The Clinical and Pathological Factors Influencing Outcomes Following Treatment for Locally Advanced or Locally Recurrent Rectal Cancer by Pelvic Exenteration

By

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Thesis abstract

Rectal cancer remains a significant oncological challenge, particularly when locally advanced or recurrent disease necessitates radical surgery. Pelvic exenteration (PE) offers the greatest potential for cure in carefully selected patients with locally advanced rectal cancer (LARC) or locally recurrent rectal cancer (LRRC), yet it is associated with considerable morbidity and variable long-term outcomes. This thesis explores the clinical, pathological, and host factors influencing outcomes following PE.

Chapters 1& 2 introduce the background, evolution, and rationale for exenteration surgery, outlining the indications, operative techniques, and perioperative management. They highlight the ongoing challenge of balancing oncological clearance with postoperative function and quality of life and identify key knowledge gaps in predicting outcomes in this complex patient group.

Chapter 3 presents a systematic review, exploring the clinicopathological determinants of outcome following resection for locally advanced and recurrent rectal cancer. Margin status consistently emerges as the strongest predictor of survival, yet the biological factors driving local recurrence remain poorly understood. Current literature gaps in defining and characterising locally recurrent tumours are explored. The chapter underscores the need for a more integrated understanding of tumour biology and host response beyond conventional staging.

Chapter 4 describes the creation of a prospectively maintained Complex Cancer Clinic (CCC) database at St Mark's Hospital. It describes patient inclusion, data collection, and methodology used to assess surgical, clinical, and pathological factors in patients undergoing exenteration. This cohort forms the foundation for subsequent clinical and translational analyses. Included in this chapter are the outcomes for patients who are referred to the CCC but do not undergo PE, which provides a valuable insight into the natural evolution of the disease.

Chapter 5 explores the boundaries of what is achievable with modern PE surgery by presenting the outcomes for patients who have undergone PE with en bloc high sacrectomy and extended lateral pelvic sidewall excision. Despite historical concerns over morbidity, the study demonstrates that R0 resection rates of 95% and 5-year survival exceeding 56% are achievable

in specialised centres. Although perioperative morbidity and mortality remain significant, most long-term survivors retain good mobility and independence. These findings challenge traditional contraindications to surgery for high sacral or sidewall involvement and emphasise the importance of centralised multidisciplinary care.

Chapter 6 evaluates outcomes of perineal reconstruction following complex rectal cancer resections, comparing standard versus high-complexity exenterations to assess if a greater magnitude of surgery influences perineal wound-related morbidity. In a cohort of 194 patients, flap-related complications were common but not significantly increased by surgical complexity, with no cases of total flap failure. Obesity and total pelvic exenteration were independent predictors of short-term wound morbidity, while urinary tract leaks drove late complications. The study concludes that gluteal flaps provide a durable, versatile reconstructive option even in high-risk settings, highlighting the importance of multidisciplinary planning and patient optimisation.

Chapters 7 and 8 examine clinical, surgical and tumour-related factors influencing both short- and long-term outcomes. These chapters confirm that achieving an R0 resection remains paramount but demonstrate that other host factors, such as comorbidity, inflammation, and metabolic state, also contribute to postoperative risk and survival variability. They also reveal that the key factors that appear to influence outcome in patients with LARC differ from those in LRRC.

Chapter 9 extends the analysis to host body composition, using computed tomography (CT)–based body composition profiling to assess sarcopenia, myosteatosis, and visceral obesity. Myosteatosis and visceral obesity were significantly associated with increased postoperative morbidity and prolonged hospital stay, while sarcopenia showed a weaker association, likely reflecting selection bias within this fitter surgical cohort. Although no CT-derived body composition measures significantly influenced long-term survival, a trend toward reduced local recurrence-free survival was observed among patients with myosteatosis. These findings emphasise the interplay between tumour biology, systemic inflammation, and host physiology in shaping patient outcomes.

Chapter 10 provides a unique insight into the tumour microenvironment in locally recurrent rectal cancer, focusing primarily on immune cell infiltration and tumour stromal composition. It highlights significant variability in immune and stromal profiles between primary and

recurrent disease, suggesting distinct biological behaviour. These findings underscore the importance of tumour–host interactions in influencing local control and recurrence patterns.

In conclusion, this thesis demonstrates that outcomes following pelvic exenteration are determined not only by surgical and pathological factors but also by host-related characteristics, including systemic inflammation and altered body composition. Integrating these elements into preoperative assessment frameworks may enhance patient selection, enable risk-adapted perioperative care, and guide the development of prehabilitation and nutritional optimisation strategies. Future research exploring the molecular mechanisms linking tumour–host interaction, metabolic dysfunction, and immune modulation could provide novel therapeutic insights and refine multidisciplinary management in this complex field.

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Dedications

To my husband, for your steadfast belief in me; to my children Max and Margot, whose curiosity, laughter, and resilience remind me every day why perseverance matters and to my parents, whose love and sacrifices made everything possible.

Author Declaration

The work presented in this thesis was undertaken during a period of research between 2018 and 2022 at St Mark's Hospital, London and the University of Glasgow. The work was completed whilst working as a specialist registrar in General Surgery in North East and Central London deanery between 2022 and 2025.

I declare the work presented in this thesis was undertaken by myself except where indicated below:

Chapter 3: The non-operative data and analysis of this was conducted by Baha Siam (Consultant General Surgeon, Beilinson Hospital, Rabin Medical Centre, Petah Tikva, Israel) using my data to draw comparisons with the operative cohort.

Chapter 10: The data for the Glasgow Primary cancer cohort was collected and analysed by Ross McMahon (University of Glasgow, PhD Research Fellow). Dr Kathryn Pennel (Postdoctoral Fellowship, School of Cancer Sciences, University of Glasgow) assisted in the analysis of the tumour microenvironment and scoring of tissue samples.

Publications

The work presented in this thesis has resulted in the following publications:

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Presentations

The work presented in this thesis has resulted in the following conference presentations:

- Pathological determinants of outcome following resection of complex rectal cancer

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- Clinical determinants of outcome following resection of complex rectal cancer

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- Perineal complications after flap reconstruction following extended resections for advanced pelvic malignancy

Poster. ACPBGI, 2023

- Histological evaluation of tumour characteristics of locally recurrent rectal cancer specimens

Poster. ACPBGI, 2023

- Rehabilitation pathway for complex colorectal cancer surgery patients.

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- Evaluation of Extended Lateral Pelvic Sidewall Excision [ELSiE] for Locally Advanced & Recurrent Rectal Cancer (RCC) involving the lateral pelvic sidewall

Poster. UEG, Barcelona. October 2019

- Perineal flap reconstruction following pelvic exenteration

Poster. UEG, Barcelona. October 2019

- Utility of High Subcortical Sacral resection {HiSS] for Locally Advanced & Recurrent Rectal Cancer extending onto L5/S1/2

Poster. UEG, Barcelona. October 2019

- Outcomes from a dedicated complex cancer service for locally advanced and recurrent colorectal and anal cancers

Poster. ESCP, Vienna. September 2019

- An assessment of R1/R2 excisions and their outcomes after pelvic exenteration surgery for locally advanced and recurrent rectal cancer

Poster. ESCP, Vienna. September 2019)

- The evolution of pelvic salvage surgery for locally advanced and recurrent rectal cancer in a specialist centre

Poster. ACPGBI, Dublin. July 2019

List of abbreviations

ACPGBI	The Association of Coloproctology of Great Britain and Ireland
AJCC	The American Joint Committee on Cancer
APC	Adenomatous polyposis coli
APE	Anterior pelvic exenterations
ASR	Age-standardised rate
BMI	Body mass index
CCC	Complex Cancer Clinic
CCI	Charlson Comorbidity Index
CEA	Carcinoembryonic antigen
CIMP	CpG island methylator phenotype
CPET	Cardiopulmonary Exercise Tolerance
CRC	Colorectal cancer
CRM	Circumferential resection margin
CRP	C-reactive protein
CRT	Chemoradiotherapy
CT	Computerised tomography
CTBC	Computerised tomography body composition
CVD	Cardiovascular disease
DFS	Disease free survival
ELAPE	Extralevator abdominoperineal excision
EMVI	Extramural venous invasion
ERAS	Enhanced recovery after surgery
ESMO	European Society of Medical Oncology
FAP	Familial adenomatous polyposis
IBD	Inflammatory bowel disease
IGAP	Inferior gluteal artery perforator
IORT	Intraoperative radiotherapy
IQR	Interquartile range
JPS	Juvenile polyposis syndrome
KM	Klintrup–Mäkinen
LARC	Locally advanced rectal cancer
LR	Local recurrence
LRFS	Local recurrence free survival
LRRC	Locally recurrent rectal cancer
LSMI	Lumbar skeletal muscle index
LVI	Lymphovascular invasion
MA	Muscle attenuation
MAP	MUTYH-Associated Polyposis MUTYH-associated polyposis
MDT	Multidisciplinary team
MMR	Mismatch Repair
MPE	Modified pelvic exenteration
MRF	Mesorectal fascia
MRI	Magnetic resonance imaging
MSI	Microsatellite instability
NHS	National Health Service
NICE	National Institute of Clinical Excellence

