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

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

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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, but may be associated with major morbidity, functional impairment and at least a temporary reduction in quality of life. Therefore, whether or not PE should be recommended for an individual patient presents a major decisional conflict. Currently, decision-making around whether PE is recommended does not follow an evidence-based approach, and is traditionally made with anticipated survival as the main outcome of interest. 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 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 locally advanced or recurrent rectal cancer and their carers (phase 1b). In phase 2, a survey of individuals who have undergone PE, 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 to predict priority outcomes using comprehensive multivariate modelling, and externally validated using data from an international PE collaboration.

Ethics and dissemination: Ethical approval has been granted by the Sydney Local Health District human research ethics committee for phases 1 and 2 (X22-0422 & 2022/ETH02659) and for maintenance of the PE database used in phase 3 (X13-0283 & HREC/13/RPAH/504).

Registration: PROSPERO registration number CRD42022351909.

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STRENGHTS & LIMITATIONS OF THIS STUDY

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

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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

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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 & 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 pelvic exenteration (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 pre-operatively

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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 CORMAC (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 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.

Multi-Disciplinary Advisory Committee

This study will be governed by a multi-disciplinary advisory committee (MAC), which will comprise of cancer specialists (surgeons, medical and radiation oncologists, senior surgical

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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 guidelines (15) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (16). A comprehensive search strategy

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has been created in conjunction with an experienced medical librarian. The protocol, including inclusion criteria and search strategy, has been published a priori on the PROSPERO registry (17).

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 undergo PE and their carers will be conducted using opened semi-structured interview format to maintain a participant-led dialogue. Two topic frameworks have been developed - for individuals who have undergone PE and for carers (supplementary file 1). 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 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 target sample size will be 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

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include age at time of surgery, gender, place of residence and tumour type. Carers for individuals who have undergo 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 audio-recorded, transcribed verbatim and imported into NVivo qualitative analysis software (NVivo 11, QSR International, Burlington, MA, 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.

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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 and colleagues (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. Outcomes will be excluded if considered to be of minimal clinical relevance and grouped domain. Standardised outcome terms and domains for each outcome will be ratified at a multi-disciplinary advisory committee (MAC) subcommittee meeting, attended by cancer specialists, an academic with experience in surgical outcomes, senior PE nursing staff and consumer advocates. 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

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managing advanced pelvic cancer) and Australia and New Zealand Pelvic Exenteration Multi-disciplinary teams (MDT).

- 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 five 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 timeframe. 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 utilised where all participants will be invited to forward the first round invitation email to anyone who is eligible to participate.

Data collection & 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 2 main sections:

- Section 1 will include demographic information specific to each participant group:
    - Patients: age, gender, tumour type (primary or recurrent rectal), months since

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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 multi-disciplinary 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 outcomes 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 re-distributed (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.

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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 standard deviations 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.

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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. A 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.

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 & analysis

For eligible patients, priority outcome data (e.g. survival, quality of life, complication rate) and all potential preoperative risk factors for those outcomes (e.g. demographics,

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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 utilised, 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 & 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 & 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 & 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.

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

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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.

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FIGURE LEGENDS

Figure 1. Schematical representation for the development of the pelvic exenteration risk prediction tool.

AUTHOR CONTRIBUTIONS

All authors made significant contributions to the design and development of this study and achieving ethical approval. KGMB was a major contributor in writing this paper. MJS, DS, KSN, PS, CK and KW contributed to the drafting and editing of this paper and approved the final manuscript.

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COMPETING INTERESTS

None declared.

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

Characteristics	Target number 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

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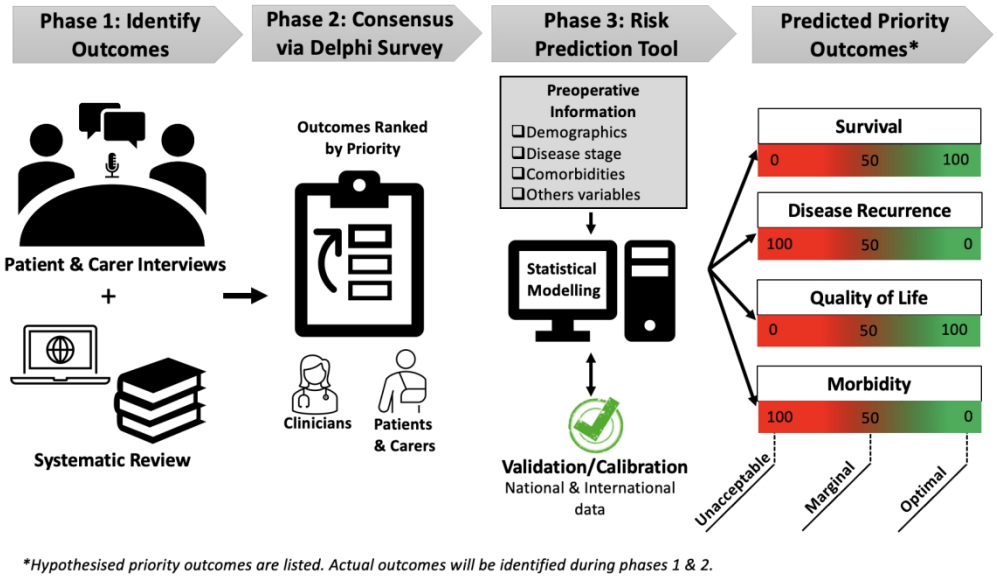

Schematical representation for the development of the pelvic exenteration risk prediction tool.

310x181mm (144 x 144 DPI)

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'?

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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'?

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Manuscripts

Title: **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 & 2022/ETH02659) and for maintenance of the database used in phase 3 (X13-0283 & 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.

