: survival, cancer recurrence, patient-reported outcomes and functioning, and pathological outcomes. In the systematic review component of this study, which included 156 studies of exenterative or multivisceral resections for locally advanced primary or recurrent rectal cancer, the most commonly reported domain was ‘complications’ (146 studies, 94%); however, no complication-related outcomes reached consensus criteria to be included as priorities in this study. Conversely, four of nine priority outcomes were categorized as ‘patient-reported outcomes and functioning’, which was the least commonly reported domain in the literature (26% of studies)⁵. This highlights the disparity between consensus-based priority outcomes (that is considering the views of patients and carers) and those commonly reported in the contemporary literature (that is by clinicians). In future, the identified priority outcomes should be considered during study design and, in particular, prospective patient-reported outcome measurement should be considered a mandatory component of audit and quality assessment at specialist exenteration units.

The strengths of this study include patient involvement in its design and conduct, particularly in the multidisciplinary review of outcomes and piloting of the first-round survey. Importantly, for participating patients, the median time since exenteration surgery was 36 months, which ensured that the views of those living with the long-term consequences of surgery were

captured (beyond the immediate recuperation interval). The outcome longlist development process was comprehensive, involving an extensive review of outcomes reported in the contemporary literature (2756 outcomes from 156 studies) and those extracted from in-depth interviews with a large sample of patients and carers (34 patients and 5 carers). This ensured that a wide range of outcomes was captured and considered during the Delphi phase of the study. The consensus criteria, which were defined a priori, ensured that the final priority outcomes reflected the shared priorities of patients, carers, and an international group of exenteration clinicians, despite unequal numbers of participants in each stakeholder group. The attrition rate across rounds was acceptable at 49% for the overall cohort. A limitation of the study is that the patients (and their carers) invited to participate were from one country (Australia) due to practical limitations with regard to seeking ethical approval in multiple countries. Importantly, the clinician cohort represented 22 countries. The number of clinicians invited to participate in the surveys (and therefore the denominator in the calculation of response rate) is unknown due to the use of snowball sampling, where participants were asked to forward the invitation to their local multidisciplinary teams.

The priority outcomes identified in this study reflect the shared priorities of patients who have undergone pelvic exenteration for locally advanced or recurrent rectal cancer, their carers, and treating clinicians. These priorities include survival, cancer recurrence, quality of life, and resection margin status. These findings will inform the development of a risk prediction tool, which aims to predict these consensus-based priority outcomes for individual patients using information available at the point of diagnosis and to facilitate reproducible,

evidence-based decision-making, thus addressing the issue of unwarranted variation in treatment decision-making in this group of patients.

Collaborators

EviSurg Collaborative Group

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Author contributions

Kilian G. M. Brown (Conceptualization, Data curation, Formal analysis, Writing—original draft), James Morkaya (Conceptualization, Data curation, Formal analysis, Writing—review & editing), Michael J. Solomon (Conceptualization, Methodology, Supervision, Writing—review & editing), Kheng-Seong Ng (Conceptualization, Formal analysis, Methodology, Writing—review & editing), Kate White (Conceptualization, Data curation, Methodology, Writing—review & editing), Paul Sutton (Conceptualization, Methodology, Writing—review & editing), Desmond C. Winter (Conceptualization, Data curation, Writing—review & editing), Daniel Steffens (Conceptualization, Methodology, Data curation, Supervision, Writing—review & editing), and EviSurg Collaborative Group (Conceptualization, Methodology)

Disclosure

The authors declare no conflict of interest.

Supplementary material

Supplementary material is available at BJS online.

Data availability

Data can be made available, upon reasonable request, but requires ethical approval.

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The following tables and figures are included as supplementary information to Chapter 6.1.

Supplementary Table 1. Mean outcome scores during round 1 according to stakeholder group

Domain	Outcome	Lay description	Mean score in Round 1			
			Patients (N=30)	Carers (N=8)	Clinician (N=240)	Overall (N=278)
Surgical outcomes	Length of hospital stay	Time in hospital after surgery	5.4	5.3	5.9	6.9
	Operative time	Time taken to complete the operation	5.0	4.9	5.2	7.1
	Blood loss	The amount of blood loss that occurs during the operation	5.9	6.0	5.5	5.7
	Blood transfusion	The need for blood replacement (transfusion) during or after surgery	5.5	5.6	4.8	4.9
	Length of ICU stay	Time in the intensive care unit after surgery	5.6	5.7	5.2	6.4
	Return of bowel function	Recovery of normal bowel function after surgery, such as the ability to eat, digest, and have a bowel motion (including via a stoma bag)	5.8	5.6	6.6	6.0
	Discharge destination	The place where a patient goes after leaving hospital	5.9	5.8	6.4	7.1
	Permanent stoma rate	The need for one or more permanent stomas	5.2	4.9	6.4	7.6
	Analgesia use	The need for pain-relieving medications at any time after surgery	5.4	5.1	6.6	7.6
	Nutritional status	Nutrition levels after surgery (including weight and diet)	6.6	6.6	6.4	7.0
Patient reported outcomes and functioning	Urinary function	Ability to make, store and pass urine normally	6.5	6.4	6.8	6.0
	Psychological and Emotional functioning	Ability to think, reason, remember, make decisions, as well as experience and cope with emotions	7.3	7.2	7.5	8.0
	Physical functioning	Ability to perform daily activities, such as walking, climbing stairs and carrying out self-care tasks	7.5	7.5	7.6	8.0
	Colorectal-specific quality of life	Well-being relating to bowel health, including bowel function, gastrointestinal symptoms and stoma use	7.1	7.1	7.1	7.3
	Pain		7.0	7.1	6.0	6.1
	Global quality of life	Overall well-being, including physical health, emotional well-being, social relationships and life satisfaction	7.7	7.7	7.4	8.1
	Sexual function	Ability to engage in and enjoy sexual activities and intimacy	5.5	5.7	4.6	4.9
	Long term bowel function	Symptoms relating to bowel function, including diarrhoea, emptying difficulties, changes to stoma output, frequency, incontinence and urgency	6.6	6.6	6.6	6.4
	Mobility	Being able to walk or get around	7.5	7.5	7.5	8.0
	Social functioning	Ability to engage in and navigate social interactions, relationships, and activities	7.1	7.1	6.9	7.9
Role function	Ability to fulfill responsibilities and tasks in various domains of life, such as work, family, and social interactions	7.1	7.1	7.1	7.3	

	Energy / vitality	Overall sense of energy, vigor, and liveliness	6.7	6.7	6.7	7.1
	Lower limb function	Being able to feel and move legs normally	7.0	7.0	6.6	7.6
	Appetite and weight		6.1	6.2	5.6	7.0
	Stoma-related problems	Problems managing stoma/s such as leakage, sore skin or difficulty attaching the bag	6.4	6.5	6.1	6.7
Pathological outcomes	Resection margins	Surgical removal of the entire tumour in one piece, with clear margins	8.6	8.6	8.4	8.4
Cancer recurrence	Disease recurrence	The cancer coming back	8.2	8.2	8.2	7.9
	Local recurrence	The cancer coming back in the pelvis	8.2	8.3	7.9	7.7
	Distant recurrence	The cancer coming back elsewhere in the body, other than the pelvis	7.7	7.6	8.0	8.0
Survival	Overall survival	The length of time until death from any cause (including cancer and non-cancer causes)	8.0	8.1	7.6	8.0
	Disease free survival	The length of time a person lives without cancer coming back	7.8	7.7	7.7	8.3
	Disease specific survival	The length of time until death from cancer	7.5	7.5	7.4	7.6
	Survival with disease	The length of time a person lives after the cancer has come back	7.0	7.0	6.9	7.6
	Local recurrence free survival	The length of time a person lives without cancer coming back in the pelvis	7.6	7.7	7.4	7.7
Overall/non-specific complications	Perioperative mortality	Death during or while recovering from surgery	8.0	8.2	6.7	6.1
	Postoperative complications	Number / chance of complications after surgery	7.0	7.1	6.2	6.9
	Complication severity	Seriousness of complications after surgery	7.4	7.5	6.2	7.6
	Surgical reintervention	Complications that require another operation	6.8	6.9	6.3	6.9
	Haemorrhage	Bleeding during or after surgery	6.5	6.6	5.7	7.0
	Hospital readmission	Being re-admitted to hospital after surgery	5.7	5.7	5.5	6.4
	Late or long-term complications	Complications that occur months to years later	6.6	6.7	6.0	7.1
	Unplanned ICU admission	Being unexpectedly admitted to intensive care due to a complication	5.9	5.9	5.7	6.4
	Cause of postoperative mortality	The cause of death during or while recovering from surgery	6.9	7.1	5.6	7.3
	Intraoperative complication rate	Complications during surgery	6.5	6.6	5.9	6.3
Wound-related complications	Perineal wound dehiscence	Separation or opening of the edges of the surgical wound on your bottom	6.4	6.4	6.3	5.7
	Perineal flap loss or dehiscence	Separation or death of the skin flap used to repair the wound around your bottom	6.7	6.8	6.1	6.6

	Abdominal wall hernia	Bulging of organs or tissues through the wall of the abdomen	5.5	5.4	6.0	6.9
	Perineal hernia	Bulging of organs or tissues through the perineum (the area between the bottom and genitals)	5.8	5.7	6.0	7.0
Gastrointestinal complications	Anastomotic leak, gastrointestinal	Leakage of bowel contents from the join between two segments of bowel	7.3	7.5	6.0	7.6
	Ileus	Temporary disruption or blockage of normal intestinal movement	5.2	5.0	6.0	7.6
	Intestinal obstruction	Blockage of the bowel causing pain, abdominal swelling, vomiting or requiring a change to diet	6.1	6.1	6.3	6.7
	Gastrointestinal injury/perforation	A hole or rupture in the wall of the bowel	7.1	7.2	6.7	7.6
	Other gastrointestinal complications	Other complications relating to the stomach or bowel after surgery	6.0	5.9	6.3	7.4
Urinary complications	Anastomotic leak, urinary	Leakage of urine from a surgical connection of the urine system	7.1	7.2	6.3	7.4
	Ureteric stricture	Abnormal narrowing of the ureter, the tube which drains urine from the kidney	6.7	6.7	6.5	7.4
	Other urological complications	Other complications after surgery relating to the urinary system	6.2	6.1	6.3	7.0
Vascular complications	Venous thromboembolism	Developing a blood clot (thrombus) in a vein, typically in the legs or lung	6.2	6.2	5.6	7.6
	Limb ischaemia	Inadequate blood flow to the legs	7.2	7.5	5.6	7.0
	Other vascular/haematological complications	Complications after surgery relating to the blood or blood vessels	6.3	6.4	5.4	6.9
Other complications	Nerve injury	Injury to a major pelvic nerve during surgery, potentially causing problems with leg movement or feeling	7.0	7.0	6.9	7.3
	Other neurological complications	Other complications after surgery relating to the nervous system	6.2	6.3	5.9	6.9
	Infection-related complication	Infection after surgery anywhere in the body, such as a urine, wound or abdominal infection	6.0	5.9	6.2	7.4
	Respiratory complications	Complications after surgery relating to the lungs, such as a collapsed lung or pneumonia	5.8	5.8	5.4	6.9
	Cardiac complications	Complications after surgery relating to the heart, such as a heart attack or abnormal heart rhythm	6.0	6.1	5.5	7.0
	Renal complications	Problems with kidney function after surgery	6.1	6.0	6.0	7.3
	Ostomy complications	Problems relating to the stoma, such as a bulge next to the stoma, protrusion of excess bowel through the stoma, infection in the skin or deeper tissue around the stoma, or shrinkage of the stoma opening	6.0	6.0	6.0	7.9
	Empty pelvic syndrome	Complications due to the empty space left after pelvic organs are removed, such as fluid collections, problems with perineal wound healing (between the bottom and genitals), leakage of abdominal or bowel fluid, or bulging	6.2	6.2	6.0	6.9
	Miscellaneous complications	Other complications after surgery not listed above	5.1	5.1	4.9	6.0
Miscellaneous	Relief of tumour related symptoms	Relief of symptoms related to the tumour, such as pain, a mass, or discharge	7.5	7.7	6.2	6.9
	Carer impact	Psychological, emotional or physical consequences for the patient's carer after surgery	6.9	6.8	7.4	8.6

Supplementary Table 2. Consensus status of outcomes included in Round 2 according to stakeholder group

Domain	Outcome	Consensus status after round 2		
		Carers (N=4)	Patients (N=22)	Clinicians (N=140)
Surgical outcomes	Length of hospital stay	IN	No Consensus	No Consensus
	Operative time	IN	No Consensus	No Consensus
	Blood loss	No Consensus	No Consensus	No Consensus
	Blood transfusion	No Consensus	No Consensus	No Consensus
	Length of ICU stay	No Consensus	No Consensus	No Consensus
	Return of bowel function	No Consensus	No Consensus	No Consensus
	Discharge destination	No Consensus	No Consensus	No Consensus
	Permanent stoma	No Consensus	No Consensus	No Consensus
	Analgesia use	IN	No Consensus	No Consensus
	Nutritional status	IN	No Consensus	No Consensus
Patient reported outcomes and functioning	Urinary function	No Consensus	No Consensus	No Consensus
	Psychological function	IN	IN	IN
	Physical functioning	IN	IN	IN
	Colorectal Specific Quality of Life	IN	No Consensus	No Consensus
	Pain	IN	No Consensus	No Consensus
	Global quality of life	IN	IN	IN
	Sexual function	No Consensus	No Consensus	No Consensus
	Long term bowel function	No Consensus	No Consensus	No Consensus
	Mobility	IN	IN	IN
	Social functioning	IN	No Consensus	IN
	Role function	IN	No Consensus	IN
	Energy/Vitality	IN	No Consensus	No Consensus

	Lower limb function	IN	No Consensus	No Consensus
	Appetite and weight	No Consensus	No Consensus	No Consensus
	Stoma-related problems	No Consensus	No Consensus	No Consensus
	Decisional regret	No Consensus	No Consensus	No Consensus
Pathological outcomes	Resection margins	IN	IN	IN
Cancer recurrence	Disease recurrence	No Consensus	IN	IN
	Local recurrence	No Consensus	IN	IN
	Distant recurrence	IN	IN	IN
Survival	Overall Survival	IN	IN	IN
	Disease free survival	IN	IN	IN
	Disease specific survival	No Consensus	IN	IN
	Survival with disease	IN	No Consensus	IN
	Local recurrence free survival	IN	IN	IN
Overall/non-specific complications	Perioperative mortality	No Consensus	No Consensus	IN
	Postoperative complications	IN	No Consensus	IN
	Complication severity	No Consensus	No Consensus	IN
	Surgical re-intervention	No Consensus	No Consensus	IN
	Haemorrhage	No Consensus	No Consensus	No Consensus
	Hospital readmission	No Consensus	No Consensus	No Consensus
	Late or long term complications	IN	No Consensus	No Consensus
	Unplanned ICU admission	No Consensus	No Consensus	No Consensus
	Cause of post-operative mortality	IN	No Consensus	IN
	Intraoperative complications	No Consensus	No Consensus	No Consensus
Wound-related complications	Perineal wound dehiscence	No Consensus	No Consensus	No Consensus
	Perineal flap loss or dehiscence	No Consensus	No Consensus	No Consensus
	Abdominal wall hernia	IN	No Consensus	No Consensus
	Perineal hernia	IN	No Consensus	No Consensus

Gastrointestinal complications	Anastomatic leak, gastrointestinal	IN	No Consensus	IN
	Ileus	IN	No Consensus	No Consensus
	Intestinal obstruction	IN	No Consensus	No Consensus
	Gastrointestinal injury/perforation	IN	No Consensus	IN
	Other gastrointestinal complications	IN	No Consensus	No Consensus
Urinary complications	Anastomatic leak, urinary	IN	No Consensus	IN
	Ureteric stricture	IN	No Consensus	No Consensus
	Other urological complications	IN	No Consensus	No Consensus
Vascular complications	Venous thromboembolism	IN	No Consensus	No Consensus
	Limb ischaemia	IN	No Consensus	IN
	Other vascular/haematological complications	IN	No Consensus	No Consensus
Other complications	Nerve injury	IN	No Consensus	IN
	Other neurological complications	IN	No Consensus	No Consensus
	Infection related complications	IN	No Consensus	No Consensus
	Respiratory complications	IN	No Consensus	No Consensus
	Cardiac complications	No Consensus	No Consensus	No Consensus
	Renal complications	IN	No Consensus	No Consensus
	Ostomy complications	IN	No Consensus	No Consensus
	Empty pelvic syndrome	No Consensus	No Consensus	No Consensus
	Miscellaneous complications	IN	No Consensus	No Consensus
Miscellaneous	Relief of tumour related symptoms	IN	No Consensus	IN
	Carer impact	IN	IN	No Consensus
	Cost of treatment	No Consensus	No Consensus	No Consensus

CHAPTER 7: PREDICTING PRIORITY OUTCOMES OF EXENTERATION PREOPERATIVELY

CHAPTER OVERVIEW

Chapter 7 addresses *Thesis Aim 1*: to address unwarranted variation in treatment decision-making in patients with LARC and LRRC. This chapter follows on from *Chapters 6*, where consensus-based priority outcomes of pelvic exenteration were defined. In *Chapter 7*, multivariable regression analysis was conducted using an institutional database to identify independent predictors of the priority outcomes, using information available preoperatively at the point of diagnosis.