NLR	Neutrophil-to-lymphocyte ratio
NS	Not stated
OR	Odds ration
OS	Overall survival
PE	Pelvic exenteration
PET	Positron emission tomography
PLR	platelet-to-lymphocyte ratio
PNI	Perineural invasion
PPE	Posterior pelvic exenterations
RCPath	Royal College of Pathologists
RFS	Recurrence-free survival
RT	Radiotherapy
SGAP	Superior gluteal artery perforator
SM	Skeletal muscle
SPS	Serrated polyposis syndrome
TAMIS	Transanal minimally invasive surgery
TME	Total mesorectal excision
TNM	Tumour, Node, Metastasis
TNT	Total neoadjuvant therapy
TPE	Total pelvic exenteration
TRG	Tumour regression grade
TSP	Tumour stromal percentage
UC	Ulcerative colitis
UICC	Union for International Cancer Control
UK	United Kingdom
UKPEN	United Kingdom Pelvic Exenteration Network
USA	United States of America
VAC	Vacuum assisted closure
VAT	Visceral adipose tissue
VRAM	Vertical rectus abdominis myocutaneous
WHO	World Health Organisation

Chapter 1: Introduction

1.1 Epidemiology of colorectal cancer

Colorectal cancer (CRC), characterised by a malignant growth in the colon or rectum, is the third most common cancer worldwide and accounts for up to 10% of all cancers[1]. According to Global Cancer Observatory data an estimated 1.9 million new cases were diagnosed worldwide in 2022, and the disease accounted for 904,019 deaths globally[1]. The incidence of disease worldwide is projected to increase to 3.2 million by 2040, demonstrating the significant global health burden of CRC[2]. There is significant geographical variation in its incidence, with the highest rates reported in Europe, Australia and New Zealand[1]. The age-standardised rate (ASR) of colorectal cancer in Oceania and Europe is 31.1 per 100,000 and 30.5 per 100,000, respectively. This contrasts with the low incidence in continents such as Africa (ASR 8.2 per 100,000) and Asia (ASR 15.6 per 100,000)[1]. This suggests both environmental and genetic factors are likely to influence the differences observed between different populations. There are also significant geographical variations in mortality rates from CRC worldwide, with the highest rates seen in Eastern Europe[1]. Variation in incidence and mortality exists between males and females, with a higher incidence in males observed worldwide: ASR 21.9 per 100,000 males compared to ASR 15.2 per 100,000 females in 2022[1].

In the United Kingdom, there were 49,429 new cases of colorectal cancer diagnosed in 2022, and more than 22,868 deaths were attributed to the disease. 54% of cases were observed in men and 46% in women, with most cases diagnosed over the age of 70 years (61%)[3,4]. The commonest site of cancer is the rectum (31% in males, 22% females), followed by the sigmoid colon (22% males, 19% females), then the caecum (12% males, 18% females)[4]. The incidence varies across the UK, with the highest rates seen in Scotland, with an ASR of 75.1 per 100,000 compared with an ASR of 69.1 in England in 2017-2019[4]. Social deprivation appears to influence the incidence of CRC in males in England, with a 9% increase in incidence in the most deprived quintile compared to the least deprived[4]. There is no difference in the incidence of cases in females in England when comparing the most deprived and least deprived quintiles. Social deprivation also influences mortality due to lower gastrointestinal cancer in the UK, with 31% more deaths in males and 25% more female deaths when the most deprived quintile is compared to the least deprived[5].

Over the last decade, there has been a reduction in the overall incidence of cases, with the greatest reduction observed in men (10% reduction in males and 4% in females)[4]. The National Bowel Cancer Screening Programme was launched in 2006 and is likely to have contributed to this reduction in incidence[6]. Despite this overall fall in annual incidence, there is a worrying increase in cases in young adults over the last two decades[7,8]. In Europe, the most concerning rise in incidence was for those aged 20-29 years, where there was a 7.9% increase in annual incidence observed from 2004 to 2016. Incidence also increased to a lesser extent for those aged 30-39 (4.9% from 2005-2016) and 40-49 years (1.6% from 2004-2016)[8]. Reassuringly, despite this rising incidence, mortality rates have not shown a corresponding increase. This may be related to improved screening programmes and better oncological and surgical treatment options.

1.2 Pathogenesis of colorectal cancer

Colorectal cancer develops through a multistep process involving genetic and epigenetic mutations that lead to unregulated cell growth and proliferation of cells, leading to tumour invasion and metastasis[9]. Approximately 80% of cases of colorectal cancer are sporadic, with most cases arising from an adenoma that transforms into a malignant lesion over a period of 10-20 years. Environmental factors, diet, and gut microbiota also influence CRC pathogenesis.

1.3 Molecular mechanism of colorectal carcinogenesis

Sporadic CRC arises from the accumulation of genetic and epigenetic alterations in colon epithelial cells, primarily driven by three molecular pathways: chromosomal instability (CIN), microsatellite instability (MSI), and the CpG Island Methylator Phenotype (CIMP). These pathways disrupt normal cellular regulation, leading to uncontrolled proliferation and tumorigenesis. The study of the molecular basis of predominantly familial colorectal cancer has greatly enhanced our understanding of the mechanisms driving sporadic CRC, as many of the same genetic alterations are shared between the two.

The chromosomal instability pathway accounts for approximately 80% of sporadic CRCs and was traditionally thought to follow the classic adenoma-carcinoma sequence that was first proposed by Fearon and Vogelstein in 1988[10]. This model of colorectal tumorigenesis describes an initial acquisition of genetic mutations that lead to increased function of oncogenes and loss of function of tumour suppressor genes, such as the adenomatous polyposis coli (APC) gene,

KRAS and TP53, leading to a selective advantage to clones of cells[10]. The APC gene, considered to be a gatekeeper of normal colonic epithelium, when altered by somatic mutations or hypermethylation, can lead to the development of adenomas due to activating Wnt/β-catenin signalling, promoting adenoma formation[11,12]. Somatic mutations predominantly cause a truncation of APC, resulting in its inactivation, and are thought to be an initiating event in up to 80% of colorectal adenomas and carcinomas[13,14]. Mutations of the oncogene KRAS may occur, which drive uncontrolled cell growth by constitutively activating the MAPK pathway, whilst later events include TP53 gene loss that disables apoptosis and promotes genetic instability[15]. However, more recent work, including that of Tomlinson *et al.*, has refined this paradigm by proposing that colorectal carcinogenesis represents a dynamic process of branched clonal evolution rather than a strictly linear progression. In this model, multiple subclones with distinct genetic alterations coexist and compete within the tumour microenvironment, with selective pressures, such as immune surveillance and oncological therapy, driving heterogeneity and influencing tumour behaviour and outcome[16].

Approximately 10-15% of sporadic cancers exhibit microsatellite instability due to defective DNA mismatch repair (MMR) caused by inactivation of one of the four mismatch repair genes MLH1, MSH2, MSH6, and PMS2[15,17]. MMR genes are responsible for encoding proteins that identify and repair errors that arise due to DNA polymerase slippage during DNA replication[18]. Microsatellites are short repetitive sequences of DNA that are scattered throughout the genome and are prone to errors during replication. Therefore, replication errors can accumulate in the presence of defective MMR genes, leading to variations in the length of microsatellites in tumour DNA, which is called microsatellite instability[19]. A panel of five microsatellites are assessed, and if two or more are unstable, this is termed high frequency MSI (MSI-H) and low frequency MSI if only one of the five markers show instability[20]. MSI-H tumours typically have a better prognosis than those with MSI low or microsatellite stable tumours and are likely to respond well to immunotherapy[21].

Lastly, a proportion of sporadic CRC will be due to CIMP that involves widespread promoter hypermethylation, silencing tumour suppressor genes such as MLH1 and CDKN2A and these tumours are strongly associated with BRAF mutations[22]. Both CIMP and BRAF mutations are strongly associated with serrated adenomas which makes then distinct as they are not initiated through the classical APC mutations[21].

1.4 Aetiology of colorectal cancer

The aetiology of colorectal cancer CRC is multifactorial, involving genetic, environmental, and lifestyle factors.

1.4.1 Inherited syndromes

Although approximately 20% of those with CRC will have a family history of a primary relative having the disease, only 5-10% of these cancers are due to an identifiable inherited genetic alteration[23]. These inherited syndromes arise due to germline mutations that significantly increase lifetime cancer risk. Identification of these syndromes is critical for implementing targeted surveillance, genetic counselling, and risk-reduction strategies. The two most common hereditary CRC syndromes are hereditary non polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP).

1.4.1.1 Hereditary Non Polyposis Colorectal Cancer

Hereditary non polyposis colorectal cancer is the commonest hereditary CRC, accounting for approximately 50% of these cases. At least half of the patients with HNPCC have an autosomal dominantly inherited disorder caused by germline mutations in DNA MMR genes, predominantly MLH1, MSH2, MSH6, and PMS2 or deletions in EPCAM leading to MSH2 silencing[24,25]. These patients have Lynch syndrome, which accounts for approximately 5% of all CRCs and predisposes individuals to various malignancies, including endometrial, ovarian, gastric, small bowel, hepatobiliary, and urinary tract cancers[24,26].