Study registration: PROSPERO, CRD42022351909.

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STRENGHTS AND LIMITATIONS OF THIS STUDY

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

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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

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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 pelvic exenteration (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 pre-operatively

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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 CORMAC (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 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

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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 guidelines (15) and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (16). A comprehensive search strategy

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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 25th April 2023 for combinations of the following medical subject headings and keywords: pelvic exenteration or extended radical resection or multi-visceral 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 the supplementary file 1.

Retrospective and prospective cohort studies, cross-sectional studies, qualitative studies and randomised trials reporting outcomes of PE or multi-visceral 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.

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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 undergo PE and their carers will be conducted using opened semi-structured interview format to maintain a participant-led dialogue. Two topic frameworks have been developed - for individuals who have undergone PE and for carers (supplementary 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 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 undergo PE will also be invited to participate. According to

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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 audio-recorded, transcribed verbatim and imported into NVivo qualitative analysis software (NVivo 11, QSR International, Burlington, MA, 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

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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 and colleagues (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. Outcomes will be excluded if considered to be of minimal clinical relevance and grouped domain. Standardised outcome terms and domains for each outcome will be ratified at a MAC subcommittee meeting, attended by cancer specialists, an academic with experience in surgical outcomes, senior PE nursing staff and consumer advocates. 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 (MDT).

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- 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 five 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 timeframe. 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 utilised where all participants will be invited to forward the first round invitation email to anyone who is eligible to participate.

Data collection & 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 2 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

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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 outcomes 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 re-distributed (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:

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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 standard deviations 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

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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. A 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 & analysis

For eligible patients, priority outcome data (e.g. survival, quality of life, complication rate) and all potential preoperative risk factors for those outcomes (e.g. 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

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developed. An experienced biostatistician will be involved in conducting and interpreting these analyses. Two main approaches will be utilised, 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 & 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 & 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

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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)

CONTRIBUTORS

All authors made significant contributions to the design and development of this study and achieving ethical approval. KGMB was a major contributor in writing this paper. MJS, DS, KSN, PS, CK and KW contributed to the drafting and editing of this paper and approved the final manuscript.

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COMPETING INTERESTS

None declared.

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FIGURE LEGEND

Figure 1. Schematical representation for the development of the pelvic exenteration risk prediction tool

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

Characteristics	Target number 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

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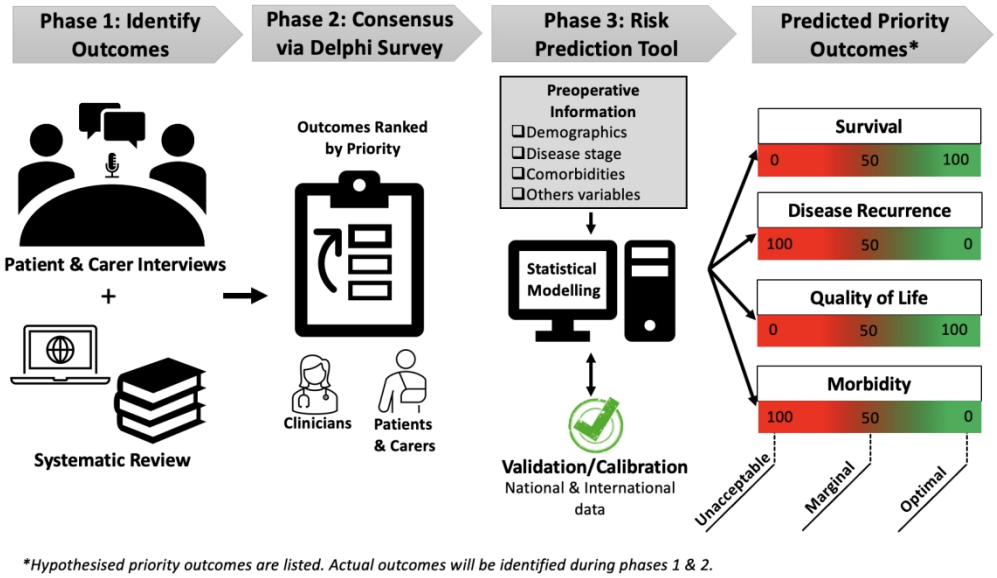

Schematical representation for the development of the pelvic exenteration risk prediction tool.

310x181mm (144 x 144 DPI)

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")

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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")

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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")

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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

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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"))

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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'?

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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'?

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PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol*

Section and topic	Item No	Checklist item	Location where item is reported
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Not applicable
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	Not applicable
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	p10, paragraph 1
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	p1
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	p21, paragraph 2
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	Not applicable
Support:			
Sources	5a	Indicate sources of financial or other support for the review	p21
Sponsor	5b	Provide name for the review funder and/or sponsor	Not applicable
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	Not applicable
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	p6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	p9 paragraph 1
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	p10, paragraph 2,3
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	p10, paragraph 2
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Supplementary data

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Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	p10, paragraph 4
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	p10, paragraph 4
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	p10, paragraph 4
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	p10, paragraph 4
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	p10, paragraph 4
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Not applicable
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Not applicable
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Not applicable
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Not applicable
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	p10, paragraph 4
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Not applicable
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Not applicable

*** It is strongly recommended that this checklist be read in conjunction with the PRISMA-P Explanation and Elaboration (cite when available) for important clarification on the items. Amendments to a review protocol should be tracked and dated. The copyright for PRISMA-P (including checklist) is held by the PRISMA-P Group and is distributed under a Creative Commons Attribution Licence 4.0.**

From: Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M, Shekelle P, Stewart L, PRISMA-P Group. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015 Jan 2;349(jan02 1):g7647.

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