CHAPTER 7.1

Preoperative predictors of consensus-derived priority outcomes of pelvic exenteration for locally recurrent rectal cancer: Results of the mixed-methods EviSurg study

Chapter 7.1 is under peer review at the time of thesis submission:

Brown KGM, Ng KS, Solomon MJ, Vu J, Lo S, Sutton P, EviSurg Collaborative Group; Steffens D. Preoperative predictors of consensus-derived priority outcomes of pelvic exenteration for locally recurrent rectal cancer: Results of the mixed-methods EviSurg study. *Manuscript under peer review*.

ABSTRACT

Objective: To identify preoperative predictors of priority outcomes following pelvic exenteration for locally recurrent rectal cancer (LRRC), specifically R0 resection, overall survival, and quality of life (QOL).

Summary Background Data: For patients with LRRC, the potential benefit of exenteration (long-term disease control or cure) must be weighed against the morbidity and functional consequences of surgery. Consensus-derived priority outcomes of exenteration were recently established through a comprehensive series of studies, and represent shared priorities of patients, carers, and clinicians.

Methods: Prospectively collected data for 300 patients who underwent pelvic exenteration for LRRC between 1994-2023 were extracted from an institutional database. Preoperative prediction models for R0 resection, overall survival, and global QOL at 12 months (priority outcomes) were developed using logistic regression (R0 resection), Cox regression (survival), and linear regression (QOL).

Results: R0 resection was achieved in 81% of patients (244/300). Neoadjuvant radiotherapy (OR=2.773, 95% CI=1.384-5.555, p=0.004) and the need for pelvic bone excision (OR=2.311, 95% CI=1.20-4.45, p=0.012) were associated with improved R0 resection rates. The need for sciatic nerve resection was associated with lower R0 resection rates (OR=0.365, 95% CI=0.177-0.753, p=0.006). Age was independently associated with overall survival (HR=1.022, 95% CI=1.006-1.039, p=0.007). Baseline QOL score was independently associated with a decline in QOL between baseline and 12 months (β =-1.011, 95% CI=-1.196 - -0.825, p<0.001).

Conclusions: These findings enable evidence-based prediction of R0 resection, survival and QOL following exenteration for LRRC. This will support development of clinical prediction

tools to improve patient selection, enhance preoperative counseling, and inform shared decision-making.

INTRODUCTION

Pelvic exenteration involves radical en bloc resection of multiple pelvic organs, bone, neurovascular and other soft tissue structures for the treatment of advanced pelvic tumours.^{1,2} For patients with locally recurrent rectal cancer (LRRC), salvage exenterative surgery is the only established treatment that may be potentially curative.^{1,3-5} This ultra-radical procedure is, however, associated with significant morbidity, permanent changes to body image and function, and has consequent implications for post-surgical quality of life (QOL).⁶⁻⁸ Although the ultimate decision to undergo pelvic exenteration is shared between the treating clinician/s and patient, this is informed and heavily influenced by the multi-disciplinary team (MDT) recommendation for or against surgery. This represents a major treatment decision where the potential for long term disease control or cure must be weighed against the consequences of surgery.⁹ Currently, the MDT decision-making process is based on institutional or individual clinician experiences and an evidence-based approach to decision-making that is reproducible both within and between exenteration centres is lacking^{10,11}.

Priority outcomes of pelvic exenteration for rectal cancer have been recently defined, and include nine outcomes relating to survival, cancer recurrence, QOL, and resection margin status.¹² These outcomes of surgery, defined using rigorous consensus methodology, were considered the most important by patients, carers and clinicians, and represent the shared priorities of these groups. This study aimed to identify preoperative predictors of the identified priority outcomes for patients with LRRC. It is hoped that identification of patient and disease-related factors which predict priority outcomes may facilitate evidence-based, individualised treatment recommendations, based on the anticipated outcome of surgery for an individual patient.¹³

MATERIALS & METHODS

This study was part of a multi-phase, mixed methods research program which aimed to address variation and facilitate standardisation in treatment decision making for patients with LRRC.¹³ After extracting all previously reported outcomes of pelvic exenteration surgery by systematic review of the contemporary literature,¹⁴ and exploring the perspectives of patients and their carers as to the outcomes of importance through in-depth interviews,^{8, 9} identified outcomes were reviewed by a multi-disciplinary research committee, refined, and then used to populate a three round Delphi study of patients, carers and international experts in pelvic exenteration. The Delphi studied gained consensus among these stakeholder groups as to the outcomes of highest priority after exenteration, and based on which treatment decisions should be made.¹² The current study aimed to identify preoperative factors which predict these priority outcomes using data from a high volume referral centre.

Data from consecutive patients who underwent pelvic exenteration for LRRC with curative intent at Royal Prince Alfred Hospital, Sydney, Australia between 1st September 1994 and 1st January 2023 were extracted from a prospectively maintained institutional database. PE was defined as the en bloc resection of at least three of five pelvic compartments and/or resection of bone or lateral neurovascular structures.¹⁵ Multidisciplinary-based patient selection, multimodal treatment planning, and operative techniques utilised at the authors' centre have been previous described.¹⁶ R0 resection rate, overall survival, and global QOL were selected as the outcomes of interest from the nine priority outcomes.¹² These were selected based on their previously ranked importance by patients, carers and clinicians, and to ensure all domains within the priority outcomes were reflected (survival, cancer recurrence, QOL, margin status).¹²

R0 resection was defined as any evidence of normal tissue between the cancer and the closest inked resection margin. R1 (microscopic resection margin involvement) and R2 (macroscopic resection margin involvement) were grouped to create a dichotomised resection margin endpoint of R0 vs. R1/2. Overall survival time was measured from the date of surgery to the date of last follow up or date of death, and estimated using the Kaplan Meier method. QOL was measured using the Functional Assessment of Cancer Therapy – Colorectal (FACT-C)¹⁷ instrument and was completed by participants enrolled in the authors' ongoing long-term QOL after pelvic exenteration prospective cohort study¹⁸ at baseline (prior to surgery) and 12 months after surgery. The FACT-C consists of five domains and the total score ranges 0 to 136 where higher scores represent better QOL.

Candidate variables that were considered potential preoperative predictors of the selected outcomes were identified based on a recent systematic review¹⁴ and expert opinion of the authorship group. These included patient age at the time of surgery, gender, ASA score, time from primary rectal cancer treatment to exenteration (months), local recurrence vs. local re-recurrence, neoadjuvant chemotherapy and radiotherapy prior to exenteration (within 6 months), presence of synchronous metastases, local complication at presentation (local perforation, abscess or bowel obstruction), preoperative QOL, and the need for pelvic bone, sciatic nerve or major vascular (common or external iliac vessel) resection. Variables that were not captured within the existing, prospective database were retrospectively collected from patient medical records.

Statistical analysis

Continuous variables were reported as mean (standard deviation [SD]) for normally distributed variables and as median (interquartile range [IQR] or range) for non-normal distributions.

Categorical variables were reported as frequencies and percentages. Logistic regression tested association(s) between R0 status and explanatory variables. Verification of patient death was obtained from medical records or the New South Wales State Registry of Births Deaths and Marriages. Survival estimates were modelled using the Kaplan-Meier function with log-rank test performed to determine difference in survival distributions. The association between explanatory variables and overall survival was assessed by Cox regression. Linear regression tested association between FACT-C score and explanatory variables. For each of the three regression models, multivariable modelling was performed by including variables that were potentially associated ($P < 0.20$) with the respective outcomes. $P < 0.05$ was considered significant. All analyses were performed using Stata version 18 (StataCorp LLC, College Station, TX, USA).

The study protocol was approved by the Royal Prince Alfred Hospital Human Research Ethics Committee prior to commencement.

RESULTS

Cohort characteristics

A total of 300 patients underwent pelvic exenteration with curative intent for LRRC during the study period. The majority of patients were male (193, 64%) and the median age was 62 years (IQR 54 - 68). Twenty-one patients (7%) had locally re-recurrent rectal cancer and 18 patients (6%) had synchronous metastases at the time of treatment for LRRC. Median baseline (preoperative) QOL was 97.7 (82.7 - 114). Two hundred and two (67%), 53 (18%) and 35 patients (12%) required excision of pelvic bone, nerve or common/external iliac vasculature, respectively. Baseline demographic data are summarised in Table 1.

Preoperative predictors of resection margin status

R0 resection was achieved in 244 patients (81%). Results of the univariate and multivariate analysis of preoperative factors associated with R0 resection are presented in Table 1. On multivariate analysis, preoperative variables that were independently associated with R0 resection included neoadjuvant radiotherapy (OR 2.773, 95% CI 1.384-5.555, p=0.004) and need for pelvic bone resection (OR 2.311, 95% CI 1.20-4.45, p=0.012), while need for sciatic nerve excision was associated with a lower odds of achieving an R0 resection (OR 0.365, 95% CI 0.177-0.753, p=0.006).

Preoperative predictors of overall survival

The median follow-up of the cohort was 2.8 years (interquartile range 1.57 - 4.82). The median overall survival was 45.5 months (95% CI 40.0 - 54.7). Results of the univariate and multivariate analysis of preoperative factors associated with overall survival are presented in Table 2. Age was the only preoperative factor independently associated with overall survival, with each additional year increasing the hazard of death by 2.2% (HR 1.022 per year, 95% CI 1.006-1.039, p=0.007). The proportional hazards assumption was not violated.

Preoperative predictors of quality of life

Two hundred and seven patients were enrolled in the prospective quality of life study and completed the FACT-C questionnaire prior to surgery, of which 96 patients (46%) completed it at 12 months follow up. The median change in FACT-C total score from baseline to 12 months was -2.9 points (IQR -19.3 - 17.2) (Table 3). Neoadjuvant radiotherapy was independently associated with an 8 point positive difference between 12 month and baseline QOL compared with patients who did not receive radiotherapy (β 8.419, 95% CI 0.796 - 16.042, p=0.031). A higher baseline FACT-C total score was independently predictive of a

decline in QOL between baseline and 12 months (β -1.011, 95% CI -1.196 - -0.825, $p < 0.001$).

The association between baseline QOL and change in QOL at 12 months is presented in Figure 1.

DISCUSSION & CONCLUSION

This study represents the culmination of a comprehensive, multi-phase research program designed to improve treatment decision-making for patients facing pelvic exenteration for LRRC. Following systematic identification of priority outcomes through patient, carer, and clinician consensus using Delphi methodology, this study of 300 patients demonstrates that specific preoperative factors can reliably predict the outcomes that matter most to all stakeholders. Independent predictors of R0 resection included neoadjuvant radiotherapy and the need for pelvic bone resection, while sciatic nerve resection was independently associated with R1/2 resection. Age was the sole predictor of overall survival, with younger patients having better outcomes. Patients with lower baseline QOL scores and those receiving neoadjuvant radiotherapy showed greater improvement in QOL at 12 months.

The identified predictors of R0 resection relate primarily to the local extent of tumour invasion, as might be expected. The finding that bone and major vascular resection predicted R0 resection likely reflect our unit's radical operative approach to LRRC, where any structure involved or even abutting the tumour is radically excised en bloc rather than shaved free,^{2, 16} resulting in a wider resection margin. En bloc sacrectomy accounted for the majority of pelvic bone resections and the consequent additional margin in LRRC tumours, which invariably have a presacral component, likely contributed to the finding of bone resection predicting R0 resection. Sciatic nerve involvement reflects extensive pelvic sidewall invasion, which is potentially due to tumour growth along the nerve fascicles as well as the limited anatomical

access to the sciatic notch and proximity of major blood vessels, and defines a subgroup at comparatively higher risk (albeit an acceptable rate) of R1 resection.¹⁹ The authors' unit also does not re-irradiate patients with LRRC who received radiotherapy during the treatment of their primary rectal cancer. While it is possible that the tumour response to radiotherapy increased the chance of R0 resection, patients in this series who received neoadjuvant radiotherapy were those who had radiotherapy omitted during primary treatment, and therefore may represent a biologically favourable group with lower risk of involved margins during surgery for their local recurrence.

Although long term survival is achievable in 30-50% of patients with LRRC following exenterative surgery,^{4, 10, 20-23} the finding that age was the only predictor of survival demonstrates the difficulty that multidisciplinary teams face in anticipating the long term oncological outcomes of exenteration for an individual patient prior to surgery. Similarly, with respect to predicting quality of life after surgery, only baseline QOL and neoadjuvant radiotherapy were significant predictors. Major neurovascular and bone resections have been historically considered highly morbid and to be associated with major QOL impairment after exenteration, but were not associated with change in QOL at 12 months from baseline in this study or other recent series.^{19, 24, 25} The finding that a lower baseline QOL predicts a comparatively positive change in postoperative QOL is likely explained by the relief that surgery provides for patients with severe tumour-related local symptoms at presentation, while those who are symptom-free preoperatively have a comparatively worse QOL trajectory in the first 12 months after surgery. This finding has been previously reported by the authors in a cohort of patients undergoing exenteration for refractory or recurrent squamous cell carcinoma of the anus, who were found to have an improvement in QOL even in the short term following

exenteration, likely due to a high rate of tumour-related local symptoms at baseline such as anal ulceration, fistulae, and pain.²⁶

While previous studies have identified predictors of patient outcomes after surgery for LRRC, these have mostly evaluated traditional clinicopathological factors as potential predictive variables, of which many are only available postoperatively.²⁷⁻²⁹ R0 resection margin status is well established as an important predictor of long term oncological outcomes, and other previously identified prognostic pathological factors include signet ring morphology, nodal involvement and lymphovascular invasion.^{28, 30-33} Many of these factors are not available preoperatively and therefore their utility in guiding preoperative decision making is limited. Furthermore, most previous studies have been limited by relatively small sample sizes, mixed cohorts with respect to tumour type (including both primary and recurrent rectal tumours), and use of arbitrary outcome measures. Our study involved a comprehensive, multi-phase, mixed methods approach to rigorously define and predict the most important outcomes of exenteration surgery for this group of patients. We evaluated only preoperative predictors of these outcomes to facilitate utility of the findings at the point of diagnosis. This study also overcomes some of the described issues with existing literature by its large sample size, homogenous cohort of LRRC patients and prospective data collection.

Although preoperative predictors were identified for the three selected priority outcomes in this study, initial exploratory work on the development of risk prediction scores for these outcomes suggest a lack of predictive discrimination for individual patient outcomes. Therefore, evaluation of additional predictive variables including molecular biomarkers based on preoperative liquid and tissue biopsy are planned at the authors' centre using a newly

established biobank. Increasing the cohort sample size through international collaboration is also planned. It is hoped that this further work will facilitate the development of a risk prediction tool (EviSurg) which could accurately predict the priority outcomes of exenteration surgery for patients with LRRC preoperatively and therefore support reproducible treatment decisions. In the meantime, given that R0 resection is an established predictor of and therefore surrogate for both survival and QOL,^{27, 28, 33, 34} the recommendation for surgery may be most appropriately made based on the reasonable chance of R0 resection according to preoperative imaging, in an otherwise fit and motivated patient.