The hallmark of Lynch syndrome-associated cancers is MSI resulting from MMR deficiency (as previously discussed). Universal testing of all CRCs for MMR deficiency has been recommended by the National Institute for Clinical Excellence (NICE) since 2017 to improve the detection rates of Lynch syndrome[27].

Clinically, Lynch syndrome-associated CRCs tend to occur at a younger age, are often right-sided, and may have a better prognosis than sporadic cases[19]. Surveillance colonoscopy from age 25 significantly reduces CRC incidence and mortality in those with Lynch syndrome and is recommended for those with MLH1 and MSH2 gene mutations and from age 35 for those with MSH6 and PMS2 gene mutations[28]. Genetic counselling and cascade testing of relatives are essential components of its management.

1.4.1.2 Familial Adenomatous Polyposis

Familial adenomatous polyposis (FAP) is a rare, inherited colorectal cancer syndrome caused by germline mutations in the APC gene located on chromosome 5q21[29]. It follows an autosomal dominant pattern of inheritance with nearly 100% penetrance. The most frequently observed germline mutations in the APC gene occur at codons 1061 and 1309, together accounting for nearly one-third of all pathogenic variants identified in patients with FAP[12]. The two-hit hypothesis proposed by Knudson is central to understanding its pathogenesis: individuals inherit a germline APC mutation in one allele, and tumourigenesis occurs when the remaining wild-type allele is inactivated through somatic events such as point mutation, promoter hypermethylation, or most frequently, loss of heterozygosity[12]. This loss of heterozygosity results in functional inactivation of the APC protein[30].

FAP is characterised by the development of hundreds to thousands of adenomatous polyps in the colon and rectum, typically beginning in adolescence. If untreated, CRC develops in almost all affected individuals by the age of 40[31].

Extracolonic manifestations are common and include duodenal adenomas, desmoid tumours, osteomas, congenital hypertrophy of the retinal pigment epithelium and increased risk of hepatoblastomas, thyroid and pancreatic cancers[32].

1.4.1.3 MUTYH-Associated Polyposis

MUTYH-associated polyposis (MAP) is an autosomal recessive colorectal cancer syndrome caused by biallelic mutations in the MUTYH gene, involved in base excision repair. MAP typically presents with 10–100 adenomas and a lifetime colorectal cancer risk of up to 80%[33]. Onset is usually in the fourth or fifth decade, resembling attenuated FAP. Extra-colonic manifestations include duodenal polyps and increased risk of other cancers, such as ovarian and bladder[34].

1.4.1.4 Serrated polyposis syndrome

Serrated polyposis syndrome (SPS) is characterised by numerous serrated polyps throughout the colon with an associated increased risk of CRC. Currently, no genetic mutations have been identified. The World Health Organisation (WHO) have defined clinical criteria to aid diagnosis based on the number and size of serrated colonic polyps. Patients must fulfil one of two criteria: criteria one is the presence of at least five serrated lesions/polyps proximal to the

rectum, with all being >5mm in size or more than two being ≥10mm; criteria two includes more than 20 serrated lesions/polyps of any size distributed throughout the large bowel with ≥ 5 being proximal to the rectum [35]. The prevalence of CRC in patients with SPS is estimated to be between 15-30%[36,37]

1.4.1.5 Hamartomatous Polyposis Syndromes

Hamartomatous polyposis syndromes are a group of rare inherited disorders characterised by the development of hamartomatous polyps in the gastrointestinal tract and an increased risk of gastrointestinal and extraintestinal cancers. The main syndromes include Peutz-Jeghers syndrome (PJS)**, j**uvenile polyposis syndrome (JPS)**,** and PTEN hamartoma tumour syndrome**,** which includes Cowden syndrome**.**

PJS is caused by mutations in the STK11 gene and is associated with peri-oral pigmentation and a high lifetime risk of colorectal, pancreatic, breast, and other cancers[38]. Juvenile polyposis syndrome**,** typically due to mutations in SMAD4 or BMPR1A, is characterised by multiple juvenile polyps and a significantly elevated risk of colorectal and gastric cancers[39]**.**Cowden syndrome**,** caused by PTEN mutations, is linked with multiple hamartomas and increased risk of breast, thyroid, and endometrial cancers[40].

1.4.2 Host factors and colorectal cancer

Several host factors significantly influence the development and progression of colorectal cancer that will now be discussed, including age, sex, obesity, inflammation and the gut microbiome.

1.4.2.1 Age

Age is a major risk factor for CRC, with incidence increasing significantly after age 50[41]. This is attributed to the accumulation of genetic mutations over time, age-related immune decline, and prolonged exposure to environmental carcinogens. However, despite an increase incidence of colorectal cancer with age, the incidence of metastatic disease decreases suggesting these tumours may have a less aggressive phenotype [42,43].

1.4.2.2 Sex

The influence of sex on the development of colorectal cancer is multifactorial through hormonal, genetic and lifestyle factors. As previously discussed, men have a higher incidence of CRC compared to females. Sex hormones are thought to play a protective role in females and hormone replacement therapy has been shown to reduce the incidence of CRC incidence in post- menopausal women in large scale population analysis[44]. The influence of oestrogen on colorectal cancer tumorigenesis is not fully understood but thought to be mediated through the oestrogen receptor ERβ which has a role in colonic cell haemostasis[45]. Furthermore, anatomical differences in tumour location and microsatellite instability patterns have been observed between sexes, influencing tumour biology and prognosis [46].

1.4.2.3 Obesity

Obesity, particularly excess visceral adiposity, is a significant modifiable risk factor in the development and progression of CRC. In a UK population-based study, it was reported that each 5kg/m^2 increase in body mass index was associated with a 10% higher risk of CRC[47]. Several causative mechanisms have been identified that link excess body fat and CRC, including chronic inflammation, adipokine dysregulation, insulin resistance and hyperinsulinaemia.

Visceral adiposity, unlike subcutaneous fat, is metabolically active and enriched with adipocytes, macrophages and other immune cells that promote a chronic inflammatory state, by secreting a range of pro-inflammatory cytokines such as Interleukin-6 (IL-6) and Tumour Necrosis Factor-alpha (TNF- α), which contribute to a tumour-promoting microenvironment[48]. These inflammatory mediators can enhance cell proliferation, inhibit apoptosis, and disrupt immune surveillance within the colonic mucosa.

Adipocytes secrete several bioactive peptides, including leptin and adiponectin, which are involved in cellular metabolism and inflammation. Adiponectin exerts anti-inflammatory, insulin-sensitising and anti-proliferative effects, and its production is reduced in obesity[49]. Reduced plasma levels of adiponectin have been associated with both colonic adenomas and adenocarcinomas[50]. Leptin is produced by white adipose tissue, and its circulating levels are proportional to the amount of body fat; therefore, elevated levels are present in obesity. Leptin enhances the production of inflammatory mediators and has been reported to promote colonic carcinogenesis[51].

Obesity is associated with hyperinsulinaemia and elevated insulin-like growth factor-1, which are determinants of cellular proliferation and apoptosis. Therefore, this may further stimulate colorectal carcinogenesis through mitogenic and anti-apoptotic pathways[52].

1.4.2.4 Local and systemic inflammation

Both local inflammation, within the colorectal mucosa, and systemic inflammation play a pivotal role in the initiation, progression, and prognosis of CRC.

1.4.2.4.1 Inflammatory bowel disease

Patients with inflammatory bowel disease (IBD), particularly ulcerative colitis (UC) and Crohn's colitis, face an increased risk of developing colorectal cancer. The chronic mucosal inflammation characteristic of IBD promotes a pro-tumorigenic environment, where repeated cycles of injury and repair lead to dysplasia and malignant transformation[53]. The risk of CRC in IBD correlates with several factors: disease duration, extent of colonic involvement, severity of inflammation, and presence of co-existing conditions such as primary sclerosing cholangitis[54].

In UC, pancolitis and long-standing inflammation significantly increase CRC risk. In a large meta-analysis incidence rate of CRC in patients with UC has been demonstrated to be 2% at 10 years, 8% at 20 years and 18% at 30 years[55]. Surveillance colonoscopy is a key strategy for early detection, with regular screening advised after 8 years of disease onset in high-risk patients[56]. Despite this, CRC accounts for up to 15% of deaths in patients with IBD[54].

Although many of the same molecular mechanisms occur in sporadic CRC and IBD associated CRCs these may not occur in the same order and the tumour biology is different. Chronic inflammation is likely the initiating step in tumour development and unlike the adenoma-carcinoma sequence in sporadic cases, IBD CRC develops through an inflammation-dysplasia-carcinoma sequence[57]. The typical series of genetic mutations seen in tumour suppressor genes and oncogenes observed in sporadic CRC is 'reversed' with early loss of TP53 function, a hallmark of early IBD CRC and APC mutations occurring late (and only in <40% cases)[58,59].

14.2.4.2 Systemic inflammation and use of anti-inflammatories

Systemic inflammation is increasingly recognised as a key mediator in the development of CRC. Chronic inflammation contributes to a pro-tumorigenic environment through the generation of reactive oxygen species, promotion of genomic instability, and stimulation of cell proliferation and angiogenesis[60]. Observational studies have shown that elevated inflammatory markers, such as C-reactive protein (CRP), IL-6, and TNF-α, are associated with an increased risk of CRC[61].

Aspirin and other non-steroidal anti-inflammatory drugs (NSAIDs) have been extensively studied for their chemopreventative effects in CRC. Aspirin inhibits cyclooxygenase (COX) enzymes, particularly COX-2, which is often upregulated in colorectal adenomas and carcinomas and is involved in prostaglandin-mediated inflammation and tumour progression[62]. Randomised trials and meta-analyses have demonstrated that long-term aspirin use is associated with a significant reduction in CRC incidence and mortality, particularly in individuals at high risk, such as those with Lynch syndrome or a history of adenomas[63]. The Cancer Prevention Programme 2 (CAPP2) trial showed that 600 mg of aspirin daily for two years significantly reduced CRC incidence in Lynch syndrome patients over long-term follow-up[64]. However, the use of aspirin must be balanced against the risks of gastrointestinal bleeding and other adverse effects. Results of the CAPP3 trial that compared the effect of 600mg, 300mg or 100mg daily should be available soon[65]. The benefits of aspirin after CRC diagnosis have also been demonstrated, and this may be influenced by genetic and molecular tumour characteristics, such as PIK3CA mutation status [66].

1.4.2.5 Gut microbiome

The gut microbiome has been shown to influence inflammation, immune function and metabolism. Dysbiosis, the imbalance in normal microbial composition, has been linked with CRC. Specific bacterial species such as Fusobacterium nucleatum and enterotoxigenic Bacteroides fragilis have been implicated in CRC development. These bacteria may influence tumour progression by activation of Wnt/β-catenin signalling pathways[67,68].

In addition to the bacterial composition of the microbiome, its metabolites have also been implicated in disease. Bacterial fermentation of dietary fibres releases short-chain fatty acids, which have anti-inflammatory and anti-proliferative effects through maintenance of intestinal homesostasis[69,70]. A reduction in short-chain fatty acid producing bacteria has been observed

in CRC[71,72]. This demonstrates the complex interplay between the microbiome, diet and colonic mucosa in colorectal cancer development.

1.4.3 Environmental and lifestyle factors

Environmental and lifestyle factors play a crucial role in the aetiology of CRC, influencing both risk and disease progression. Among the most significant modifiable risk factors are physical inactivity, diet, alcohol consumption, and smoking.

1.4.3.1 Physical activity

A sedentary lifestyle and lack of regular physical activity have been consistently linked to increased CRC risk[73]. In a study using UK Biobank data, this effect was most pronounced in men and for proximal colon cancers, with limited effects seen in rectal cancer[74]. Physical activity improves gut motility, reduces insulin levels and inflammation, and enhances immune surveillance, all of which contribute to cancer prevention[73]. Trial data have also demonstrated that it may improve disease-free survival (DFS). A phase III randomised trial of a 3-year structured exercise programme versus health education in 889 patients with colon cancer who had completed adjuvant chemotherapy demonstrated improved DFS at 5 years[75].

1.4.3.2 Diet

Numerous food types have been implicated in the development of CRC. Many meta-analyses have demonstrated that diets high in red and processed meats are associated with increased CRC incidence[76]. These foods contain haem iron, nitrates, and nitrites, which can form carcinogenic N-nitroso compounds and promote oxidative stress[77]. High-temperature cooking methods, such as grilling or frying, also produce heterocyclic amines and polycyclic aromatic hydrocarbons, which are linked to colorectal carcinogenesis[76].

In contrast, diets rich in fibre are protective against CRC[78]. Fibre increases stool bulk, reduces intestinal transit time, and supports the growth of beneficial gut microbiota, which produce short-chain fatty acids like butyrate with anti-inflammatory and anti-tumour properties[79]. An umbrella review of dietary influences on CRC also found that calcium and yoghurt were associated with reduced CRC incidence[78]. Calcium binds to unconjugated bile salts and free fatty acids which may minimise their toxic effects in the colonic lumen[80]. The protective effects of yoghurt may be mediated through both its calcium contents and its modulation of the gut microbiome due to the presence of lactic acid producing bacteria[81].

High intake of refined carbohydrates, saturated fats, and sugar-sweetened beverages, which are typical of Western dietary patterns, has been associated with a higher CRC risk, partly through their contribution to obesity, insulin resistance, and chronic inflammation[78].

Alcohol is a well-established risk factor for colorectal cancer with risk increasing in a dose dependant manner[78,82]. Ethanol is metabolised to acetaldehyde, a known carcinogen that can cause DNA damage and promote oxidative stress. Chronic alcohol intake may also impair folate metabolism and disrupt gut barrier function, contributing to carcinogenesis[83].

The association between smoking and increased risk of CRC, particularly for cancers of the rectum and in individuals with long-term or heavy tobacco use, has been demonstrated by a large-scale meta-analysis[84]. Carcinogens in tobacco smoke, such as polycyclic aromatic hydrocarbons and nitrosamines, can induce DNA damage and contribute to tumour initiation[84].

1.5 Tumour staging and prognosis

Colorectal cancer staging and grading are critical components in determining prognosis, guiding treatment, and predicting response to therapy. The first published classification of colorectal cancer stage was by Dr Cuthbert Dukes, a pathologist at St Mark's Hospital, in 1932[85]. The Dukes staging system categorised CRC into three stages: Dukes A- tumour confined to the mucosa or submucosa, Dukes B- Tumour invading the muscularis propria or beyond but no lymph node involvement and Dukes C- Tumour with regional lymph node metastasis. The staging had a good correlation with five-year survival. The Dukes' system was gradually replaced by the TNM (Tumour, Node, Metastasis) system**,** which offers greater specificity and is better suited to guiding modern treatment decisions and clinical trials.

1.5.1 TNM staging

Tumour stage refers to the extent of disease and is most commonly classified using the TNM system developed by the Union for International Cancer Control (UICC). This was first introduced in the 1950s as a standardised way to describe the anatomical extent of cancer across different tumour types. The classification system was designed by a French oncologist, Pierre Denoix, who aimed to create a universally applicable system that could guide treatment decisions, predict prognosis, and facilitate communication among clinicians and researchers[86].

Initially, the TNM system was adopted for a few cancers, but over time it expanded to cover nearly all solid tumours, including colorectal cancer**.** The American Joint Committee on Cancer (AJCC) also adopted the TNM classification, and the two organisations now collaborate to ensure consistency in periodic updates, which usually occur every few years. Each edition of the TNM system incorporates advances in clinical practice and research. In colorectal cancer, refinements have included the recognition of tumour deposits, changes in how lymph node involvement is categorised, and better definitions of extramural invasion. The most recent 8th edition, published in 2017, continues to emphasise the importance of precise pathological and radiological assessment[87].

The 8th edition TNM staging is shown in Table 1.1. T stage describes the depth of tumour invasion through the bowel wall**,** N stage refers to regional lymph node involvement, and M stage indicates the presence or absence of distant metastasis. The TNM classification is then used to categorise disease into stages from one to four (Table 1.2).

Table 1.1: TNM staging, adapted from UICC TNM 8th edition[87]

Primary Tumour	
Tx	Tumour cannot be assessed
T0	No evidence of tumour
Tis	Carcinoma in situ: invasion of lamina propria
T1	Invades submucosa
T2	Invades muscularis propria
T3	Invades subserosa or into non peritonealised pericolorectal tissues
T4	Invades other organs or structures and/or perforated visceral peritoneum
T4a	Perforated visceral peritoneum
T4b	Directly invades adjacent organs or structures
Regional Lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1 – 3 regional lymph nodes
N1a	1 regional lymph nodes
N1b	2 – 3 regional lymph nodes
N1c	Tumour deposits in the subserosa or non-peritonealised pericolorectal tissues without regional lymph node metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	4 – 6 regional lymph nodes
N2b	7 or more regional lymph nodes
Distant metastasis	
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Confined to one organ
M1b	More than one organ
M1c	Peritoneal metastasis +/- other organ