The findings of this study may have limited generalisability to other centres, where the approach to neoadjuvant treatment (particularly re-irradiation) and radicality of surgery may differ and the findings should be interpreted with this in mind. Furthermore, the evolution in practice over the 28-year study period, where increasingly radical resections were undertaken, which may have influenced outcomes over that time. Because involvement of specific anatomical structures on preoperative imaging is not recorded in the institutional database used for this study, the predictive variables relating to pelvic bone, iliac vessel and sciatic nerve resection were recorded postoperatively and used as surrogates for suspected preoperative tumour involvement. This is not expected to have influenced outcomes, however, given the diagnostic accuracy of high resolution MRI, particularly when interpreted by an expert pelvic and soft tissue tumour radiologist, and also given the authors' approach to plan to resect all structures for which there is concern for tumour involvement.

In conclusion, this study identified preoperative patient and tumour related factors that independently predict the priority outcomes of exenteration surgery for patients with LRRC. These evidence-based predictors should be integrated into multi-disciplinary assessment of

patients presenting with LRRC, and decision-making conversations with patients and their carers. While the current predictive discrimination remains limited for individual patient outcomes, ongoing work incorporating additional preoperative factors, including molecular biomarkers, and international collaboration holds promise for developing robust risk prediction models. This work represents a critical step toward personalized, reproducible treatment decisions for patients undergoing pelvic exenteration for LRRC.

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Table 1. Baseline patient and disease information for patients who underwent pelvic exenteration for locally recurrent rectal cancer, and their association with resection margin status on univariate and multivariate analysis (OR > 1 indicates a higher chance of R0 resection).

Characteristics	Overall (N = 300)	R1/2 margin (N = 56)	R0 margin (N = 244)	Univariate analysis			Multivariate analysis		
				OR	95% CI	p value	OR	95% CI	p value
Gender									
Male	193 (64%)	35 (62.5%)	158 (65%)	Ref					
Female	107 (36%)	21 (37.5%)	86 (35%)	0.907	0.497-1.655	0.751			
Age									
Median, years (interquartile range)*	62 (54 - 68)	61 (54 - 66)	62 (55 - 68)			0.265			
Time since primary rectal cancer treatment									
Median, months (interquartile range)*	35 (23 - 56)	40 (28 - 56)	34 (21 - 56)			0.151	0.995	0.985-1.005	0.314
Presentation									
Locally recurrent rectal cancer	279 (93%)	51 (91.1%)	228 (93.4%)	Ref					
Locally re-recurrent rectal cancer	21 (7%)	5 (8.9%)	16 (6.6%)	0.716	0.251-2.043	0.532			
ASA score									
1	24 (9%)	5 (10.0%)	19 (8.6%)	1.173	0.746-1.843	0.490			
2	114 (42%)	22 (44.0%)	92 (41.4%)						
3	130 (48%)	23 (46.0%)	107 (48.2%)						
4	4 (2%)	0 (0.0%)	4 (1.8%)						
Neoadjuvant radiotherapy	121 (41%)	14 (25.5%)	107 (44.4%)	2.338	1.211-4.514	0.011	2.773	1.384-5.555	0.004
Neoadjuvant chemotherapy	35 (12%)	6 (10.9%)	29 (12.0%)	1.119	0.438-2.825	0.824			
Synchronous metastatic disease	18 (6%)	4 (7.1%)	14 (5.7%)	0.791	0.250-2.502	0.690			
Local complication at presentation	15 (5%)	4 (7.1%)	11 (4.5%)	0.613	0.188-2.004	0.419			
Baseline quality of life*									
Median, total FACT-C (interquartile range)*	99.7 (82.7 - 114)	92.3 (75.0 - 114.0)	99.2 (84.0 - 114.0)			0.229			
Pelvic bone involvement	202 (67%)	30 (53.6%)	172 (70.5%)	2.070	1.144-3.746	0.016	2.311	1.200-4.450	0.012
Sciatic nerve involvement	53 (18%)	17 (30.4%)	36 (14.8%)	0.397	0.203-0.776	0.007	0.365	0.177-0.753	0.006
Common or external iliac vessel involvement	35 (12%)	12 (21.4%)	23 (9.4%)	0.382	0.177-0.824	0.014	0.485	0.209-1.124	0.092

* Mann Whitney test

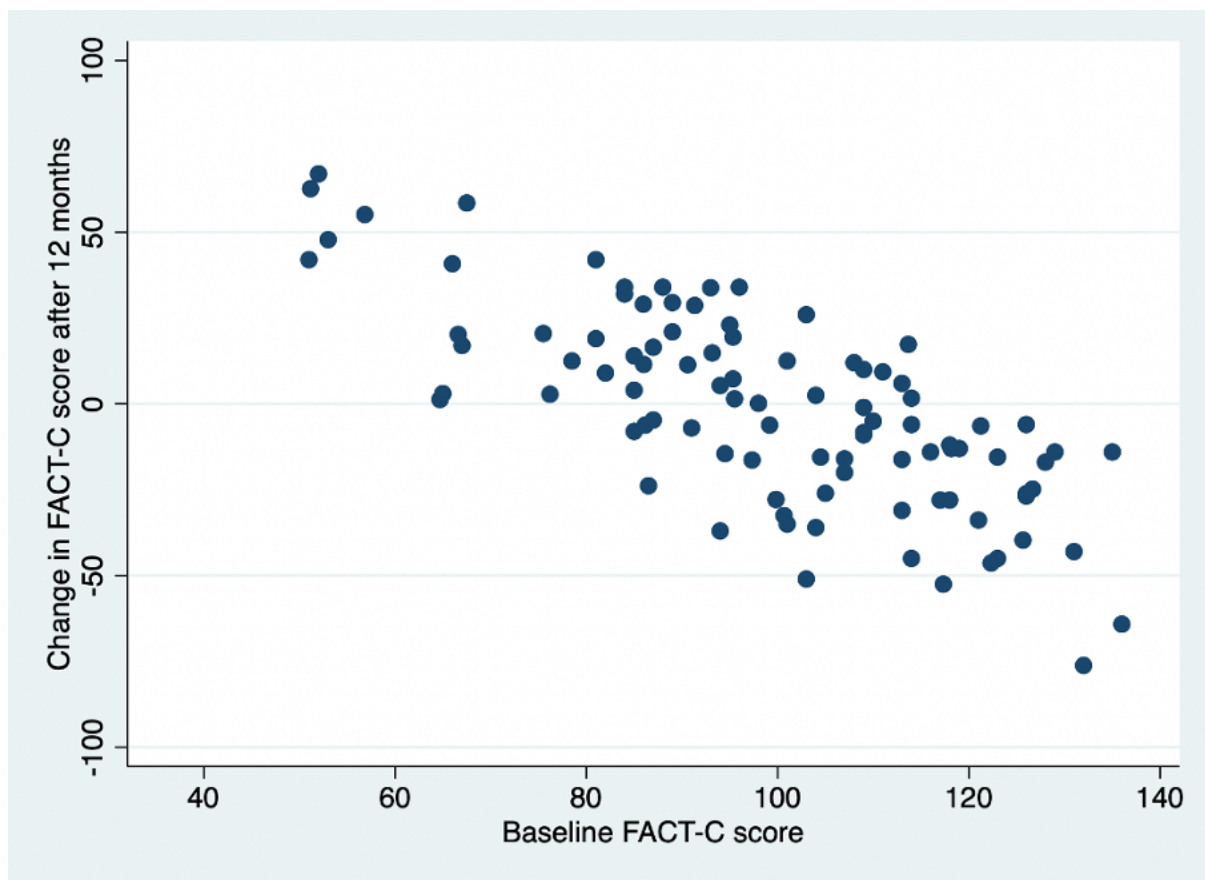
Table 2. Preoperative predictors of overall survival among patients who underwent pelvic exenteration for locally recurrent rectal cancer (HR >1 indicates a shorter overall survival).

Characteristics	Univariate analysis			Multivariate analysis		
	HR	95% CI	p value	HR	95% CI	p value
Gender						
Male	Ref					
Female	0.925	0.671-1.276	0.636			
Age	1.023	1.008-1.038	0.003	1.022	1.006-1.039	0.007
Time since primary rectal cancer treatment	0.997	0.992-1.002	0.240			
Presentation						
Locally recurrent rectal cancer	Ref					
Locally re-recurrent rectal cancer	0.935	0.530-1.650	0.817			
ASA score	1.190	0.943-1.503	0.143	1.092	0.848-1.407	0.494
Neoadjuvant radiotherapy	0.816	0.598-1.115	0.203	0.811	0.581-1.132	0.218
Neoadjuvant chemotherapy	1.067	0.668-1.706	0.785			
Synchronous metastatic disease	1.188	0.644-2.194	0.581			
Local complication at presentation	1.433	0.755-2.721	0.271			
Baseline quality of life	1.002	0.993-1.010	0.742			
Pelvic bone involvement	1.410	1.004-1.978	0.047			
Sciatic nerve involvement	1.344	0.919-1.963	0.127	1.325	0.884-1.987	0.173
Common or external iliac vessel involvement	1.183	0.755-1.855	0.463	1.300	0.887-1.906	0.179

Table 3. Preoperative predictors of change in quality of life from baseline to 12 months among patients who underwent pelvic exenteration for locally recurrent rectal cancer (higher beta indicates a larger difference between baseline and 12 month QOL).

Characteristics	Univariate analysis			Multivariate analysis		
	Beta	95% CI	p value	Beta	95% CI	p value
Gender						
Male	Ref					
Female	9.567	-2.422 - 21.556	0.116	3.996	-3.997 - 11.989	0.323
Age	-0.183	-0.836 - 0.470	0.579			
Time since primary rectal cancer treatment	-0.010	-0.198 - 0.178	0.918			
Presentation						
Locally recurrent rectal cancer	Ref					
Locally re-recurrent rectal cancer	2.336	-18.679 - 23.351	0.826			
ASA score	-2.319	-12.077 - 7.440	0.638			
Neoadjuvant radiotherapy	8.157	-3.488 - 19.803	0.168	8.419	0.796 - 16.042	0.031
Neoadjuvant chemotherapy	3.282	-17.749 - 24.313	0.757			
Synchronous metastatic disease	0.791	-28.283 - 29.865	0.957			
Local complication at presentation	23.370	-2.335 - 49.076	0.074	13.432	-3.568 - 30.431	0.120
Baseline quality of life*	-1.034	-1.223 - -0.844	<0.001	-1.011	-1.196 - -0.825	<0.001
Pelvic bone involvement	-3.572	-15.976 - 8.831	0.569			
Sciatic nerve involvement	-1.830	-17.415 - 13.755	0.816			
Common or external iliac vessel involvement	-6.579	-22.985 - 9.827	0.428			

Figure 1. Change in postoperative QOL at 12 months compared to baseline (measured by FACT-C total score) according to baseline QOL.



CHAPTER 8: SURGICAL QUALITY BENCHMARKS FOR EXENTERATION

CHAPTER OVERVIEW

Chapter 8 addresses **Thesis Aim 2**: To establish internationally applicable surgical quality benchmarks for pelvic exenteration surgery. The results of an international multicentre benchmarking analysis are presented *Chapter 8.1*, which defines quality standards against which assessment of surgical performance can be rigorously compared. *Chapter 8.2* reports the outcomes of a subset of patients with LARC and LRRC requiring 'high complexity' pelvic exenteration using the same multicentre dataset. These outcomes reflect those that are achievable for high-complexity exenteration at expert centres, and which may serve as a point of comparison for this group of patients.

CHAPTER 8.1

Defining benchmarks for pelvic exenteration surgery: a multicentre analysis of patients with locally advanced and recurrent rectal cancer

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ABSTRACT

Objective: To establish globally applicable benchmark outcomes for pelvic exenteration (PE) in patients with locally advanced primary (LARC) and recurrent rectal cancer (LRRC), using outcomes achieved at highly specialised centres.

Background data: PE is established as the standard of care for selected patients with LARC and LRRC. There are currently no available benchmarks against which surgical performance in PE can be compared for audit and quality improvement.

Methods: This international multicentre retrospective cohort study included patients undergoing PE for LARC or LRRC at 16 highly experienced centres between 2018 and 2023. Ten outcome benchmarks were established in a lower-risk subgroup. Benchmarks were defined by the 75th percentile of the results achieved at the individual centres.

Results: 763 patients underwent PE, of which 464 patients (61%) had LARC and 299 (39%) had LRRC. 544 patients (71%) who met predefined lower risk criteria formed the benchmark cohort. For LARC patients, the calculated benchmark threshold for major complication rate was $\leq 44\%$; comprehensive complication index (CCI): ≤ 30.2 ; 30-day mortality rate: 0%; 90-day mortality rate: $\leq 4.3\%$; R0 resection rate: $\geq 79\%$. For LRRC patients, the calculated benchmark threshold for major complication rate was $\leq 53\%$; CCI: ≤ 34.1 ; 30-day mortality rate: 0%; 90-day mortality rate: $\leq 6\%$; R0 resection rate: $\geq 77\%$.

Conclusions: The reported benchmarks for PE in patients with LARC and LRRC represent the best available care for this patient group globally and can be used for rigorous assessment of surgical quality and to facilitate quality improvement initiatives at international exenteration centres.

INTRODUCTION

Pelvic exenteration surgery is now widely considered the standard of care for selected patients presenting with locally advanced primary (LARC) and locally recurrent rectal cancer (LRRC) (1). Due to the encouraging survival and quality of life outcomes reported for these patients in recent decades, there has been increasing interest in pelvic exenteration globally and a corresponding increase in the number of colorectal surgeons, surgical oncologists and specialist centres offering exenterative surgery. Such radical surgery is, however, associated with substantial morbidity (2), functional consequences and at least a temporary reduction in quality of life (3), and is therefore only justified by the reasonable chance of long term survival, for which clear (R0) resection margins have been consistently identified as the most important predictor (4, 5). Several recent comparative studies have demonstrated substantial variability in outcomes between PE centres, particularly with respect to rates of R0 resection (6-8). Therefore, as interest in this highly complex treatment increases, it is critical that structured methods to assess surgical quality are established to drive standards within both existing and newly established exenteration programs.

Benchmarking is well-established in business and economics as a tool for quality improvement. In surgery, benchmarking involves continuous assessment of an individual surgeon's or centre's performance by comparison to the best possible outcome (the benchmark), where the difference between actual performance and the benchmark reflects the potential for improvement (9). It is important that these surgical quality thresholds or benchmarks are defined by the best achievable outcome, rather than the average outcome. The latter may occur if the results of a single centre, multicentre or even nation-wide study

are used for benchmarking (10). Furthermore, such benchmarks may not be applicable outside of the country or region in which the study is conducted (11).

Recently, the University Hospital Zurich group described novel surgical benchmarking methodology (9, 12, 13), which has been successfully used to define outcome benchmarks in liver (14, 15), pancreatic (16) and oesophageal surgery (17), as well as non-extended resections for primary colon and rectal cancer (18). There are currently no established benchmarks against which the performance of a surgeon or centre offering pelvic exenteration for the treatment of LARC or LRRC can be compared for quality assurance. Furthermore, a recent report of variation in outcome measurement and reporting in exenteration literature raises concern about the validity of results of collaborative multi-centre studies, some of which have been previously used to define safety thresholds (19, 20).

This study aimed to report benchmark thresholds for pelvic exenteration, based on the outcomes achieved in lower risk patients with LARC and LRRC treated at highly experienced, specialist centres. This will allow centres (particularly those early in their learning curve) to continuously compare their performance to internationally applicable benchmarks and drive quality improvement.

METHODS

Study design

This international multicentre retrospective cohort study was based on previously described methodology for benchmarking in surgery (9, 12, 13). Using this method, patients at lower risk of morbidity and mortality who undergo surgery at highly experienced centres are identified and the 75th percentile of the results achieved at these centres is used to define the

best possible outcome (the benchmark). Gero and colleagues reported a methodological checklist, supported by expert Delphi consensus, which was used in the development of this study (13).

Setting

Potentially eligible centres were identified by investigators at the coordinating centre. Centres were identified based on their international reputation as an expert exenteration centre, via participation in established international collaborations, through review of published articles (including those identified in a recent systematic review) (19) and book chapters, and review of conference presentations. These centres were contacted by the senior author (MJS) and those who met the 'benchmark centre' criteria (Table 1) were invited to participate. The annual centre case volume requirement of 20 procedures (partial or complete pelvic exenterations) was based on the definition of a high-volume centre identified by the PelvEx Collaborative (21). Additional criteria relating to the presence of a dedicated multi-disciplinary team, fellowship training capability and prospective data audit were included based on the concept that centre expertise relates to more than case volume (22). Efforts were made to ensure global representation and therefore international applicability of the benchmarks, by including centres from North and South America, Europe, Asia, Australia and New Zealand. 21 centres were invited to participate, of which two did not meet the benchmark centre inclusion criteria and three were excluded due to data-sharing restrictions or inability to submit data within the required time frame. The remaining 16 benchmark centres were from 12 countries and five continents.

Participants

Consecutive patients with LARC or LRRC who underwent total pelvic exenteration between 1st January 2018 and 1st January 2023 at participating benchmark centres were eligible for inclusion. Total pelvic exenteration was defined as complete *en bloc* resection of the anus, rectum, genitourinary viscera, reproductive internal organs, regional lymph nodes, and peritoneum. Patients who underwent an anus-preserving or restorative procedure, partial exenteration or less extensive beyond-total mesorectal excision surgery were excluded. Patients who underwent minimally invasive or palliative intent surgery, or who had synchronous metastases, were also excluded. A 'benchmark' subgroup of patients expected to be at lower risk of perioperative morbidity and mortality were defined *a priori* based on medical and surgical factors identified from existing literature (Table 1). Surgical criteria for exclusion from the benchmark subgroup included high sacral (at or above the S2 – S3 junction), pubic or ischial bone excision, major vascular resection (common or external iliac vessels, aorta) or major nerve resection (sciatic or femoral nerves, lumbosacral trunk, high sacral nerve roots). Low sacrectomy, internal iliac vessel resection and myocutaneous flap reconstruction were not benchmark subgroup exclusion criteria.

Data collection

All benchmark centres maintained a prospective database from which data were extracted and retrospectively reviewed (one centres database was under construction). Where a centre's database did not contain all required data, or a different variable definition was used, this additional information was retrospectively collected from patient medical records.

Variables and outcome measures

Benchmark thresholds were defined for 10 clinically relevant surgical outcomes, including operative time and blood loss, length of intensive care unit and hospital stay, postoperative

complications and mortality. Separate benchmark thresholds were calculated for LARC and LRRC cohorts, given the outcomes of these groups are expected to differ (23, 24).

Complications were graded according to the Clavien-Dindo system (25) and used to calculate the Comprehensive Complication Index (CCI) (26). All complication-related outcomes (overall, major, CCI) were measured from surgery until the time of hospital discharge. The definitions of high versus low sacrectomy and major neurovascular resections are provided in Table 1. The Charlson Comorbidity Index was used to quantify comorbidity burden preoperatively (27). Neoadjuvant treatment was defined as a treatment course that finished within 6 months of exenteration surgery.

Importantly, long term oncological (i.e. cancer recurrence) and survival outcomes were deliberately not included in this study, because these outcomes are heavily influenced by factors other than surgical performance (such as neoadjuvant and adjuvant treatments) and therefore cannot be benchmarked using this method (18). The primary purpose of benchmarking in surgery is to identify outcomes which can be improved by making perioperative or intraoperative modification. Therefore, R0 resection rate was considered a surrogate oncological outcome, reflecting the oncological quality of surgery, and was defined as any amount of normal tissue present microscopically between the tumour and the closest surgical margin. This definition was based on recent data demonstrating that any clear margin was associated with improved survival in LRRC, but a wider margin was not associated with additional survival benefit (5,28).

Statistical analysis

To define benchmark thresholds for each outcome of interest, median values (for continuous variables) and the proportions (categorical variables) were calculated for each participating

centre. The median and interquartile range of the benchmark centre results were calculated, and the 75th percentile was used to define the benchmark threshold, where a value above the lowest 25% was considered to be within the benchmark range. For R0 resection rate, the 25th percentile was used to define the benchmark threshold, where the higher value reflected a better outcome. The 75th percentile threshold has been used in previous benchmarking analyses (14-18) and was supported in a recent Delphi study. Using the 75th percentile rather than the median helps to ensure that the benchmark thresholds, while representing the best available care for this patient group globally, are still achievable by less experienced centres (13). Centres which contributed less than 10 patients with LARC or LRRC were excluded from the benchmarking analysis for that tumour type. Centres contributed equally to the calculation of benchmark thresholds, i.e. no weighting based on centre volume was applied.

Internal validation of the criteria used to define the benchmark cohort was performed by comparing outcomes between the benchmark (lower risk) and non-benchmark (higher risk) cohorts.

LARC and LRRC cohorts were compared using the Chi-square test for categorical variables and an independent-samples t-test or Mann-Whitney U-Test for continuous variables, when appropriate. Pearson coefficients were calculated to assess correlation between variables, where 0.1 - 0.39 was considered a weak correlation, 0.40 - 0.69 was moderate, 0.70 - 0.89 was strong and 0.90 - 1.00 was very strong (29). A 2-sided p value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 29 software (IBM, Armonk, New York, NY).

Ethical approval for this study was granted by the Royal Prince Alfred Hospital Human Research Ethics Committee. Additionally, all benchmark centres obtained ethical approval or waiver according to local requirements.

RESULTS

A total of 763 patients underwent total pelvic exenteration during the study period, of which 464 patients (61%) had LARC and 299 (39%) had LRRC. The median number of patients per centre was 41 (range 12 - 100) in the five year study period (Figure 1). 605 patients (79%) were male and the median age at surgery was 61 years (range 53 - 70). *En bloc* sacrectomy was required in 249 patients (33%), while pubic bone, ischial bone, major nerve or vascular resections were required in 19 (3%), 48 (6%), 56 (7%) and 23 (3%), respectively.

Demographic and clinical information for the study cohort, including comparison of the LARC and LRRC cohorts, is provided in Table 2. There was no difference between the LARC and LRRC cohorts with respect to age ($p=0.689$) or comorbidity index ($p=0.456$). Patients with LARC were more likely to have been treated with neoadjuvant long course radiotherapy (45% vs. 28%) or total neoadjuvant therapy (23% vs. 5%), while the proportion of patients who did not receive any neoadjuvant treatment was higher in the LRRC group (39% vs. 13%, $p<0.001$). Sacrectomy was more commonly performed in patients with LRRC (46% vs. 24%, $p<0.001$). LRRC patients were also most likely to require major vascular or other pelvic bone (ischium, pubis) resection (Table 2).

Benchmark cohort and thresholds

There were 544 patients who met the predefined lower risk criteria (Table 1) for inclusion in the benchmark cohort (71% of entire cohort), of which 364 patients (67%) had LARC and

180 (33%) patients had LRRC. After excluding centres that contributed less than 10 LARC benchmark patients, 355 patients with LARC (from 13 centres) were included in the LARC benchmark analysis (Table 3). The benchmark threshold for major complication rate in LARC was $\leq 44\%$; CCI: ≤ 30.2 ; 30-day mortality rate: 0% ; 90-day mortality rate: $\leq 4.3\%$; R0 resection rate: $\geq 79\%$. After excluding centres who contributed less than 10 LRRC patients, 123 patients from 7 centres were included in the LRRC benchmark analysis (Table 4). LRRC benchmark thresholds for major complication rate was $\leq 53\%$; CCI: ≤ 34.1 ; 30-day mortality rate: 0% ; 90-day mortality rate: $\leq 6\%$; R0 resection rate: $\geq 77\%$. Most benchmark thresholds for LRRC were higher than those calculated for LARC, with the exception of the length of hospital stay, which was higher for LARC (≤ 22 vs. ≤ 14 days). Benchmark thresholds for all 10 surgical outcomes are presented in Table 3 (LARC) and Table 4 (LRRC).

Internal validation of the benchmark criteria

When compared to the non-benchmark (high risk) cohort, the benchmark cohort (including patients with LARC and LRRC) had a shorter median operating time (509 vs 576 minutes, $p < 0.001$), lower median blood loss (1500 mL vs 2500 mL, $p < 0.001$) and shorter median hospital stay (15 vs 21 days, $p < 0.001$). The benchmark cohort also had a lower major complication rate (33% vs 40%), median CCI (23.4 vs 26.2), and 30- and 90-day mortality (1.1% vs 2.3% and 2.6% vs 3.7%, respectively), although these clinically significant differences did not reach statistical significance.

Variation in outcomes between centres

Figures 2 and 3 demonstrate the variation in outcomes between centres included in the benchmarking analysis for LARC and LRRC, respectively. For LARC, 90-day mortality rates ranged from 0% to 8% ($p = 0.341$), major complication (\geq grade IIIA) rates ranged from 11%

to 55% ($p=0.014$), R0 resection rates ranged from 70% to 100% ($p=0.014$) and CCI ranged from 20.9 to 42.7 ($p<0.001$). For LRRC, 90-day mortality rates ranged from 0% to 30.8% ($p=0.005$), major complication rates ranged from 10% to 60% ($p=0.023$), R0 resection rates ranged from 13% to 92% ($p<0.001$) and CCI ranged from 20.9 to 34.6 ($p=0.335$).

Centre volume and case mix

The proportion of LRRC cases relative to overall centre volume ranged from 4% to 71% (median 40%), and the proportion of benchmarking cases relative to overall centre volume ranged from 43% to 92% (median 77%).

Centre volume showed a moderate inverse correlation with CCI for LARC patients ($r = -0.454$), although this did not reach statistical significance ($p=0.120$), and there was no correlation with R0 resection rate ($r = -0.021$, $p=0.945$) or major complication rate ($r = -0.037$, $p=0.905$). In the LRRC group, centre volume showed weak inverse correlation with CCI ($r = -0.363$, $p=0.424$), and there was no correlation with R0 resection rate ($r = 0.077$, $p=0.869$) or major complication rate ($r = -0.092$, $p=0.844$).

There was no correlation between a centres' case mix (proportion of LRRC cases) and CCI ($r = -0.170$, $p=0.578$), R0 resection ($r=0.050$, $p=0.872$) or major complication rate ($r = 0.014$, $p=0.965$) in patients with LARC, while for those with LRRC there was moderate correlation between the proportion of LRRC cases and R0 resection ($r = 0.473$, $p=0.284$).

For LARC patients there was no correlation or weak correlation between a centres' proportion of benchmark cases and major complication rate ($r = -0.343$, $p=0.251$), CCI ($r = 0.042$, $p=0.891$) and R0 resection ($r=0.128$, $p=0.678$). For the LRRC cohort there was no or only

weak correlation between a centres' proportion of benchmark cases and major complication rate ($r = -0.086$, $p=0.855$), CCI ($r = 0.033$, $p=0.943$) and R0 resection ($r=0.188$, $p=0.686$).

DISCUSSION

This large multicentre study provides internationally applicable benchmark thresholds for 10 surgical outcomes of total pelvic exenteration, calculated separately for LARC and LRRC. These outcome benchmarks reflect the intraoperative (operative time, blood loss) and postoperative (morbidity, mortality) outcomes, as well as R0 resection rate (representing quality of oncological resection), achieved at highly specialised exenteration centres from 12 countries and five continents. These benchmarks likely reflect the best available care for this patient group and can be used globally as surgical quality thresholds for comparison of performance between centres and across time periods, and to facilitate quality improvement initiatives. This becomes increasingly relevant as the number of centres offering these complex procedures increases and the surgeons and centres adopting exenteration embark on their learning curve.

In future, the individual benchmark variables identified in this study will be used to calculate a cumulative, overall benchmark score for individual exenteration units (30). This will allow a centre to benchmark their overall surgical performance against international standards, while also reviewing the individual components of the score to identify the exact areas of potential improvement (i.e. operating time vs perioperative mortality vs R0 resection rate). For example, a centre with a 90-day mortality rate that exceeds the benchmark (31% for LRRC at one centre in this study) could review potentially contributing factors and institute measures to reduce this seemingly high rate. This will form a valuable continuous audit and feedback tool for exenteration centres and prompt quality improvement initiatives. The

relative importance of individual benchmark metrics can be interpreted by an individual unit as part of this audit process. As the surgical treatment of LARC and LRRC is refined and improves, it will be important to reconsider the identified benchmark values to ensure these important metrics are adjusted accordingly and continue to provide valuable information for specialised exenteration units, administrators, and policymakers.

Several previous collaborative studies of radical surgery for LARC and LRRC have included patients who required less extensive resections, such as extended total mesorectal excision or partial exenteration, in addition to total pelvic exenteration (23, 24, 31, 32). This results in a heterogeneous cohort and the inclusion of these less extensive resections, unless outcomes are presented separately, would be expected to lower the reported operative time, blood loss, length of stay and complication rates. To address this issue, the current study had a very narrow inclusion criteria, where only patients who underwent total pelvic evisceration (including complete resection of the anus) were included. Patients in whom the anus and levator ani were preserved were excluded to further promote a homogenous cohort and ensure the potential morbidity associated with a large perineal wound (and its contribution to the empty pelvis syndrome) was accounted for in the benchmarks. These narrow criteria most likely substantially reduced the number of patients contributed per centre (as well as the likely impact of the COVID pandemic), which represents only a small proportion of each centres overall experience with complex pelvic oncology, and also likely increased the reported operative time, blood loss and complications rates. However, the benefit a homogenous cohort with respect to extent of surgery was favoured to make the benchmark thresholds more meaningful by being specifically applicable to total pelvic exenteration (not less extensive procedures).

The above issues also make it difficult to compare the benchmark thresholds defined in the current study to previous collaborative studies, which may include a different patient cohort and use different outcome definitions. Nonetheless, although many results from the most recent PelvEx Collaborative time period (2014 - mid 2015) fall within the benchmark range, it is worth noting that the reported 30-day mortality exceeds the benchmark threshold for both LARC (1.7%) and LRRC (2.5%). Importantly, the R0 resection rate reported by PelvEx for LRRC (55.5%) is below the benchmark threshold of $\geq 77\%$ defined by the current study (21). This may be partly explained by variation in the definition of R0 resection. Total pelvic exenterations only constitute approximately one third of the PelvEx cohort, which may include anus-preserving procedures (23, 24), and it would be interesting to compare the outcomes of that group to the benchmarks defined by the current study. While extremely useful, these real-world data should not be considered quality or safety standards, as has been previously suggested (20, 21). Rather, the authors would propose that the internationally applicable benchmarks rigorously defined in the current study should serve this purpose.

The variation in case volume and case mix (with respect to both the proportion of LRRC cases and the proportion of benchmarking cases) between centres reported in this study are most likely explained by variation in the size of the population serviced by the centre as well as socioeconomic factors and local referral pathways. Similarly, variation in outcomes (including hospital and intensive care unit stay) between benchmark centres may, at least partially, be explained by differences in patient selection, adjuvant treatments and/or socio-political differences between healthcare systems. Although there was weak to moderate correlation between higher centre volume and lower CCI, there was no correlation with major complication rate or R0 resection rate in the benchmark cohort. Furthermore, the proportion of benchmark cases (i.e. lower complexity) performed also did not correlate with morbidity

or R0 resection rate. This indicates that among already highly experienced units, those with higher case volumes or more complex patients do not necessarily achieve better outcomes in lower risk patients. However, it is interesting to note the moderate correlation between the proportion of LRRC cases performed and R0 rate in LRRC patients (but not LARC patients). It is possible that even among highly specialised exenteration centres, those which deal with LRRC regularly achieve higher rates of R0 resection (8).

Operating time and blood loss may have been influenced by the proportion of patients requiring distal sacrectomy, myocutaneous flap reconstruction or lateral compartment excision (which were included in the benchmark cohort) and these benchmarks should be interpreted in the context of a specific population. It is important to note that lower values for these intraoperative metrics do not necessarily reflect superior surgical quality, especially for more complex cases where additional procedures are required to achieve an optimal oncological and reconstructive outcome. The purpose of defining these benchmarks is not to encourage the elimination of such procedures to meet a target, but rather to provide a reference point that reflects the typical intraoperative metrics achieved at highly experienced exenteration centres for the studied cohort. Such metrics must always be interpreted in the context of a specific case mix and ultimate oncological and patient-centered outcomes.

This study used established benchmarking methodology that has been successfully applied to other complex surgical procedures (14-18), where benchmark thresholds are calculated for a predefined lower-risk subgroup at expert centres meeting strict criteria. The strengths of the study include explicit centre and patient inclusion criteria, which resulted in a homogenous patient cohort with respect to extent of surgery (total pelvic exenteration) and therefore meaningful benchmarks. All but one centre had a prospectively maintained database from

which data were extracted. Expert exenteration centres from 12 countries across 5 continents were included to ensure the benchmarks are internationally applicable. Outcomes were explicitly defined, which is highly relevant given the findings of a recent systematic review of the exenteration literature demonstrating substantial variation in outcome measurement and reporting (19).