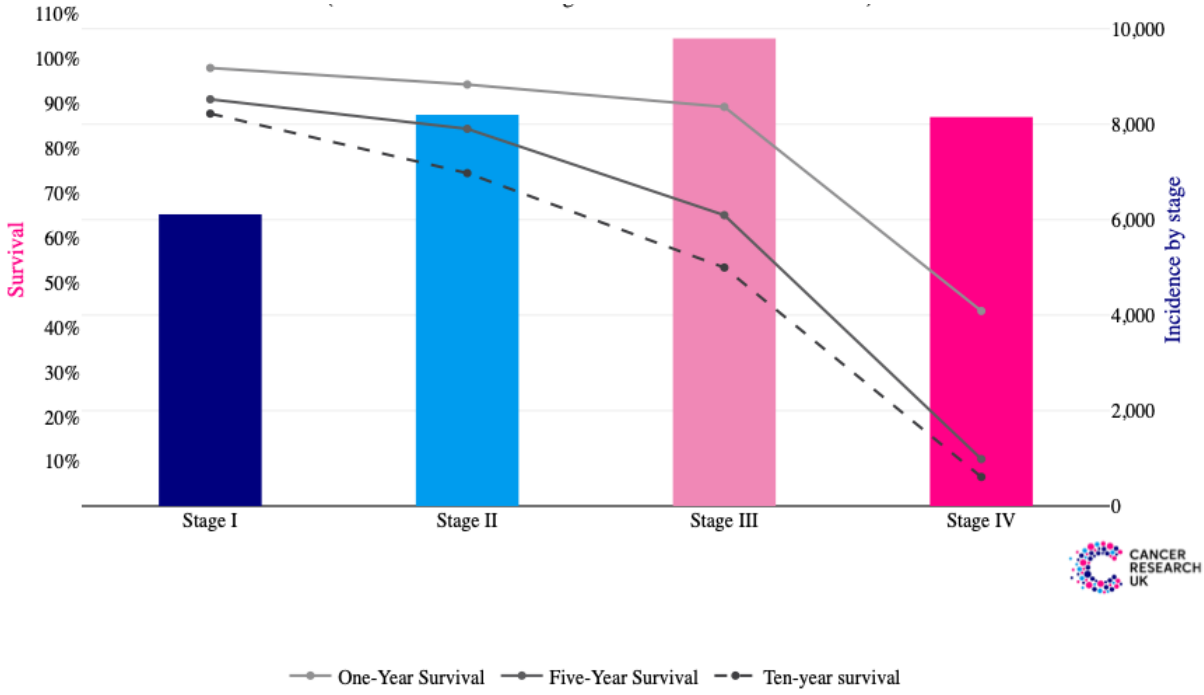
Table 1.2. American Joint Committee on Cancer Prognostic Stage Groups, 8th edition[87]

Stage	
0	Tis, N0, M0
I	T1-2, N0, M0
IIA	T3, N0, M0
IIB	T4a, N0, M0
IIC	T4b, N0, M0
IIIA	T1, N2a, M0 T1-2, N1, M0
IIIB	T1-T2, N2b, M0 T2-3, N2a, M0 T3-T4a, N1, M0
IIIC	T3-T4a, N2b, M0 T4a, N2a, M0 T4b, N1-2, M0
IVA	T1-4, N0-2, M1a
IVB	T1-4, N0-2, M1b
IVC	T1-4, N0-2, M1c

1.5.2 Tumour stage and outcomes

Cancer Research UK provides up-to-date survival data for cancers diagnosed across England. For cases of colorectal cancer diagnosed between 2016 and 2020, five-year survival rates vary significantly by stage at diagnosis, as illustrated in Figure 1.1. The incidence for each stage is shown using data from 2018. The data clearly show a decline in survival as cancer stage progresses.

Figure 1.1. 5% year net bowel cancer survival in England by stage at diagnosis, cases diagnosed 2016-2020, incidence for 2018. (Reproduced with permission from Cancer Research UK)[88]



While tumour stage is a strong independent predictor of prognosis, the TNM classification has limitations. It does not account for certain adverse pathological features that can significantly impact outcomes, even among patients within the same stage[89,90]. Tumour grade, which reflects the degree of histological differentiation, is another key prognostic factor. Poorly differentiated (high-grade) tumours tend to behave more aggressively and are associated with a higher risk of recurrence and worse overall survival, regardless of stage[91].

In recognition of this variability, additional pathological and molecular characteristics are increasingly integrated into prognostic assessment. Features such as lymphovascular invasion, perineural invasion, and tumour deposits are associated with more aggressive disease with increased risk of local or systemic recurrence[91]. Moreover, genetic mutations, including KRAS and BRAF mutations and MSI status, offer further prognostic and predictive insights. These factors help refine risk stratification and guide personalised treatment approaches, such as the selection of targeted therapies or immunotherapy.

Thus, while TNM staging remains the cornerstone of prognostication and treatment planning in colorectal cancer, a more nuanced approach incorporating tumour grade, adverse

histological features, and molecular profiling provides a more comprehensive understanding of disease behaviour and informs tailored clinical decision-making.

1.6 Investigation and management of colorectal cancer

Patients with CRC may present with a range of symptoms depending on tumour location and stage.

1.6.1 Patient presentation

According to Cancer Research UK data from 2020, the most common route to diagnosis for CRC in England was via the two-week wait referral pathway, accounting for 36.6% of cases. Emergency presentations comprised 24%, while 10.6% of cases were detected through the National Bowel Cancer Screening Programme (BCSP). The remaining diagnoses were made through routine GP referrals or other outpatient pathways. These proportions have remained relatively stable over the past decade, aside from a trend of an increasing proportion of patients being referred via the urgent two-week wait pathway, replacing a decline in routine GP referrals[92].

The BCSP in England currently uses the quantitative faecal immunochemical test (FIT), which is sent by post every two years to adults aged 50 to 74 to detect haemoglobin in faeces[93]. Following an abnormal result, a colonoscopy is offered. The FIT test is also used in primary care to guide referral of symptomatic patients for suspected colorectal cancer[94]. A threshold of ≥10 μg Hb/g faeces was demonstrated to have an 87% sensitivity (95% CI 81.0% to 91.6%) and 84.4% specificity (95% CI 79.4% to 88.3%) for CRC in a pooled analysis of nearly 50,000 patients[95].

1.6.2 Diagnosis and staging investigations

The diagnosis of CRC involves a combination of clinical assessment, endoscopic evaluation, histopathological confirmation, and imaging for staging. First-line diagnostic investigation is colonoscopy, which allows direct visualisation of the bowel and biopsy of suspicious lesions for histological confirmation. The definition of what constitutes the rectum varies worldwide with some experts advocating the use of imaged based definitions and other defining it based on endoscopy findings. Lesions occurring 15cm or less from the anal verge at rigid sigmoidoscopy in the outpatient clinic are typically considered to be rectal with more proximal tumours considered as colonic. On MRI or CT the junction of the mesorectum and mesocolon called the “sigmoid take-off” may also be used to define the boundary of the rectum and

sigmoid[96]. Rectal cancers are then further subdivided into low (up to 6cm), middle (>6-10cm) or high (>10-15cm) rectal cancers based on their proximity to the anal margin[97]. Both MRI and flexible sigmoidoscopy are used to help define the level of the tumour by both distance from the anal verge and relation to the levators, in particular, for low rectal cancers as defined by the Low Rectal Cancer Development Programme (LOREC)[98]. The Association of Coloproctology of Great Britain and Ireland (ACPGBI) recommend that histological confirmation of a highly suspicious colonic lesion is desirable but not essential before surgery whereas it is essential for rectal lesions[99]. The incidence of synchronous CRCs is 2-3% therefore, it is recommended that all patients have a full colonoscopy, or CT colonoscopy if an impassable lesion is present, prior to resection[99]. For those patients presenting as an emergency, initial investigations and histological diagnosis may not be possible if there is a clinically urgent need for surgery.

Once a diagnosis is confirmed, staging investigations are essential to assess disease extent. These include computerised tomography (CT) scans of the chest, abdomen, and pelvis to identify distant metastases. Pelvic magnetic resonance imaging (MRI) is the gold standard for staging rectal cancer, providing a detailed assessment of local tumour invasion, lymph node involvement, and the relationship to the mesorectal fascia (MRF). Involvement of the mesorectal fascia, which predicts the likelihood of achieving a clear circumferential resection margin (CRM), is a key determinant of surgical resectability and long-term outcomes. The importance of MRI in preoperative planning was strongly supported by the MERCURY study, which demonstrated that high-resolution MRI accurately predicts CRM status and correlates with both local recurrence risk and disease-free survival [100]. Additional imaging, such as liver MRI may be performed to assess for liver metastasis and Fluorodeoxyglucose (FDG) Positron emission tomography (PET) in selected cases with equivocal findings regarding metastatic disease[99]. Endoanal ultrasound may be used for early tumours to assess if they may be suitable for local resection and for locally advanced cancers to better determine margin involvement, where MRI is equivocal[97]. All patients must have an evaluation of their investigations in a colorectal cancer multidisciplinary meeting before commencing treatment.

1.6.3 Treatment of primary operable rectal cancer

The terms early-stage and locally advanced rectal cancer are defined slightly differently in Europe and the USA, and these nuances shape the use of neoadjuvant therapy. The European Society of Medical Oncology (ESMO) stratifies tumours by MRI-predicted risk in addition to AJCC stage: early stage includes T1–2N0 or selected good-risk T3a/b with a clear MRF and

no EMVI; locally advanced tumours include T4 or high-risk T3 (T3c/d), threatened/positive MRF/CRM, EMVI+, N2, enlarged lateral nodes, or very low tumours[101]. In the USA, the National Comprehensive Cancer Network (NCCN) primarily classifies by AJCC stage groups and anatomy and then modifies treatment by high-risk features. They consider early stage to be stage I (T1–2N0) and locally advanced to be stage II/III (T3–4 and/or N+), then refine by MRI features (e.g., CRM threat, EMVI, low location)[102].

1.6.3.1 Chemoradiotherapy

Chemotherapy and radiotherapy are used to help downstage disease, enhance resectability, reduce local recurrence rates and eradicate distant micrometastases. Across both colon and rectal cancer there is trial data (e.g. FOxTROT, UNICANCER-PRODIGE 23, RAPIDO) to support a paradigm shift towards neoadjuvant regimens, which are likely to result in the evolution of the current guidelines used in the UK over the next few years[103–105].