This study had several limitations. Firstly, the fact that some data were retrospectively collected raises the possibility of incomplete reporting. Secondly, only short-term morbidity data were included, with complication rates reported at discharge and mortality at 30 and 90-days. These time points were deliberately chosen to ensure complete data, because the included benchmark centres are, by definition, national or regional referral centres, where care of patients is often transferred back to local colorectal surgical teams after discharge from the referral centre and follow up may be incomplete. Longer term morbidity associated with total pelvic exenteration therefore cannot be evaluated using these benchmarks, but is a significant issue for this group of patients (33). It is also possible that not all potentially eligible centres were identified and invited to participate.

This is the first study to define internationally applicable benchmarks for total pelvic exenteration in patients with LARC and LRRC. These benchmarks reflect the outcomes achieved at highly experienced exenteration centres, and represent the best available care for this patient group globally. The benchmarks can be used for rigorous assessment of surgical quality at exenteration centres in different phases of the learning curve, and to facilitate quality improvement initiatives. The identified benchmarks will be used to develop a cumulative benchmark score which can be calculated for an individual centre, and it is hoped

this will become a valuable tool for continuous audit and feedback at exenteration centres globally.

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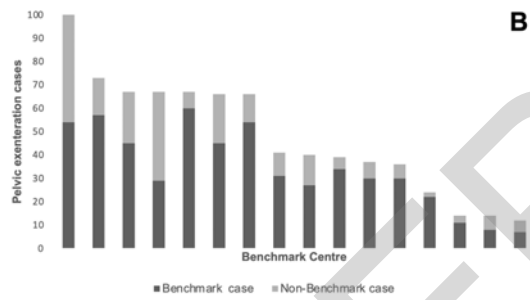
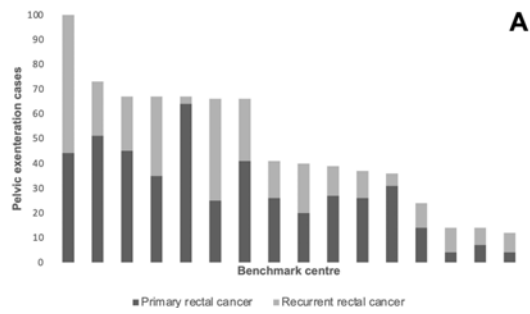
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Figure 1. Number of patients who underwent pelvic exenteration at benchmark centres, demonstrating proportion with locally advanced primary and locally recurrent rectal cancer (A) and proportion of benchmark vs non-benchmark cases (B).



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Figure 2. Variation in outcomes of total pelvic exenteration for locally advanced primary rectal cancer between benchmark centres (13 centres, N=355). Columns and boxplots represent individual centres, which have been ordered from highest to lowest value in each figure. 90-day mortality rates (A), major complication (\geq grade IIIA) rates (B), R0 resection rate (C), and comprehensive complication index (D) are demonstrated. In D, the boxes represent the interquartile range, within which the horizontal line represents the median. The whiskers demonstrate the range and outliers (more than 1.5 times beyond the upper or lower quartiles) are represented by circles.

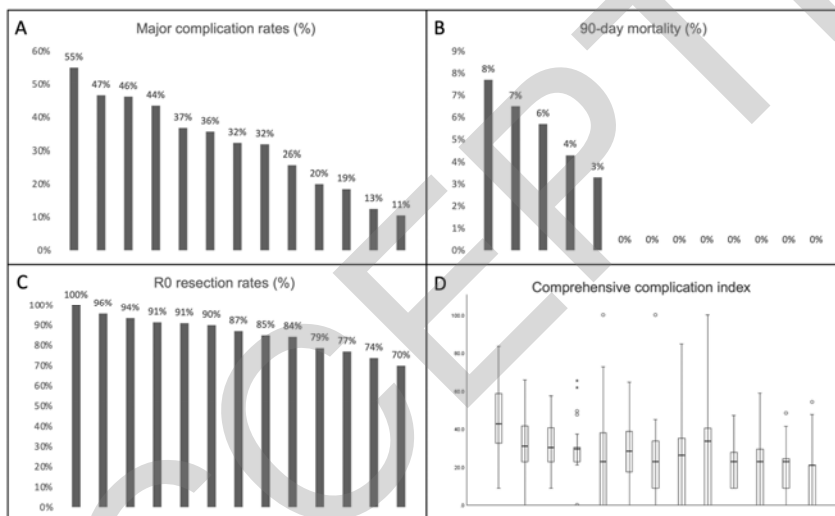


Figure 3. Variation in outcomes of total pelvic exenteration for locally recurrent rectal cancer between benchmark centres (7 centres, N=123). Columns and boxplots represent individual centres, which have been ordered from highest to lowest value in each figure. 90-day mortality rates (A), major complication (\geq grade IIIA) rates (B), R0 resection rate (C), and comprehensive complication index (D) are demonstrated. In D, the boxes represent the interquartile range, within which the horizontal line represents the median. The whiskers demonstrate the range and outliers (more than 1.5 times beyond the upper or lower quartiles) are represented by circles.

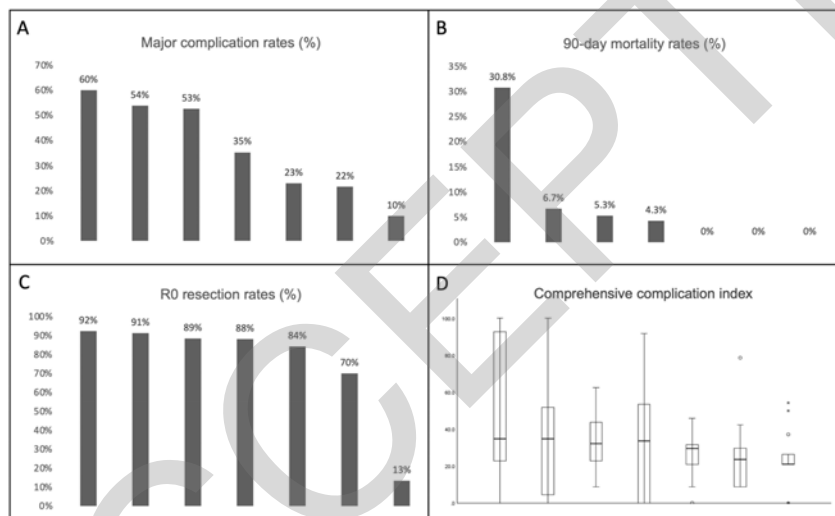


Table 1. Centre and patient eligibility criteria

Benchmark centre eligibility criteria	<ul style="list-style-type: none"> • Referral centre for advanced pelvic oncology and pelvic exenteration surgery • Dedicated advanced pelvic oncology multi-disciplinary team • Dedicated fellowship training position in advanced colorectal pelvic oncology • Annual volume of 20 or more exenterative procedures • Prospective database • Published research in the area of pelvic exenteration
Patient eligibility criteria	<p><i>Inclusion Criteria</i></p> <ul style="list-style-type: none"> • Locally advanced primary or locally recurrent adenocarcinoma of the rectum • Total pelvic exenteration (complete <i>en bloc</i> resection of the anus, rectum, genitourinary viscera, reproductive internal organs, regional lymph nodes, and peritoneum) <p><i>Exclusion criteria</i></p> <ul style="list-style-type: none"> • Minimally invasive procedures • Synchronous metastases • Palliative intent
Benchmark cohort criteria	<p><i>Medical exclusion criteria</i></p> <ul style="list-style-type: none"> • BMI < 16 or ≥ 35 • ASA score ≥ 4 • Charlson comorbidity index ≥ 6 <p><i>Surgical exclusion criteria</i></p> <ul style="list-style-type: none"> • High sacrectomy (resection level at or above the S2 – S3 junction) • Pubic or ischial bone resection • Major vascular resection (common or external iliac vessels, aorta) • Major nerve resection (sciatic or femoral nerves, lumbosacral trunk, high sacral nerve roots)

BMI - body mass index; ASA - American Society of Anesthesiologists

Table 2. Demographic and clinical information for patients who underwent total pelvic exenteration, according to tumour type.

Variables	Overall cohort (N=763)	Locally advanced primary rectal cancer (N=464)	Locally recurrent rectal cancer (N=299)	p-value
Age, median (range), years	61 (53-70)	61 (53-71)	62 (54-70)	0.689
Male sex	605 (79)	389 (84)	216 (72)	<0.00
ASA Score				1
1	121 (16)	100 (22)	21 (7)	
2	369 (48)	219 (47)	150 (50)	
3	257 (34)	134 (29)	123 (41)	
4	16 (2)	11 (2)	5 (2)	
Body mass index*	25 (22-28)	24 (21-28)	27 (23-30)	<0.00
Charlson Comorbidity Index**	3 (2-4)	3 (2-4)	3 (2-4)	0.456
Neoadjuvant treatment				<0.00
Chemotherapy	114 (15)	53 (11)	61 (20)	1
Short course radiotherapy	54 (7)	33 (7)	21 (7)	
Long course radiotherapy	293 (38)	210 (45)	83 (28)	
Induction TNT	87 (11)	72 (16)	15 (5)	
Consolidation TNT	35 (5)	34 (7)	1 (0.3)	
None	177 (23)	60 (13)	117 (39)	
Missing	3 (0.4)	2 (0.4)	1 (0.3)	
Sacrectomy				<0.00
Low	206 (27)	102 (22)	104 (35)	1
High	43 (6)	8 (2)	35 (12)	
None	514 (67)	354 (76)	160 (54)	
Pubic bone resection	19 (3)	6 (1)	13 (4)	0.008
Ischial bone resection	48 (6)	20 (4)	28 (9)	0.005
Major nerve resection	56 (7)	16 (3)	40 (13)	<0.00
Major vascular resection	23 (3)	12 (3)	11 (4)	1
Perineal myocutaneous flap repair	204 (40)	176 (38)	128 (43)	0.389
				0.179

BMI - body mass index; ASA - American Society of Anesthesiologists

*Data missing for 1 patient

**Data missing for 109 patients

Table 3. Benchmark thresholds for total pelvic exenteration in benchmark cohort patients with locally advanced primary rectal cancer (N=355)

Benchmark outcomes	Median (range)	Benchmark threshold (75th percentile)
Duration of surgery (minutes)	480 (207-720)	≤ 522
Blood loss (mL)	1450 (700-2000)	≤ 1800
Intensive care unit stay (days)	1.5 (0-4)	≤ 2
Length of stay (days)	17 (8-26)	≤ 22
Overall complication rate (%)	90 (66-100)	≤ 96%
Major complication rate (%)	32 (11-55)	≤ 44%
CCI	26.2 (20.9-42.7)	≤ 30.2
30-day mortality rate (%)	0 (0-7.7)	0%
90-day mortality rate (%)	0 (0-7.7)	≤ 4.3%
R0 resection rate* (%)	87 (70-100)	≥ 79%

CCI - comprehensive complication index

*Benchmark threshold for R0 resection rate is defined as the 25th percentile

Table 4. Benchmark thresholds for total pelvic exenteration in benchmark cohort patients with locally recurrent rectal cancer (N=123)

Benchmark outcomes	Median (range)	Benchmark threshold (75th percentile)
Duration of surgery (minutes)	540 (218-720)	≤ 591
Blood loss (mL)	2400 (800-3000)	≤ 2800
Intensive care unit stay (days)	1 (0-4)	≤ 3
Length of stay (days)	13 (10-23)	≤ 14
Overall complication rate (%)	92 (67-100)	≤ 98%
Major complication rate (%)	35 (10 to 60)	≤ 53%
CCI	32 (20.9-34.6)	≤ 34.1
30-day mortality rate (%)	0 (0-30.8)	0%
90-day mortality rate (%)	4.3 (0-30.8)	≤ 6%
R0 resection rate* (%)	88 (13-92)	≥ 77%

CCI - comprehensive complication index

*Benchmark threshold for R0 resection rate is defined as the 25th percentile.

CHAPTER 8.2

Conventional versus high-complexity total pelvic exenteration for locally advanced and locally recurrent rectal cancer: an international multicentre study

Chapter 8.2 is under peer review at the time of thesis submission:

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*Equal contribution

ABSTRACT

Background: Pelvic exenteration is the treatment of choice for selected patients with locally advanced primary (LARC) and recurrent rectal cancer (LRRC). Involvement of major pelvic neurovascular structures and bone were historically considered contraindications due to unacceptably high rates of morbidity and low R0 resection rates.

Objective: To compare the outcomes of these ‘high-complexity’ exenterative resections to those of ‘conventional’ pelvic exenteration.

Design: International multicentre retrospective cohort study.

Settings: 16 specialised exenteration centres.

Patients: Those who underwent total pelvic exenteration (TPE) for LARC or LRRC between 2018 and 2023 at participating centres.

Main Outcome Measures: Perioperative resource utilisation, morbidity, mortality and R0 resection rates were reported.

Results: 763 patients underwent TPE, of which 478 (63%) and 285 patients (37%) required conventional and high-complexity TPE, respectively. High-complexity TPE was associated with longer operating time (600 vs 480 mins, $p < 0.001$ for LARC, 623 vs 480 mins, $p < 0.001$ for LRRC), ICU stay (2 vs 1 day, $p < 0.001$ and 3 vs 1 day, $p < 0.001$), hospital stay (19 vs 15 days, $p = 0.008$ and 23 vs 15 days, $p < 0.001$) and higher blood loss (2000 vs 1236 mL, $p < 0.001$ and 3000 vs 1600 mL, $p < 0.001$). Morbidity and mortality outcomes, including comprehensive complication index, and R0 resection rates were similar between conventional and high-complexity TPE patients.

Limitations: Generalisability of findings outside of expert units

Conclusions: High-complexity TPE for the treatment of LARC and LRRC is associated with morbidity, mortality, and R0 resection rates comparable to conventional TPE in high volume, specialised centres where these techniques are considered the standard of care for appropriately selected patients with tumours that involve major pelvic bone or neurovascular structures.

INTRODUCTION

In patients with locally advanced primary (LARC) and locally recurrent rectal cancer (LRRC), radical surgery beyond traditional total mesorectal excision (TME) planes is required to achieve complete oncological resection.^{1,2} Pelvic exenteration is now widely accepted as the treatment of choice for selected patients with LARC and LRRC,^{3,4} where achieving a clear (R0) resection margin has been consistently demonstrated to be the most important predictor of survival.^{5,6} Historically, pelvic exenteration has been considered a single, standardised operation for tumours confined to the central pelvic compartment, i.e. abdominoperineal excision with en bloc resection of all genitourinary organs. However, exenterative techniques have evolved significantly in recent decades,⁷ prompted by an improved understanding of the prognostic importance of R0 resection and in order to offer potentially curative surgery to patients with more extensive local tumours. As a result, many historical technical contraindications to surgery no longer apply in 2025.⁸ These include tumour involvement of major neurovascular (iliac vessels, sciatic nerve) and bony structures of the pelvis, all of which are now routinely excised en bloc during exenteration at specialised centres.⁹⁻¹⁵ Therefore, the conventional (soft tissue) exenteration now represents the more straightforward end of the technical exenterative spectrum at such centres.

The more recently developed techniques of en bloc bone and neurovascular resection have been designated 'high-complexity' in the recent Pelvic Exenteration Lexicon.¹⁶ Studies reporting the outcomes of such procedures have been mostly limited to single centre series to date.^{17,18} This large international, multicentre retrospective cohort study aimed to compare the short-term outcomes (operative outcomes, morbidity and R0 resection rate) of 'conventional' and 'high-complexity' total pelvic exenteration (TPE) for LARC and LRRC.

MATERIALS AND METHODS

Study design and patient selection

This was an international multicentre retrospective cohort study that utilised a dataset established for a previous benchmarking analysis of TPE for LARC and LRRC.¹⁹ Patients who underwent TPE for LARC or LRRC between 1st January 2018 and 1st January 2023 at 16 specialised exenteration centres from 12 countries were included. ‘Conventional’ TPE was defined as en bloc resection of the rectum, anus, genitourinary viscera, regional lymph nodes, and peritoneum. ‘High-complexity’ TPE was defined (according to the Pelvic Exenteration Lexicon) as a conventional TPE with en bloc resection of bony (sacrum, pubic or ischium), neurological (sciatic or femoral nerves, lumbosacral trunk, high sacral nerve roots) and/or vascular (common iliac, external iliac or aorta) pelvic structures.¹⁶ High sacrectomy was defined as transection at or above the level of S2-S3 junction. Patients were excluded if they underwent minimally invasive surgery, surgery with palliative intent, or had synchronous distant metastases.

Setting

The selection of participating centres has been previously reported.¹⁹ Briefly, these were national or regional referral centres for advanced pelvic oncology and pelvic exenteration surgery, which had a track record of scientific contribution to the pelvic exenteration literature, a dedicated pelvic oncology multi-disciplinary team, fellowship training capability, maintained a prospective database, and had an annual case volume of ≥ 20 exenterative procedures.

Data collection

Data were extracted from prospectively maintained databases at each centre, and missing data was retrospectively collected from patient medical records. Surgical outcomes (operation duration, estimated blood loss, length of intensive care unit (ICU) and hospital stay, overall and major complications, Comprehensive Complication Index (CCI) and 30- and 90-day mortality) and

oncological outcomes (surgical resection margin) data were collected. Length of hospital stay was defined as duration of postoperative admission at the treating exenteration centre, and did not include subsequent admission to a local hospital or rehabilitation centre. R0 resection was defined by evidence of any normal tissue microscopically between the tumour and the closest surgical margin.²⁰ Major complications were defined as Clavien-Dindo grades III and IV.²¹ The Charlson Comorbidity Index and American Society of Anaesthesiologists (ASA) classification were used to quantify comorbidity burden and predict anaesthetic risk preoperatively. Neoadjuvant treatment was defined as chemotherapy or radiotherapy that finished within six months of exenteration surgery.

Statistical analysis

A descriptive analysis was performed. Continuous variables were presented as medians and interquartile ranges. The surgical and oncological outcomes of conventional TPE were compared to high complexity TPE using the Chi-squared and Mann-Whitney U tests, and was performed separately for LARC and LRRC patients as the outcomes of these groups are expected to differ. A two-sided *p*-value of < 0.05 was considered statistically significant. Statistical analysis was performed using SPSS version 29 software (IBM, Armonk, New York, NY).

Ethical approval for this study was granted by the Royal Prince Alfred Hospital Human Research Ethics Committee (X23-0141&2023/ETH00829). All participating centres obtained ethical approval or waiver according to local requirements.

RESULTS

A total of 763 patients underwent TPE during the study period, of which 478 (63%) and 285 patients (37%) required conventional and high-complexity TPE, respectively. The median age at surgery was 61 years (range 20-85) and the majority of patients were male (605, 79%). 464 patients (61%) had

LARC, while 299 (39%) had LRRC. Demographic and clinical information is provided in Table 1, including comparison of the conventional and high-complexity cohorts. Among the high-complexity TPE group, en bloc sacrectomy was the most common high complexity operative characteristic (249 patients, 87%), including 206 patients who required a low sacrectomy (72%) and 43 who required a high sacrectomy (15%). Major nerve resection was performed in 56 patients (20%), ischial bone resection in 48 (17%), major vascular resection in 23 (8%) and pubic bone resection in 19 (7%). High-complexity TPE was more commonly required in patients with LRRC than those with LARC (53% vs 27%, $p < 0.001$). Perineal reconstruction using a myocutaneous flap was performed in 304 (40%) patients, of which 175 (37%) had a conventional TPE and 129 (45%) had a high-complexity TPE.

Locally advanced primary rectal cancer

In patients with LARC, high-complexity TPE was associated with a longer median operating time (600 vs 480 mins, $p < 0.001$), ICU stay (2 vs 1 day, $p < 0.001$), hospital stay (19 vs 15 days, $p = 0.008$) and higher blood loss (2000 vs 1236 mL, $p < 0.001$) when compared to conventional TPE (Table 2). Morbidity and mortality outcomes, including CCI, as well as R0 resection rate (87% vs 82%, $p=0.196$) were similar between conventional and high-complexity TPE patients.

Locally recurrent rectal cancer

In patients with LRRC, high-complexity TPE was similarly associated with a longer median operating time (623 vs 480 mins, $p < 0.001$), ICU stay (3 vs 1 day, $p < 0.001$) hospital stay (23 vs 15 days, $p < 0.001$), and higher blood loss (3000 vs 1600 mL, $p < 0.001$) when compared to conventional TPE (Table 3). Morbidity and mortality outcomes, including CCI, as well as R0 resection rate (75% vs 76%, $p=0.877$) were similar between conventional and high-complexity TPE patients.

Bony resections

In patients who underwent high sacrectomy, median operative time was 840 minutes (interquartile range 606-960), blood loss was 5000 ml (2625-8750), ICU stay was four days (range 2-7), and length of hospital stay was 35 days (19-59) (Table 4). The major complication rate in high sacrectomy patients was 54% and the CCI was 34.6. 30-day and 90-day mortality rates were both 0%. The R0 resection rate of patients who underwent high sacrectomy, ischial bone resection and pubic bone resection were 79%, 79% and 68%, respectively. Eight patients had concurrent resection of all three pelvic bones (pubis, ischium and sacrum) during exenteration.

Major vascular resections

In patients who underwent major vascular resection, median operative time was 480 minutes (interquartile range 405 - 759), blood loss was 3000 ml (2150 - 3813), ICU stay was 2 days (1 - 4), and length of hospital stay was 14 days (10-27) (Table 4). The major complication rate in vascular resection patients was 39% and the CCI was 22.6. 30-day and 90-day mortality rates were both 0%.

DISCUSSION

This international multicentre cohort study reported the outcomes of high-complexity TPE in patients with LARC and LRRC at 16 highly experienced exenteration centres from 12 countries. The key finding was that high-complexity exenterative procedures can be performed safely at specialised centres, with excellent morbidity, mortality, and R0 resection rates that are comparable to conventional TPE. These techniques are, however, resource intensive and are associated with significantly higher operative time, blood loss, and hospital resource utilisation (ICU and hospital stay). Collectively, these findings support high-complexity TPE as a reasonable curative and safe treatment option with good outcomes for appropriately selected patients with LARC and LRRC, as well as the centralisation of such techniques to specialised units.

Rates of perioperative major morbidity were substantial in this study, albeit comparable between conventional and high-complexity groups (30-42%). In patients requiring high sacrectomy, the median intraoperative blood loss was 5L, the median length of hospital stay was 35 days, and the major complication rate was 54%. The safe perioperative management of such highly complex patients, including the early, proactive management of complications, requires 'institutional experience' where familiarity with the unique issues facing exenteration patients extends beyond the immediate surgical and perioperative team to all allied specialities and healthcare professionals. Recent registry data has raised concerns about the quality of exenteration surgery for LARC where the majority of patients undergo surgery at low volume, non-specialised centres which may not have accumulated such experience.²² Reports from Europe and the United Kingdom have identified similar patterns of practice for LRRC in those regions.^{23,24} Furthermore, the healthcare costs associated with 'low volume, high cost' complex exenteration surgery is significant,^{17,25} and require institutional 'buy in' from both clinical and administrative teams. These issues may be, at least in part, addressed by a system of coordinated centralisation of referrals to appropriately funded 'state-wide' services, as has evolved in Australia and New Zealand,²⁶ and Scandinavia.

The findings of this study reflect the outcomes achieved in contemporary practice (2018-2023) at highly experienced exenteration units. The number of included patients was commensurate to less than four high-complexity TPEs per centre per year. This is likely, at least in part, due to the fairly restrictive inclusion criteria of the study, which only permitted inclusion of patients undergoing total pelvic exenteration with excision of all organs, the anus and levator ani. Patients who underwent partial exenteration or other less extensive beyond-TME resections, and probably make up a high proportion of each units practice, were excluded to minimise heterogeneity. For example, patients undergoing abdominoperineal excision with en bloc sacrectomy, although undoubtedly

complex surgery, were not included in this study. Nonetheless, the sample size highlights that high-complexity TPE remains relatively uncommon, even at major academic referral centres.

In a recent report from the Southampton group, West and colleagues found that R0 resection rate and postoperative mortality were comparable between high-complexity and conventional exenteration, while the former was associated with increased major morbidity and perioperative cost.¹⁷ Importantly, however, the definition of pelvic exenteration in that study was the resection of two or more pelvic organs, and the definition of high-complexity included lateral compartment lymphadenectomy, division of distal internal iliac branches, and resection of the levator ani, all of which are commonly performed routinely in TPE and thus not considered high-complexity in our study. West and colleagues' cohort was also biologically heterogeneous, including both rectal and non-rectal pelvic tumours. For these reasons it is difficult to compare the findings to those of the current study, which included only TPEs for LARC and LRRC.

It is also noteworthy that patients with LRRC were far more likely to require a high-complexity resection compared to patients with LARC. This reflects the fundamental biological difference between LARC, which arises within the rectum and extends beyond the TME plane, and LRRC, which most commonly arises and grows outside the neo-mesorectal fascia in the presacral space and pelvic sidewall.

The strengths of this study were the large sample size for what remains an uncommon operation, the participation of 16 major academic exenteration centres from 12 countries, the use of restrictive inclusion criteria which resulted in a homogenous cohort both with respect to tumour biology and extent of surgery, mostly prospective data collection, and use of clearly defined endpoints (the lack of which has been a historical concern in exenteration literature).²⁷ Limitations of the study were

that only short-term outcomes were available in the dataset, which was designed for a previously published benchmarking analysis of surgical outcomes,¹⁹ and some data were retrospectively collected from medical records. Hospital and intensive care unit stay may also vary significantly between healthcare systems. Importantly, the findings of this study may not be generalisable beyond expert units, and should be interpreted with caution.

In conclusion, despite technically challenging operations, high-complexity TPE for the treatment of LARC and LRRC is associated with morbidity, mortality, and R0 resection rates comparable to conventional TPE when performed at specialised centres. These techniques should therefore be considered the standard of care for appropriately selected patients with tumours that involve major pelvic bone or neurovascular structures. Institution wide experience and appropriate resourcing, including high quality data collection, is required to support such highly complex surgical programmes.

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Table 1. Demographic and clinical information of patients undergoing ‘high-complexity’ and ‘conventional’ TPE

Variables	Overall (n=763)	High complexity TPE (n=285)	Conventional TPE (n=478)	P value
Age, median (range)	61 (20-85)	61 (53-69)	62 (53-71)	0.517
Male, n (%)	605 (79)	219 (77)	386 (81)	0.197
ASA score				0.007
1	121 (16)	44 (15)	77 (16)	
2	369 (49)	122 (43)	247 (52)	
3	257 (34)	116 (41)	141 (30)	
4	16 (2)	3 (1)	13 (3)	
Presentation				< 0.001
Locally advanced rectal cancer	464 (61)	127 (45)	337 (71)	
Locally recurrent rectal cancer	299 (39)	158 (55)	141 (30)	
Body mass index	25 (11-49)	25.9 (22-29)	24.3 (22-28)	0.002
Charlson comorbidity index	3 (1-11)	3 (2-3)	3 (2-4)	0.003
Neoadjuvant treatment				0.127
Chemotherapy	114 (15)	44 (15)	70 (15)	
Short course radiotherapy	54 (7)	14 (5)	40 (8)	
Long course radiotherapy	293 (38)	109 (38)	184 (39)	
Induction TNT	87 (11)	26 (9.1)	61 (13)	
Consolidation TNT	35 (5)	13 (5)	22 (5)	
None	177 (23)	78 (27)	99 (21)	
Missing	3 (0.4)	1 (0.4)	2 (0.4)	
Surgical complexity				
Sacrectomy	249 (33)	249 (87)	0 (0)	
Low	206 (27)	206 (72)	0 (0)	
High	43 (6)	43 (15)	0 (0)	
Pubic bone resection	19 (3)	19 (7)	0 (0)	
Ischial bone resection	48 (6)	48 (17)	0 (0)	
Major nerve resection	56 (7)	56 (20)	0 (0)	
Major vascular resection	23 (3)	23 (8)	0 (0)	

ASA - American Society of Anesthesiologists; TNT - total neoadjuvant therapy

Table 2. Surgical outcomes of locally advanced primary rectal cancer patients undergoing high-complexity versus conventional total pelvic exenteration

Outcome	High Complexity TPE (n=127)	Conventional TPE (n=337)	P value
Duration of surgery (min)	600 (480-752)	480 (386-570)	< 0.001
Blood loss (mL)	2000 (1500-3500)	1236 (700-2000)	< 0.001
Intensive care unit stay (days)	2 (1-4)	1 (1-2)	< 0.001
Length of stay (days)	19 (12-30)	15 (11-23)	0.008
Overall complication rate (%)	107 (84)	277 (82)	0.601
Major complication rate (%)	43 (33)	100 (30)	0.384
CCI	22.6 (9-35)	22.6 (9-35)	0.897
30d mortality rate (%)	1 (0.8)	2 (0.6)	0.816
90d mortality rate (%)	4 (3)	6 (2)	0.365
R0 resection rate (%)	104 (82)	292 (87)	0.196

CCI - comprehensive complication index

Table 3. Surgical outcomes of locally recurrent rectal cancer patients undergoing high-complexity vs conventional total pelvic exenteration

Outcome	High complexity TPE (n=158)	Conventional TPE (n=141)	P value
Duration of surgery (min)	623.7 (505-780)	480 (402-621)	< 0.001
Blood loss (mL)	3000 (1800-5000)	1600 (800-3000)	< 0.001
Intensive care unit stay (days)	3 (1-5)	1 (0-3)	< 0.001
Length of stay (days)	23 (15-35)	15 (10-24)	< 0.001
Overall complication rate (%)	136 (86)	124 (88)	0.632
Major complication rate (%)	65 (41)	59 (42)	0.902
CCI	30.8 (21-42)	24.2 (11-42)	0.332
30d mortality rate (%)	3 (2)	5 (4)	0.378
90d mortality rate (%)	5 (3)	7 (5)	0.429
R0 resection rate (%)	120 (76)	106 (75)	0.877

CCI - comprehensive complication index

Table 4. Outcomes of high-complexity total pelvic exenteration according to individual high complexity operative characteristics

Outcomes	High sacrectomy (n=43)	Low sacrectomy (n=206)	Pubic bone resection (n=19)	Ischial bone resection (n=48)	Nerve resection (n=56)	Vascular resection (n=23)
Duration of surgery (min)	840 (330-1520)	600 (169-3720)	600 (300-1440)	710 (240-1520)	720 (363-1500)	480 (207-1440)
Blood loss (mL)	5000 (700-18000)	2100 (275-17000)	3000 (550-17000)	4000 (450-18000)	4000 (1000-18000)	3000 (600-37500)
Intensive care unit stay (d)	4 (0-28)	2 (0-25)	2 (0-14)	4 (0-20)	3 (0-28)	2 (0-23)
Length of stay (d)	35 (7-207)	19 (6-183)	22 (8-207)	25 (9-207)	31.5 (7-207)	14 (6-66)
Overall complication rate (%)	37 (86)	180 (87)	15 (79)	34 (71)	49 (88)	17 (74)
Major complication rate (%)	23 (54)	75 (36)	6 (32)	14 (29)	24 (43)	9 (39)
CCI	34.6 (0-100)	24.2 (0-100)	22.6 (0-100)	22.6 (0-74)	30.8 (0-100)	22.6 (0-79)
30d mortality rate (%)	0 (0)	2 (1)	1 (5)	1 (2)	0 (0)	0 (0)
90d mortality rate (%)	0 (0)	8 (4)	1 (5)	1 (2)	1 (2)	0 (0)
R0 resection rate (%)	34 (79)	161 (78)	13 (68)	38 (79)	44 (79)	16 (70)

CCI - comprehensive complication index

THESIS SUMMARY AND CONCLUSIONS

THESIS SUMMARY

Variation in treatment decision making, outcomes and referral practices with respect to pelvic exenteration surgery for patients with LARC and LRRC remains largely unaddressed¹⁻⁸. In this thesis a mixed methodological approach was designed with the aims of (i) identifying preoperative predictors of the outcomes of surgery which patients, carers and clinicians consider most important, in the hope that the ability to predict these outcomes may facilitate evidence-based, reproducible treatment decisions, and (ii) developing globally applicable surgical quality benchmarks against which exenteration centres around the world can compare their own outcomes as part of audit and feedback for quality improvement. A variety of methodological approaches were utilised to address the thesis aims, and included a systematic review, a large qualitative component, modified Delphi methodology, risk prediction modelling using a prospectively maintained institutional dataset, and an international, multicentre retrospective cohort study.