Current guidelines suggest that neoadjuvant therapy should be considered for patients with resectable rectal cancer not involving the CRM but with adverse features on staging MRI such as T3c disease, mesorectal lymph node involvement or EMVI, those with locally advanced rectal cancer or low rectal cancer (to improve chances of a sphincter sparing resection) (figure 1.2)[106]. There may be more than one evidence-based treatment option available for patients, depending on the intent of treatment, such as organ preservation, patient factors and patient choice. Treatment options for organ preservation are beyond the scope of this thesis and not discussed in further detail. Total neoadjuvant therapy (TNT), where chemoradiotherapy (short or long course) plus systemic chemotherapy are given prior to resection, has demonstrated improved survival outcomes for patients with locally advanced rectal cancer as evidenced by the RAPIDO and POLISH II trials[104,107]. However, the RAPDIO protocol (SCRT plus chemotherapy then surgery) has been associated with increased rates of local recurrence at five years, demonstrating further refinement of TNT is required[108]. There is little evidence to support the use of neoadjuvant radiotherapy alone, as trial data suggest no overall survival benefit (Dutch TME and MRC CR07 and NCIC-CTG C016 trials)[109,110]. Possible reasons for this may be that although RT can provide excellent pelvic control of disease, it does not eradicate micrometastatic disease, and improvements in TME resection quality may reduce the margin for RT to translate into improved survival due to lower baseline local recurrence risk. The use of neoadjuvant chemotherapy alone, when compared to chemoradiotherapy for patients with certain patients with LARC (T2 N+, T3N0, or T3 N+) who were eligible for

sphincter-sparing surgery, demonstrated non-inferiority in the PROSPECT trial with similar overall survival and local recurrence rates[111].

Figure 1.2: European Society of Medical Oncology guidance on management of rectal cancer[112]

Preoperative TN substage	**Neoadjuvant treatment**	**Surgical resection**	**Adjuvant treatment**
Upper rectal cancer			
T1 No or N1, T2 N0		PME, TME or LE for low risk T1 without high-risk features	Ch^ or Adjuvant CRT*
T2N+, T3 No or N+	CAPOX or FOLFOX^{+}	PME or TME	CRT *
T4 N0 or N+, MRF+	CAPOX or FOLFOX^{+}	PME or TME	CRT *
	TNT or CRT or SCRT if TNT not feasible	PME or TME	
		PME or TME	Ch^ or CRT*
Lower or middle third rectal cancer			
T1N0		TME or LE	Ch^ or CRT*
T1N+ or T2N0		TME	Ch^ or CRT*
T2N+, T3 N0 or N1		TME if middle third	Ch^ or CRT*
	CAPOX or FOLFOX	TME	CRT*
	SCRT or CRT	TME or LE in patients with baseline T2 or T3a N0 tumours	Ch^
High risk criteria (T4, N2, MRF+, EMVI+, lateral LN+)	TNT	TME	

CAPOX, capecitabine–oxaliplatin; Ch, chemotherapy; CRM, circumferential resection margin; CRT, chemoradiotherapy; DRE, digital rectal examination; FOLFOX, leucovorin–5-fluorouracil–oxaliplatin; LE, local excision; MRF, mesorectal fascia; N+, node positive; PME, partial mesorectal excision; RT, radiotherapy; SCRT, short-course radiotherapy; TME, total mesorectal excision; TNT, total neoadjuvant therapy.

*Only in case of CRM positivity, pT4b, pN2 with extracapsular spread close to the MRF or poor-quality TME in patients who did not receive preoperative RT.
^ Following PME/TME alone, according to clinical risk assessment
+ With salvage RT if intolerance to Chemotherapy or progression on neoadjuvant Chemotherapy

In addition to patients with locally advanced disease who are MMR-deficient patients with MSI-H tumours are also recommended to commence on immunotherapy, marking the first

routine use of biology-driven treatment selection in this disease [112]. This shift reflects emerging evidence that MMR-deficient and MSI-H rectal cancers respond poorly to cytotoxic chemotherapy but can achieve exceptional responses with programmed cell death protein 1 (PD-1) blockade[113,114].

Adjuvant chemotherapy is advised for patients with stage III colon cancer or patient with stage III rectal cancer who received no neoadjuvant therapy or only short course radiotherapy as this has been demonstrated to improve disease free and overall survival[106]. Patients with stage II disease and high-risk features may also be considered for adjuvant therapy but the evidence for its use is less strong[106]. The overall increase survival benefit following adjuvant chemotherapy (fluorouracil and folinic acid) for unselected stage 2 colorectal cancer patients was only 3.6% in the QUASAR trial, hence why it is only used in selected high-risk cases[115].

1.6.3.2 Surgical management

The management of primary operable colorectal cancer typically involves surgical resection with curative intent, supported by the use of tailored chemotherapy and, in rectal cancer, radiotherapy and chemoradiotherapy. NICE and ACPGBI have published guidelines on the management of CRC[116,117]. For colon cancers, standard treatment is oncological resection of the affected bowel segment with associated mesentery and lymph nodes by right, extended right or left hemicolectomy. For rectal cancers, the gold standard approach is mesorectal excision, either total mesorectal excision (TME) or partial (PME) providing resection of the mesorectum to reduce local recurrence [118]. Low rectal tumours may require excision by abdominoperineal resection. The vast majority of resections are performed laparoscopically with increasing numbers performed robotically[116]. The UK LAPCO programme has standardised and mentored the adoption of laparoscopic rectal cancer surgery, reducing complications and conversions, shortening hospital stay without compromising oncological outcomes[119].

1.6.3.3 Early rectal cancer treatment

Organ-preserving treatment strategies are increasingly utilised for selected patients with early rectal cancer**,** particularly those who are unfit for major surgery or who opt to avoid radical resection. These approaches include local excision and radiotherapy or contact x-ray brachytherapy (Papillon). Multiple phase II and III trials have demonstrated acceptable

outcomes with the use of neoadjuvant radiotherapy (either short course RT or CRT) and local excision such as the CARTS, STAR-TREC, ACOSOG Z6041, GRECCAR 2[120–123].

Local excision is now considered appropriate for T1 tumours less than 3 cm in size, provided there are no high-risk features such as lymphovascular invasion, tumour budding, or poor differentiation[106]. This can be achieved using advanced endoluminal techniques such as transanal endoscopic microsurgery (TEM) or transanal minimally invasive surgery (TAMIS), which allow precise excision while preserving sphincter function and avoiding permanent stoma formation.

Patients treated with local excision alone require intensive surveillance, including regular endoscopic and radiological assessments, due to the risk of local recurrence. In selected cases, contact x-ray brachytherapy may be offered either as an alternative to surgery or as an adjunct to incomplete excision, although the centres offering this are limited across the United Kingdom[106]. This modality delivers high-dose radiation directly to the tumour site with minimal damage to surrounding tissue, making it a suitable option for frail or elderly patients. These organ-sparing approaches represent an important advance in the management of early rectal cancer, balancing oncological control with quality-of-life considerations.

1.6.4 Metastatic disease

Patients with metastatic disease to the lung or liver should be discussed in the relevant MDTs (e.g. hepatobiliary/lung) to assess if surgical resection, ablation or targeted radiotherapy can be offered for potentially curative treatment. Patients with peritoneal disease should be referred to specialist centres for consideration of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC)[116,117].

1.6.5 Palliative treatments

Palliative treatment in CRC aims to relieve symptoms, improve quality of life, and prolong survival in patients with advanced or incurable disease. Common indications include unresectable metastatic disease, advanced local disease not amenable to resection or patients who have declined curative management. Systemic therapies such as palliative chemotherapy may be used to control tumour growth and alleviate symptoms. Radiotherapy may be employed to manage pain, bleeding, or local pelvic symptoms, particularly in rectal cancer. For bowel obstruction, options include stent placement**,** defunctioning stoma, or palliative resection,

depending on patient fitness and prognosis[124]. Palliative care input is essential for symptom management and end-of-life planning. Treatment decisions should be individualised considering disease burden, patient preferences, and overall performance status.

1.7. Locally advanced disease

1.7.1 Locally advanced and locally recurrent rectal cancer

Between five to ten percent of patients with rectal cancer will present with locally advanced rectal cancer (LARC) that is not amenable to curative treatment by standard approaches[125,126]. These patients frequently require input from highly specialised complex cancer services and extensive multivisceral surgery with oncological therapy. The 5-year survival from LARC is approximately 65% owing to an increased risk of tumour recurrence[127–129]. The definition of what constituents LARC has been heterogenous in the literature and as discussed previously there are variations in its definition between the USA and Europe. The Beyond TME collaborative, an international group of representatives from specialist centres, defined it as a tumour in the large bowel below the sacral promontory, surrounded by mesorectum posteriorly, that is predicted by MRI to require an extended resection beyond TME planes in order to achieve a clear resection margin (R0 resection)[126].

With combined modality treatment and TME resections, the rate of local recurrence following primary rectal cancer surgery has thankfully fallen to 5-15% from historic figures of approximately 40%[118,130]. Management of locally recurrent rectal cancer (LRRC) presents a significant therapeutic challenge, and even with modern exenteration surgery, survival rates are poor at 25-50% at 5 years[130–134]. This is due to high rates of local and systemic recurrence in this cohort reflective of the likely biological aggressiveness of these tumour types. LRRC is defined as tumour recurrence, progression or development of new tumour sites within the pelvis after previous surgical resection of a rectal tumour[126].

1.7.2 Management of LARC and LRRC

Both patients with LARC and LRRC require staging as previously discussed. Patients with LARC should be offered neoadjuvant therapy with long course chemoradiotherapy to attempt to downstage disease and reduce micrometastasis[106]. In the majority of patients with LRRC who are radiotherapy naïve, standard course radiotherapy or short course chemoradiotherapy is offered[135]. Re-irradiation to downstage disease may also be considered, although this remains controversial with little evidence to support its benefit[136]. There are currently multiple trials in

progress that are trying to address this, including the RETRY, GRECCAR15 and PelvEx II trials[137–139].

Although LARC and LRRC are often analysed together, largely because the operative principles and multidisciplinary teams overlap, their biology, prior treatments, and clinical trajectories are distinct. In LRRC, the evidence base is notably thin: there is a paucity of trial-level data to guide neoadjuvant strategies or even broader management, with most practice extrapolated from primary LARC or derived from retrospective series. Prior pelvic irradiation, distorted anatomy, dense fibrosis, and heterogeneous recurrence patterns make LRRC difficult to randomise and standardise, limiting high-quality evidence. More work is required to understand the factors associated with outcomes in this challenging group of patients.

Isolated (non-metastatic) LRRC represents a biologically intriguing state that, in many respects, parallels oligometastatic disease: a limited burden, anatomically confined, and potentially curable with radical local therapy. Therefore, the biological make-up of these tumours may differ from other CRCs.

1.8 Pelvic exenteration

Pelvic exenteration is an extensive surgical procedure performed for locally advanced or locally recurrent malignancies within the pelvis, most commonly rectal, gynaecological, or urological cancers. First described by Brunschwig in 1948 as a palliative operation, pelvic exenteration has evolved into a potentially curative treatment for selected patients, particularly those with LARC and LRRC[140] .

The procedure involves en bloc resection of the involved pelvic organs and may be classified as total, anterior, posterior, or modified exenteration depending on the organs removed. Total pelvic exenteration entails removal of the rectum, bladder, and reproductive organs, often with formation of both a colostomy and urostomy. Achieving a clear (R0) resection margin is the primary objective of surgery and determines the extent of resection required.

Pelvic exenteration is associated with significant morbidity, with major complication rates up to 40%, including wound infection, urinary leak, and pelvic sepsis[141,142]. Advances in preoperative imaging, surgical planning, and perioperative care have helped to mitigate some risks. A multidisciplinary approach is essential, involving colorectal, urological, orthopaedic,

gynaecological, plastic, and vascular surgeons when required. Quality of life, while impacted, can be acceptable postoperatively, particularly in patients who achieve long-term disease control[143]. Sharing postoperative quality of life trajectories with patients may aid informed decision-making prior to surgery[144].

Pelvic exenteration remains the cornerstone of curative-intent treatment for patients with advanced or recurrent pelvic malignancies, and optimal outcomes depend on careful patient selection, experienced surgical teams, and comprehensive perioperative support within high-volume specialist centres.

1.8.1 Disease extent and operative planning

Operative planning for LARC and LRRC is complex and requires a meticulous, multidisciplinary approach to optimise outcomes. High-resolution pelvic MRI is the foundation of preoperative staging, providing detailed information about tumour extent, involvement of adjacent organs, and potential resectability. The key anatomical compartments (central, anterior, posterior, lateral, and low/pelvic floor) must be evaluated individually, as involvement of these areas significantly increases operative complexity and risk. Preoperative imaging is used to plan a surgical 'roadmap' of the extent of the resection required. Each operation should be tailored to the patient's tumour. Several structured frameworks guide radiologic assessment and preoperative planning for pelvic exenteration. These include BONVUE, a checklist ensuring systematic review of Bones, Organs, Nerves, Vessels, Ureters/urinary tract, and Extra-pelvic disease; the Royal Marsden compartment classification, which divides the pelvis into seven surgical compartment along fascial planes to map required beyond-TME resections; and the Mayo pattern-based approach, which categorises recurrent disease on MRI by central (axial), anterior, lateral, and posterior patterns to align imaging with operative strategy[145–147].

The heterogeneity of disease is mirrored by the wide variation in exenteration procedures performed, which can limit the interpretation of patient outcomes from published studies. The ACPGBI and UK Pelvic Exenteration Network have attempted to address this with the development of a 'Pelvic exenteration lexicon' to standardise the description of operative extent and have defined complex and high complexity procedures[148].

1.8.2 Central compartment

The central compartment comprises the rectum, mesorectum (and anastomosis in LRRC), pouch of Douglas, anal sphincters and levator ani. En bloc resection of this compartment with an adjacent compartment forms the basis of an exenteration and is required for all LARC or LRRC.

1.8.3 Anterior compartment

The anterior compartment contains the bladder, pubic symphysis and pubic rami, seminal vesicles and prostate in males, uterus, vagina and fallopian tubes in females. Depending on the extent of invasion into the bladder a partial cystectomy or ureteric resection with reimplantation may be possible. Total cystectomy or radical cystoprostatectomy with formation of ileal conduit is required in advanced disease. Radical resection of the pubic bones and perineal urethrectomy are feasible and required for disease extending to and through the pubic bones with comparable survival results to those undergoing extended exenteration[149].

1.8.4 Posterior compartment

The posterior compartment contains the presacral fascia, coccyx and sacrum, sciatic nerve and its branches. For patients with LARC, breaching the posterior plane excision of the presacral fascia en bloc may be sufficient to obtain an R0 resection. For recurrent tumours, where normal planes are lost, or in those with direct posterior tumour extension, a more radical posterior resection is required. For tumours invading the body of S1 or S2 a high sacrectomy may be performed, and a distal sacrectomy if S3 or S4 are involved. High sacrectomy is associated with greater neurological deficit compared to low sacrectomy, but with acceptable patient outcomes[150]. High R0 rates have been shown to be obtainable with sacral resection and improve survival compared to palliation[151,152]. Novel techniques such as high subcortical sacrectomy (HiSS) have been developed to limit the morbidity of sacrectomy for patients where the tumour is adherent to or involving the anterior cortex only[153]. Resection of the cranial portion of S1 would result in pelvic instability and require fixation therefore tumours affecting this are and above are generally deemed inoperable[154]

1.8.5 Lateral compartment

Lateral compartment involvement, including the pelvic sidewall containing side wall lymph nodes, ureters, ischial spines, ischium, sacral nerves and nerve roots, sciatic notch, and iliac vessels, poses particular surgical challenges. Resection in this area may require en bloc removal of the internal iliac vessels or sciatic nerve, and careful consideration of functional impact,

including lower limb mobility and pain control, is essential. Major neurovascular resection of the pelvic side wall has been demonstrated to be feasible, and tumour extension in this area is no longer considered to be a contraindication to resection[155]. Surgical approaches such as Extended Lateral Side Wall Excision (ELSiE), described by St Mark's Hospital, have been developed to allow resection of tumours extensively involving the pelvic side wall structures and even tumours extending through the sciatic notch to achieve an R0 resection with acceptable functional and survival outcomes[156].

The management of involved lateral pelvic lymph nodes remains fairly controversial. These nodes lie outside the mesorectal plane of the TME, raising debate over whether they represent locoregional disease requiring surgical removal or systemic spread best treated with CRT[157]. Oncological management of these nodes differs worldwide, particularly when comparing Europe and North America to Eastern countries like Japan. In Western practice, standard treatment for LARC is neoadjuvant CRT followed by TME, without routine lateral pelvic lymph node dissection. Lateral lymph nodes are generally not resected unless clinically suspicious on imaging, as trial data from Europe suggest that there are low lateral recurrence rates balanced with concerns regarding morbidity from extended dissection[110,127,158]. In contrast, Japanese guidelines recommend routine nerve-preserving lateral pelvic lymph nodes dissection, supported by Japanese trial data, which demonstrated reduced local recurrence with the addition of lateral pelvic lymph nodes dissection compared to TME alone, though overall survival differences were limited[159]. More recently, a selective approach has gained support, and patients with suspicious lateral nodes on pre-treatment MRI (commonly defined as ≥7 mm) who fail to respond to neoadjuvant CRT may benefit from targeted lateral pelvic nodal dissection; studies suggest this strategy reduces lateral recurrence while minimising morbidity[160,161].

1.8.6 Vascular resection

Tumour invasion of major pelvic vessels, most commonly the internal iliac artery or vein, but occasionally extending to the external iliac or common iliac vessels, can occur, particularly in lateral pelvic disease. Achieving an R0 resection in these cases may require en bloc resection of involved vessels, with or without vascular reconstruction.

Preoperative assessment with contrast-enhanced CT or MRI angiography is essential to define vascular anatomy, tumour involvement, and the feasibility of resection. When major vessels such as the external or common iliac arteries are involved, vascular reconstruction with grafts

(e.g., PTFE, autologous vein, bovine pericardium, or cadaver grafts) may be necessary and requires vascular surgical expertise[162]. Intraoperative bleeding, graft thrombosis, and infection are significant risks, and multidisciplinary collaboration with vascular surgeons is vital[163]. Despite these challenges, vascular resection can enable complete tumour clearance in carefully selected patients, offering the potential for long-term survival where the alternative would be palliative treatment.[164]

1.8.7 Reconstruction

Reconstruction following pelvic exenteration is essential to restore function and improve quality of life, particularly concerning urinary diversion and perineal defect closure. Bony reconstruction and stabilisation procedures may also be required.