Key findings and their significance

The key findings of this thesis were the nine consensus-derived priority outcomes of exenteration (*Chapter 6*) and the identification of preoperative independent predictors of these outcomes (*Chapter 7*). Collectively, the priority outcomes and their predictors form a novel evidence-based preoperative prediction framework which represents a step toward personalised, reproducible treatment decisions for patients with LARC and LRRC. This addresses ***Thesis Aim 1*** (to address unwarranted variation in treatment decision-making in patients with LARC and LRRC).

Additionally, the benchmarks reported in *Chapter 8* of this thesis represent the first rigorously defined standards for quality and safety of pelvic exenteration surgery, are another key finding of the thesis, and address ***Thesis Aim 2*** (to establish internationally applicable surgical quality benchmarks for pelvic exenteration surgery). These key findings and their significance are outlined in this section.

The nine priority outcomes and the quantification of their relative importance to patients, carers and clinicians form one of the key findings of this thesis. These outcomes related to survival (overall survival, disease-free survival, local recurrence-free survival), cancer recurrence (distant recurrence), patient-reported outcomes (global quality of life, psychological functioning, physical functioning, mobility) and pathological outcomes (resection margins). When ranked by participants according to relative importance, 'resection margins', 'local recurrence-free survival', and 'overall survival' were considered the most important outcomes of exenteration surgery for LARC and LRRC. These outcomes therefore represent the shared priorities of patients who have undergone pelvic exenteration for LARC or LRRC, their carers and clinicians and were established using rigorous, consensus methodology which was adapted from existing core outcome set methodology and applied to the objectives of this thesis.

The reported priority outcomes have implications for both clinical practice and research. In clinical practice, the priority outcomes should form the basis of shared decision making with patients about whether to undergo exenterative surgery, where anticipated R0 resection, survival, risk of cancer recurrence and quality of life/functioning for an individual patient (based on presence of the preoperative risk factors identified in *Chapter 7*) are considered in the context of that patient's other treatment goals and priorities. It is hoped that further refinement of the prediction models presented in *Chapter 7* will facilitate development of a risk prediction tool which can be used to facilitate reproducible treatment decisions for this group of patients, in an evidence-based manner. This addresses *Thesis Aim 1* by reducing variation and promoting reproducible, evidence-based decision making in this group of patients. From the perspective of research and audit, the priority outcomes should be considered mandatory outcomes that exenteration units collect and audit prospectively as

part of a 'minimum dataset', and should also be considered and incorporated during the design of future studies evaluating pelvic exenteration as a treatment for patients with LARC and LRRC.

Preoperative predictors of the newly defined priority outcomes of exenteration for LRRC were evaluated in *Chapter 7*, where patient and disease-related factors that are available in the preoperative setting were considered. It is intuitive that the identified predictors of R0 resection relate primarily to the extent of local tumour invasion (pelvic bone or sciatic nerve involvement), however the finding that patient age was the sole predictor of overall survival reflects the difficulty that still exists in predicting arguably the most important and reproducible outcome of LRRC treatment. While previous studies have identified predictors of recurrence and survival after surgery for LRRC, most have included traditional clinicopathological factors as predictive variables, of which many are only available postoperatively once the surgical specimen has been analysed.⁹⁻¹¹ In *Chapter 7* of this thesis, only preoperative factors were evaluated as predictors, to ensure their utility in the preoperative setting at the time of treatment decision-making.

Despite identification of the independent predictors of priority outcomes and although future work toward development of an individual patient risk prediction tool is planned (see below), the accurate prediction of outcomes of exenteration for an individual patient with rectal cancer remains challenging. Therefore, given that R0 resection is an established predictor of and surrogate for both survival and QOL,^{9, 10, 12, 13} the recommendation for surgery in current practice is likely best made based on a multi-disciplinary team's assessment of the likelihood of achieving R0 resection, in an otherwise fit and motivated patient. This 'intuition-based' approach to treatment recommendations remains the standard of care while attempts to develop an 'evidence-' or 'theory-based' approach are in progress.

The key findings of the systematic review presented in *Chapter 4* were that 'Complications' and 'Survival' were the most commonly reported outcome domains in contemporary pelvic exenteration literature (94% and 81% of included studies, respectively), while, importantly, 'Patient-Reported Outcomes and Functioning' was the least commonly reported domain (26% of included studies). Significant variation in the quality of outcome measurement and reporting among the included studies was also documented, where only 17% of 2765 extracted outcomes were clearly and reproducibly defined. Many important outcomes of surgery were not defined in a large proportion of studies, such as local recurrence, which was only defined in 18% of studies which reported it, and similarly, resection margin status was not defined, or defined ambiguously, in most studies which reported it.

Chapter 4 presents the first study to rigorously assess the quality of outcome measurement and reporting in the exenteration literature, and was the first to identify the significant heterogeneity in outcome reporting described above. These findings have major implications for the validity of multicentre collaborative studies, which have been historically required to ensure an adequate sample size when studying what remains an uncommon patient population and treatment. The results of such studies may be impacted by variation in outcome definitions between centres (rather than comparing 'like with like'), which is a particular concern when the results of pooled multicentre data have been previously used to define surgical performance and safety benchmarks^{7, 14}. Prompted by these findings, the issue of outcome benchmarking was subsequently addressed in this thesis using outcomes that were clearly defined *a priori* (*Chapter 8*).

Another key finding of *Chapter 4* was the small proportion of studies (26%) that included patient-reported, quality of life and functional outcomes. This was the first study to highlight an apparent lack of patient reported outcomes in exenterative literature, and this finding raises the concern that

the outcomes of interest to patients and their carers are not adequately addressed in the current literature, particularly in view of the subsequent finding in *Chapter 6* that quality of life was considered critically important by patients, carers and clinicians in a Delphi consensus. This finding likely relates, at least in part, to the difficulties in measurement of quality of life in this unique population (also discussed in *Chapter 2.3*) due to the limited generalisability of generic colorectal cancer quality of life instruments and lack of patient-reported outcome tools that are validated for use in patients with LRRC. This lack of quality of life outcome reporting served as a starting point for the qualitative work in *Chapter 5*.

With the findings of *Chapter 4* in mind, the qualitative work presented in *Chapter 5* sought to explore patient and carer perspectives on both their decision-making around undergoing pelvic exenteration, as well as the long term consequences of surgery. The key findings of the qualitative evaluation of participant perspectives on the decision to undergo surgery are the four major themes identified which are presented in *Chapter 5.1*. These themes include the finding that patients and carers consider that they really had no choice but to undergo such radical and potentially morbid surgery, because it was their only chance of long-term survival (Major theme 1: *There really wasn't a choice*). For most participants, survival was their ultimate priority, with many indicating specific motivations such as time with their spouse or partner, children or grandchildren. For this reason, many participants reflect that there was no decision to be made. Participants found the magnitude of surgery and its recovery difficult to comprehend at the time they decided to proceed, with many surprised by the protracted recuperation despite extensive education and counselling (Major theme 2: *Grappling with the magnitude of surgery*). Major theme 3 (*A spectrum of psychological states and support needs*) captures the wide variation in psychological states of participants at the time they were deciding whether to undergo surgery, and also the sources of support accessed (including friends, family and healthcare professionals). Although survival was the ultimate reason most

participants underwent surgery, many considered the impact on body function and image, and quality of life more generally, as important consequences (Major theme 4: *Understanding life after surgery*).

Chapter 5.1 specifically addressed **Thesis Aim 1** (to address unwarranted variation in treatment decision-making in patients with LARC and LRRC) by providing in depth insight into the patient and carer perspective on how and based on which factors treatment decisions should be made. This ensured patient and carer perspectives were used to inform subsequent development of priority outcomes (*Chapter 6*) which form the foundation of the proposed risk prediction tool and decision-making tool to reduce variation in decision-making in LARC and LRRC.

In *Chapter 5.2*, patients and carers were asked to reflect on the long-term consequences of surgery and the key findings are presented as the three identified major themes. Permanent changes to body appearance and function were an ongoing concern for many patients, who reported issues relating to chronic pain, managing stomas, altered bowel function, mobility problems and the resulting loss of intimacy (Major theme 2: *Our lives are changed forever*). These sequelae were, however, widely considered the price paid for survival and regardless of the impact of surgery on their life, the vast majority of patients still considered surgery worthwhile (Major theme 1: *The consequences of surgery are the price you pay for survival*). Participants reflected on the ups and downs of life following the initial recovery from surgery, which was characterised by a change in outlook for many (both positive and negative), a pervasive anxiety around the possibility of cancer recurrence for some, a lack of support services and the impact on family and friends (Major theme 3: *The good days and bad days as a survivor*).

The work presented in *Chapter 5* represents the largest qualitative study of pelvic exenteration patients and their carers conducted to date. As demonstrated in the systematic review component of this thesis (*Chapter 4*), quality of life has been relatively under-reported in contemporary exenteration literature and only one of the 156 included studies employed qualitative methodology. The qualitative work in this thesis therefore addresses a significant gap in the literature. The themes and concepts identified by the in-depth interviews with patients and carers in *Chapter 5* provide important new insights into their experiences and perspectives which are difficult to capture using quantitative measures, and have major implications for both clinical practice and research (see later). Although 'quantitative' quality of life tools are useful for understanding the trajectories of cohorts of patients in broad quality of life domains, a qualitative approach was utilised in this thesis in order to gather more rich descriptions of lived experiences which give context to how patients and carers make the life altering decision to undergo such radical surgery, and shed light on how the consequences of this surgery, such as living with two ostomies, for example, impact patients' lives.

Like *Chapter 5.1*, *Chapter 5.2* specifically addressed ***Thesis Aim 1*** (to address unwarranted variation in treatment decision-making in patients with LARC and LRRC) by exploring the long-term outcomes and consequences of surgery that matter most to patients and carers. This allowed these patient-centred concepts to be incorporated into the proposed evidence-based decision-making framework developed in subsequent chapters.

The second primary aim of this thesis was to establish internationally applicable surgical quality benchmarks for pelvic exenteration surgery (***Thesis Aim 2***). The international, multicentre benchmarking analysis presented as *Chapter 8.1* included 763 patients who underwent a total pelvic exenteration (i.e. complete evisceration with two stomas) (464 LARC, 61%, and 299 LRRC, 39%) over a 5-year period at 16 expert exenteration centres from 12 countries. Benchmarks thresholds for

total pelvic exenteration were defined for ten intra- and post-operative surgical outcomes, including separate disease-specific thresholds for LARC and LRRC. For the LARC cohort, the benchmark threshold for major complication rate was $\leq 44\%$; comprehensive complication index: ≤ 30.2 ; 30-day mortality rate: 0% ; 90-day mortality rate: $\leq 4.3\%$; R0 resection rate: $\geq 79\%$. For the LRRC cohort, the benchmark threshold for major complication rate was $\leq 53\%$; CCI: ≤ 34.1 ; 30-day mortality rate: 0% ; 90-day mortality rate: $\leq 6\%$; R0 resection rate: ≥ 77 .

This was the first study to define quality standards for pelvic exenteration surgery, which thereby addresses *Thesis Aim 2*, and it is hoped that these benchmarks will serve as reference points for the comparative assessment of surgical performance among international exenteration centres to facilitate quality improvement. Indeed, the benchmarks defined in this thesis have been used as reference standards in subsequent studies reporting the outcomes of pelvic exenteration for rectal cancer at a population level in both the United States^{1, 3, 15} and the United Kingdom⁸. Using the same multicentre dataset, the outcomes achievable at expert units with high complexity pelvic exenterations were defined and may similarly serve as a reference point for comparison of performance in these even more complex and uncommon resections (*Chapter 8.2*). Collectively, *Chapters 8.1* and *8.2* address *Thesis Aim 2* - to establish internationally applicable surgical quality benchmarks for pelvic exenteration surgery.

Implications for future research

Despite the identification of several independent predictors of each priority outcome reported in *Chapter 7*, early work on the development of a prediction model (coined 'EviSurg') for quantification of an individual patient's expected outcome demonstrated a lack of predictive discrimination. Therefore, further work is required toward development of this risk prediction tool

which can predict the priority outcomes of exenteration for an individual patient with high predictive discrimination. This work will form the basis of the candidate's post-doctoral studies.

Evaluation of additional potentially predictive preoperative variables, including molecular biomarkers, is planned to improve the predictive discrimination of the modelling of priority outcomes. One aspect of the candidate's planned post-doctoral work will involve collaboration with translational scientists and medical oncologists (both locally and internationally) to identify novel prognostic biomarkers in patients with LRRC, based on preoperative liquid and tissue biopsies. Preoperative circulating tumour DNA is one example of a potentially prognostic biomarker, which could be obtained from a preoperative blood test, and may be associated with cancer recurrence, survival and quality of life in patients with LRRC. Similarly, the somatic mutational profile of the tumour may also predict these long term oncological outcomes, however the prognostic role of ctDNA and mutational status have not been evaluated in patients with LRRC. Such preoperative biomarkers could be incorporated into and improve the discrimination of a risk prediction model for priority outcomes of exenteration. Increasing the cohort sample size available for modelling through international collaboration and pooling of data is also planned, utilising the current EviSurg methodology developed in this thesis.

After development of the prediction models using additional predictive variables and a larger sample size, external validation could be performed using data from the international exenteration units that contributed to the benchmarking analysis in *Chapter 8*. Following external validation, the risk prediction model could be used as the basis for a decision-making tool which will produce a recommendation for or against surgery for an individual patient based on the predicted priority outcomes for that patient. Using predicted values for survival, quality of life and clear resection margins (the priority outcomes), MDT consensus-based cut off values will be used to determine

patient outcome clusters (EviSurg tool): (i) surgery strongly recommended, (ii) borderline/marginal recommendation and (iii) surgery not recommended. The decision model recommendations will be compared to actual decisions using current practice with concordance and agreement statistics. By generating an evidence-based, reproducible recommendation for or against surgery, this tool will be available online for local referring clinicians to access and to support them at the point of diagnosis as well as MDTs at exenteration centres when making treatment decisions. This tool will promote standardisation of treatment decisions and reduce unwarranted variation in the both the decision to refer (at the local referrer level), and the decision to recommend surgery (at the MDT level). Adaption of the tool to patient populations with other advanced abdominopelvic cancers (e.g. colorectal peritoneal metastases, retroperitoneal sarcoma, upper gastrointestinal tumours) would then be attempted.

One of the key findings of *Chapter 4* was the significant heterogeneity in outcome measurement and reporting in exenteration literature, which significantly limits comparison of outcomes between units and across time periods. This major issue may be addressed by future research directed toward standardisation of outcome reporting³. Establishing a minimum dataset utilising an agreed lexicon of variables, i.e. the minimum data variables to be collected at specialised exenteration units, will require consensus support from exenteration centres internationally and barriers to development will include persisting variation in definitions of important outcomes such as R0 resection. It would seem appropriate to include the identified priority outcomes in any such minimum dataset, given these outcomes have consensus support from patients, carers and clinicians. Ensuring uniform, prospective data collection is critical to ensuring valid comparison of outcomes, benchmarking and quality improvement. It will be extremely difficult to improve the quality of the exenteration literature and produce meaningful research which advances the field without standardisation of terminology including outcome measures.

Variation in neoadjuvant treatment strategies for LRRC persists, both with respect to re-irradiation (radiotherapy in patients who have undergone radiotherapy as part of the initial treatment of their primary tumour) and chemotherapy^{2, 16-18}. Several groups continue to routinely use both re-irradiation and neoadjuvant chemotherapy prior to surgery for LRRC, while these strategies are rarely utilised at other centres². It is hypothesised that intensification of neoadjuvant or adjuvant treatments, in addition to R0 resection, may reduce the risk of disease recurrence and further improve long term survival in these patients. However, neoadjuvant chemotherapy has failed to show an improvement in R0 resection, disease-free or overall survival^{16, 17} over upfront surgery, and there is no data comparing outcomes of salvage surgery for LRRC with and without re-irradiation. Such disparate variation in treatment of LRRC is concerning. It is possible that preoperative identification of patients at high risk of disease recurrence based on molecular biomarkers may facilitate a more selective approach to neoadjuvant treatment, accurately tailoring its use to patients who stand to benefit. A number of centres, including the candidate's institution, are establishing novel biomarker research programs, which seek to understand LRRC at a molecular level and ultimately aim to develop a molecular biomarker-informed, tailored multimodal treatment approach to LRRC. This would not only further improve oncological outcomes and long-term survival for this group of patients, but also help to define a standardised multimodal treatment algorithm and reduce variation in treatment decision making.

The qualitative work presented in *Chapter 5* identified several potentially unmet survivorship needs for patients with LRRC which require further exploration, particularly as the number of patients undergoing surgery for LRRC at exenteration centres globally, and therefore the number of survivors, is increasing^{8, 9, 19-22}. Managing two permanent ostomies, issues related to perineal wounds and the empty pelvis syndrome, as well as mobility problems related to lower limb

neurological deficits are just some of the unique day-to-day challenges faced by survivors of LRRC identified in *Chapter 5*. Addressing barriers to supportive care and improving access to survivorship services beyond the immediate recovery and short to medium term cancer surveillance period is a priority, particularly for rural, regional or interstate patients. Solutions will need to be tailored to each particular healthcare setting, due to the inherent variation in referral pathways and decentralisation of services between and within different countries. In countries like Australia, which are geographically vast but small in terms of population, it may not be feasible for an exenteration centre to manage all survivors in the long term. One potential solution to this is the formalisation of a 'hub and spoke' model of survivorship care which is primarily provided at the local referring centres, with an open line of communication with the exenteration centre. Providing virtual prehabilitation, rehabilitation, educational information and supportive care in the future is likely to be more cost effective and more convenient for patients and may improve access to these important services. This is the subject of ongoing investigation ²³.

Future work is required to implement the pelvic exenteration benchmarks defined in *Chapter 8* into a continuous audit and feedback cycle within existing exenteration centres as part of ongoing quality improvement. One option to facilitate this would be the development of a cumulative, overall benchmark score ('exenteration benchmark index') for individual exenteration units, which could be used to compare both overall and individual domain surgical performance against international standards. By using the same 75th percentile as a benchmark threshold as used in *Chapter 8.1*, the centres scoring in the bottom 25% of the overall benchmark index would be incentivised to implement quality improvement measures. In a repeated cycle of audit and feedback where centres scoring in the lowest 25% are constantly trying to improve, then outcomes of all centres should progressively improve. Expanding the benchmarked metrics to include the more important priority outcomes (survival and quality of life) presents challenges, because these

outcomes depend heavily on factors other than surgical quality, including neoadjuvant and adjuvant treatments which remain unstandardised.

Limitations

The priority outcomes and their predictors presented in this thesis serve only as a guide for clinical decision making. Although comprehensive consensus methodology was utilised to ensure the priority outcomes reflected the shared priorities of patients, carers and an international group of exenteration clinicians (even despite unequal numbers of participants in each stakeholder group), these may not align with the priorities or preferences of an individual patient, which should always form the basis of patient-centred decision-making. This, however, represents a limitation in the clinical use of the priority outcomes and their predictors, rather than a limitation of the methodology used for their development. Furthermore, the group of patients who participated in both the qualitative studies (*Chapter 5*) and Delphi (*Chapter 6*) were, by definition, survivors and therefore represent a selected group. The perspectives and experiences of patients with LARC or LRRC who either declined or were not offered pelvic exenteration surgery, or who were deceased following surgery, were not incorporated and this may have introduced unavoidable selection bias. Furthermore, the views of clinicians captured in the Delphi study may represent a select group with subspecialist interest in exenterative surgery, and may not be generalisable beyond this group. Another limitation of the findings of the thesis, particularly *Chapters 7 and 8* relate to their generalisability outside of expert exenteration centres. The authors' institutional experience with now over 1200 exenterative resections, including a high proportion requiring bone or neurovascular resections, has shaped their MDTs decisions around resectability and patient selection. Similarly, the centres that contributed to the benchmarking analysis presented in *Chapter 8* are all, by definition as 'benchmarking centres', highly experienced exenteration units. Therefore, the

presented results may not be applicable outside such centres and should be interpreted in that context.

CONCLUSION

This thesis explored strategies which may, at least in part, address variation in treatment decision-making and outcomes in patients with LARC and LRRC. Resection margin status, survival and quality of life are now established as the most important outcomes of pelvic exenteration in this context, and are supported by patients, their carers and clinicians as the basis on which patient-centred treatment decisions should be made. Preoperative factors which independently predict these outcomes have been identified and should be considered by multi-disciplinary teams when formulating recommendations for or against surgery, and also be incorporated into shared decision-making conversations with patients and their carers. However, a simple 'preoperative' tool to define an evidence based prediction of overall outcome (EviSurg) was not possible and we still require more informed 'intuition-based' MDT decisions. The first surgical quality benchmarks for pelvic exenteration have been defined and can be used at exenteration units globally for comparative assessment of performance and quality improvement. While further work is required, the findings of this thesis contribute to the standardisation of treatment decisions and outcome, by promoting evidence-based decision making and rigorous quality improvement. It is hoped these findings will ultimately contribute to improved outcomes for patients with LARC and LRRC.

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Figure 1. Meeting of the multidisciplinary study committee, which included specialist surgeons, an experienced surgical outcomes researcher, a pelvic exenteration nurse specialist and two patient advocates. In these meetings, all outcomes of pelvic exenteration identified from the literature (*Chapter 4*) and during patient interviews (*Chapter 5*) were reviewed, merged into standardised outcomes, and catalogued by domain. Lay definitions were also developed before the standardised outcomes which were then distributed in the Delphi survey (*Chapter 6*), which was piloted by the committee. These meetings were organised and chaired by the candidate.



APPENDIX I:

ADDITIONAL PUBLICATIONS DURING CANDIDATURE RELEVANT TO THIS THESIS BUT NOT FORMING PART OF IT

2025:

Vu JK, **Brown KGM**, Solomon MJ, Ng KS, Sutherland S, Mahon K, Le BK, Austin KKS, Byrne CM, Lee PJ, Steffens D. Patterns and outcomes of disease recurrence after pelvic exenteration for locally recurrent rectal cancer. *Br J Surg*. 2025 Aug 1;112(8):znaf154

Vu J, **Brown KGM**, Solomon MJ, Ng KS, Mahon K, Le BK, Sutherland S, Lee PJ, Byrne CM, Austin KKS, Steffens D. Oligometastatic disease is not an absolute contraindication to pelvic exenteration in selected patients with locally recurrent rectal cancer. *Dis Colon Rectum* 2025;68(4):408-416

Peacock O, **Brown KGM**, Waters PS, Jenkins JT, Warriar SK, Heriot AG, Glyn T, Frizelle FA, Solomon MJ, Bednarski BK. Operative Strategies for Beyond Total Mesorectal Excision Surgery for Rectal Cancer. *Ann Surg Oncol*. 2025 Jun;32(6):4240-4249

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Steffens D, Solomon MJ, Karunaratne S, **Brown KGM**, Kim B, Lee P, Austin K, Byrne C, Whitehead L, Koh C. Long-term survival and quality of life in patients more than 10 years after pelvic exenteration. *Br J Surg*. 2025 May 31;112(6):znaf123. doi: 10.1093/bjs/znaf123

O'Dell M, White K, Johnstone C, Solomon MJ, **Brown KGM**, Steffens D, Koh C. Patient Experiences of Long-term Pain and Pain Management Following Pelvic Exenteration for Locally Recurrent Rectal Cancer: A Qualitative Study. *Dis Colon Rectum* 2025;68(2):209-216

2024:

Brown KGM, Ansari N, Solomon MJ. Contemporary management of advanced colorectal cancer: the Australian experience. *Med J Aust*. 2024 Mar 18;220(5):222-224.

Brown KGM, Solomon MJ. Topical haemostatic agents in surgery. *Br J Surg*. 2024 Jan 3;111(1):znad361. doi: 10.1093/bjs/znad361.

Austin KKS, **Brown KGM**, Solomon MJ. En bloc lateral pelvic compartment excision during pelvic exenteration: video vignette. *Br J Surg*. 2024 Jan 3;111(1):znad407.

Ebrahimi N, **Brown KGM**, Ng KS, Solomon MJ, Lee PJ. Impact of Intraoperative Decision-Making on Pathological Margin Status in Patients Undergoing Pelvic Exenteration for Locally Recurrent Rectal Cancer. *Dis Colon Rectum* 2024. 67(8):1024-1029

Risbey C, **Brown KGM**, Solomon MJ, McBride K, Steffens D. Cost-analysis of pelvic exenteration surgery for advanced pelvic malignancy. *Ann Surg Oncol* 2024;31(13):9079-9087

Ephraums J, **Brown KGM**, Solomon MJ, Austin KKS, Lee PJ, Leslie S, Byrne. Pelvic exenteration for locally advanced and recurrent prostate cancer. *Eur J Surg Oncol*; 2024 Jul;50(7):108384

2023:

Brown KGM, Solomon MJ, Steffens D, Ng KS, Byrne C, Austin KKS, Lee PJ. Pelvic exenteration for squamous cell carcinoma of the anus: oncological, morbidity and quality of life outcomes. *Dis Colon Rectum*. 2023 Nov 1;66(11):1427-1434

Brown KGM, Risbey C, Solomon MJ, Austin KKS, Lee PJ, Byrne CM. Pelvic exenteration for chronic fistulating pelvic sepsis after multimodal treatment of pelvic malignancy. *Eur J Surg Oncol*. 2023 Dec;49(12):107124.

Brown KGM, McBride KE, Anderson T, Solomon MJ. Delivering complex surgical services: lessons learned from the evolution of a specialised pelvic exenteration centre. *Aust Health Rev*. 2023 Dec;47(6):735-740.

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APPENDIX II:

ETHICS REVIEW COMMITTEE APPROVALS

All aspects of the work contained within this these were approved by the Sydney Local Health Distant Human Research Ethics Committee (RPA Zone). Approval confirmations are included in this appendix.

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



TELEPHONE: (02) 9515 6766
EMAIL: SLHD-RPAethics@health.nsw.gov.au
REFERENCE: X22-0422 & 2022/ETH02659

20 January 2023

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: Protocol No: X22-0422 & 2022/ETH02659– “Core Clinical Outcomes of Pelvic Exenteration for Locally Advanced and Recurrent Rectal Cancer: Identifying Patient and Clinician Priorities”

The Executive of the Ethics Review Committee, at its meeting of 20 January 2023 considered your correspondence of 20 January 2023. In accordance with the decision made by the Ethics Review Committee, at its meeting of 14 December 2022, ethical approval is granted.

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 4, 19 December 2022)
- Protocol (Version 2, 15 January 2023)* see additional condition below
- Participant Information Sheet – Delphi (Version 2, 15 January 2023)
- Participant Information Sheet – Patient Interview (Version 2, 15 January 2023)
- Participant Written Consent Form – Patient Interview (Version 2, 15 January 2023)
- eConsent Form (Version 1.1, 17 January 2023)
- Initial Email Script – Delphi (Version 1, 5 December 2022)
- Invitation to Participate Letter – Patient Interview (Version 1, 5 December 2022)

- Survey Email Script - Delphi (Version 1, 5 December 2022)
- Text Message Recruitment Template – Patient Interview (Version 1, 5 December 2022)
- First Round Survey – Patient (Version 1, 5 December 2022)
- First Round Survey – Carer (Version 1, 5 December 2022)
- First Round Survey – Clinician (Version 1, 5 December 2022)
- Second Round Survey (Version 2, 15 January 2023)
- Third Round Survey (Version 1, 5 December 2022)
- Telephone Interview Script – Patient Interview (Version 2, 15 January 2023)
- Semi Structured Interview Topic Guide (Version 1, 5 December 2022)
- Master Code Sheet – Patient Interview (Version 1, 5 December 2022)
- Master Code Sheet – Delphi (Version 1, 5 December 2023)
- Research Data Management Plan (14 January 2022)

Special Conditions:

- Please re-submit the Research Data Management Plan via a General Amendment in REGIS with all items completed. i.e., see page 10. Refer to guidance at <https://regis.health.nsw.gov.au/media/1723/qrg-resapp-ethics-amendment-completing-and-submitting.pdf>
- Please also submit the Round 2 and Round 3 Delphi survey instruments via general amendments in REGIS when these are finalised for our records. Update the version numbers and dates (tracked copies are not required).

* (If Applicable) In accordance with the National Statement, chapter 4.7; you must seek ethical approval from the HREC of the Aboriginal Health and Medical Research Council (AHMRC) if you intend to use ATSI status in any presentation or publication.

You are asked to note the following:

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

- Institute of Academic Surgery
- 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 **January 2024**. This will be through the submission of a milestone in REGIS.
- 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.

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.

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.

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

Regards,



Rosemary Carney
Executive Officer
Ethics Review Committee (RPAH Zone)

From: no_reply@regis.health.nsw.gov.au
Subject: X22-0422 & 2022/ETH02659: Notification of an amendment to a research study - General Amendment (151864) - Approved
Date: 17 November 2023 at 12:28 pm
To: professor.solomon@sydney.edu.au
Cc: kilian.brown@sydney.edu.au



Date of Decision Notification: **17 Nov 2023**
9.51/NOV23
Greater than low risk review pathway

Dear Professor Michael Solomon,

Thank you for submitting an Amendment for the following study;

X22-0422 & 2022/ETH02659: Core Clinical Outcomes of Pelvic Exenteration for Locally Advanced and Recurrent Rectal Cancer: Identifying Patient and Clinician Priorities

The Amendment has been reviewed on 17 Nov 2023, by the Executive Officer as delegated by the HREC Chair and has been approved.

Notification of an amendment to a research study - General Amendment with form ID 151864

The following documentation is included in this approval:

- First round survey - Patient (Version 2, 16 November 2023)
- First round survey - Clinician (Version 2, 16 November 2023)
- First round survey - Carer (Version 2, 16 November 2023)

In accordance with the National Statement, chapter 4.7; you must seek ethical approval from the HREC of the Aboriginal Health and Medical Research Council (AHMRC) if you intend to use ATSI status in any presentation or publication.

It is noted that the Sydney Local Health District Ethics Review Committee (RPAH Zone) is constituted in accordance with the National Statement on Ethical Conduct in Human Research, 2007 (NHMRC).

This email constitutes ethical and scientific approval only.

For NSW authorised sites (listed in REGIS): A Site General Amendment form will need to be submitted to each affected site. You are not required to upload this form or the ethics approved documents into the site form but you will need to identify this approved amendment form ID (151864).

Please contact us if you would like to discuss any aspects of this process further, as per the contact details below.

Yours Sincerely,

Keshani Ajith Piyantha
Assistant Administrator
Research Ethics & Governance Office | Royal Prince Alfred Hospital
Missenden Road CAMPERDOWN NSW 2050
Tel 02 9515 8200 Ikeshani.ajithpiyantha@health.nsw.gov.au
****COVID-19 Response****<https://www.slhd.nsw.gov.au/rpa/Research/covid19response.html>
For information about submitting an application through REGIS <https://www.slhd.nsw.gov.au/rpa/research/regis.html>

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



TELEPHONE: (02) 9515 6766
EMAIL: SLHD-RPAethics@health.nsw.gov.au
REFERENCE: X23-0141 & 2023/ETH00829

28 April 2023

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: Protocol No. X23-0141 & 2023/ETH00829 - International Benchmarking Study of Pelvic Exenteration for Rectal Cancer.

The Executive of the Ethics Review Committee, at its meeting of 28 April 2023 considered your correspondence of 27 April 2023.

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*.
- The Committee granted a waiver of the usual requirement for the consent of the individual for the use of their health information in a research project, in accordance with the *Health Records and Information Privacy Act 2002* (NSW) and the NSW Privacy Commissioner's Statutory guidelines on research and the NHMRC Guidelines approved under Section 95A of the Privacy Act 1988.

This approval includes the following:

- HREA (Version 1, 20 April 2023)
- Protocol (Version 1, 19 April 2023)* see additional condition below
- Data Collection Form (Version 1, 19 April 2023)
- List of Participating Centres (Version 1, 19 April 2023)
- SLHD Privacy Compliance Form (Version 3, October 2020)
- Research Data Management Plan (27 April 2023)

* (If Applicable) In accordance with the National Statement, chapter 4.7; you must seek ethical approval from the HREC of the Aboriginal Health and Medical Research Council (AHMRC) if you intend to use ATSI status in any presentation or publication.

You are asked to note the following:

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 **April 2024**. This will be through the submission of a milestone in REGIS.
- 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*.
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- 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.

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.

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.

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

Regards,



Rosemary Carney
Executive Officer
Ethics Review Committee (RPAH Zone)