The Bricker ileal conduit remains the most commonly employed urinary diversion technique due to its relative simplicity and reliability. This method involves using a segment of the ileum to create a conduit for urine to pass from the ureters to a stoma on the abdominal wall. Complications following urinary diversion are frequently encountered and contribute significantly to postoperative morbidity, with acute kidney injury and urinary tract infections the most commonly experienced complications[165,166]. Longer-term complications such as urinary fistulas and ureteric strictures pose significant challenges and frequently require reoperation or radiological intervention[165,166].

Perineal defects and the resulting empty pelvic cavity following pelvic exenteration lead to significant complications and reconstructive challenges, especially in previously irradiated fields. The constellation of complications, including pelvic collections, small bowel obstruction, perineal wound dehiscence, enteroperineal fistulae and perineal hernias, has been termed ‘empty pelvis syndrome’ and affects up to 30% of patients[167,168]. There is currently no consensus on the best reconstructive approach, with a variety of strategies employed, including myocutaneous and fasciocutaneous flap reconstruction, mesh reconstruction, omental flaps, silicone expanders and use of breast prosthesis[167]. Flap-based reconstructions are preferred over primary closure to close the perineal defect due to lower rates of wound complications[169,170]. The vertical rectus abdominis myocutaneous (VRAM) flap is widely used, providing robust vascularized tissue to fill the pelvic dead space. However, it carries risks of abdominal wall morbidity, including hernia formation[171,172]. Other options include gracilis flap,

gluteal flap, and anterolateral thigh flaps. The choice of flap depends on defect size, patient anatomy, and previous treatments and will be discussed in greater detail in chapter 6.

1.8.8. Contraindications to exenteration

Over the last twenty years there has been a change in the absolute contraindications to pelvic exenteration in rectal cancer with R0 resections now being achieved with high sacral disease and disease extending into the pelvic sidewalls and through onco-vascular resection. However, absolute contraindications include the presence of non-resectable distant metastases, unless managed within a highly selected multimodal strategy, and inability to achieve an R0 resection, as incomplete clearance offers little long-term survival benefit[173]. Poor physiological fitness or significant comorbidities that preclude major surgery also represent absolute contraindications. Lastly, patients may decline pelvic exenteration surgery despite curative resection being feasible. Ultimately, pelvic exenteration should usually be offered only when there is a realistic chance of cure or meaningful long-term disease control with acceptable quality of life unless in exceptional circumstances.

1.8.9 Palliative pelvic exenteration

Palliative PE may be considered as a last-resort operation offered to a small subset of patients with incapacitating, locally uncontrolled pelvic disease, typically for intractable pain, bleeding, malodorous discharge, fistulae, obstruction, or pelvic sepsis when lesser measures (diversion, drainage, stenting, re-irradiation, systemic therapy, specialist wound care) cannot control symptoms[174]. A 2019 systematic review reported symptom relief in a median 79% of patients, but at the cost of high morbidity (median 53.6%) and in-hospital mortality (6.3%), with a median overall survival of 14 months (range 4–40)[174]. It is recommended that palliative PE be considered on a case-by-case basis with adequate patient counselling[175].

1.9 Factors influencing colorectal cancer outcomes

Outcomes in CRC are influenced by a combination of tumour-related, patient-related, and treatment-related factors. The influence of these factors on outcomes will primarily be discussed in regard to primary colorectal cancer, as the evidence for their influence on outcomes in patients with LARC and LRRC following pelvic exenteration are less well understood and will be discussed in subsequent chapters.

1.9.1 Tumour related factors

Prognostication of CRC and allocation of adjuvant therapy has traditionally relied on TNM staging, as previously discussed. However, there are a number of other pathological factors that will influence outcome and these form part of the Royal College of Pathologists (RCPath) standard histopathological reporting dataset of analysed primary colorectal cancer resection specimens in addition to TNM staging[176].

These include histological tumour type and differentiation, resection margins, tumour deposits, venous invasion, lymphatic invasion and perineural invasion. It is important to note that pathological assessment of LRRC is complex due to the distorted anatomy, scarring, and fibrosis resulting from previous surgery and radiotherapy. Given the heterogeneity of LRRC, standardised reporting is critical. The use of synoptic pathology proformas has been shown to provide a comprehensive documentation of tumour extent and margin status, although there is no currently agreed proforma by the Royal College of Pathologists [177]. The evidence for most of these high risks factors comes from the study of LARC. For LRRC there is an urgent need to better understand pathological factors that are associated with poorer outcomes.

1.9.1.1 Histological tumour type

The majority of CRCs are adenocarcinomas, but certain subtypes are associated with distinct clinical behaviours. The WHO classification describes a number of histological variants of CRC, with mucinous and signet ring cell the most frequently encountered[178]. Mucinous adenocarcinomas, defined as tumour volume containing >50% of extracellular mucin, account for 10–15% of cases, tend to present at an advanced stage and can be associated with poorer prognosis and reduced response to chemotherapy[179,180]. Signet ring cell carcinomas account for 1-2% of colorectal adenocarcinomas and are characterised by increased intracytoplasmic mucin which displaces the nuclei to the cell periphery. These tumours are highly aggressive and often diagnosed at a metastatic stage with a particularly poor outcome[180].

1.9.1.2 Histological grade

Histological tumour grade in CRC reflects the degree of glandular differentiation and is an established prognostic factor. Tumours are typically classified as well, moderately, or poorly differentiated with the assessment of grade based on the least differentiated tumour component[176]. Poorly differentiated tumours are associated with more aggressive behaviour, higher risk of lymph node and distant metastases, and worse overall survival[181,182].

1.9.1.3 Resection margin

Resection margin status is a critical determinant of oncological outcomes in CRC surgery. A clear (R0) resection margin, defined as >1mm clearance of tumour, is associated with improved local control and survival. In contrast, a positive margin (R1), indicating residual microscopic disease within 1mm of the resection margin, significantly increases the risk of local recurrence and reduces disease-free and overall survival[183,184]. An R2 resection is one with macroscopic margin involvement. In rectal cancer, the CRM is especially important. A CRM of ≤1 mm is considered involved and correlates strongly with poor outcomes, particularly after TME[183–185].

For primary rectal cancer, positive margin (R1/CRM ≤1 mm) rates are audited as a quality standard: in England & Wales, the National Bowel Cancer Audit (NBOCA) reports provider-level outcomes and explicitly includes positive circumferential rectal resection margin rates among published audit indicators; units are benchmarked and outlier-managed via the national audit programme[186]. In Scotland, colorectal cancer Quality Performance Indicators (QPIs), implemented through the regional cancer networks, specify reporting of CRM and the proportion with positive margins, with public reporting against these standards[187]. Contemporary population studies show positive resection margins of approximately 4-8% after standard rectal resection[188–190].

In resections for LARC and LRRC, higher R1 rates are generally expected and accepted given the anatomical complexity and prior treatments that limit resection planes. There is no national reporting of outcome data, like primary TME resections. The PelvEx collaborative has attempted to benchmark some pathological and preoperative outcomes, including resection margin status, as have other major exenteration units[175,191]. Unlike primary rectal cancer, where standardised protocols enable consistent margin assessment, LRRC specimens frequently comprise irregular dissection planes and en bloc resections of adjacent organs, making margin evaluation inherently complex. In this setting, the pathologist's expert mapping of tumour extent and true resection surfaces is pivotal to determining margin status and, ultimately, resection completeness[177].

Like many aspects in the management of LRRC, the definition of a positive resection for primary rectal cancer is usually applied in cases of recurrence. This view has been challenged by some experts due to the anatomical differences in cases of recurrence. In a study by the

large pelvic exenteration service at the Royal Prince Alfred Hospital in Syndey, they found that margins of 0.1–0.5 mm reduced local recurrence versus 0 mm but did not translate into an overall-survival gain, supporting the view that 0 mm should define R1 in LRRC[192].

1.9.1.4 Tumour deposits

Tumour deposits in CRC are discrete foci of cancer cells found in the pericolonic or perirectal fat, away from the primary tumour and without identifiable lymph node, vascular or neural tissue. They are considered an adverse prognostic factor and are associated with more aggressive disease, increased lymphovascular invasion, and worse overall survival[90]. The presence of tumour deposits is included in the TNM staging system: in the absence of lymph node metastases, they are classified as N1c (AJCC 8th edition), highlighting their prognostic significance[87]. The identification of tumour deposits can be difficult to distinguish in patients who have received neoadjuvant therapy and their presence may be a result of tumour fragmentation during tumour regression which is associated with poor outcomes[193].

1.9.1.5 Venous invasion

Venous invasion in CRC is a significant pathological feature associated with increased risk of distant metastases and poorer prognosis[182,194]. It refers to the presence of tumour cells within venous structures, typically in the peritumoral tissue, and reflects the tumour's ability to disseminate haematogenously. Its presence is associated with reduced disease-free and overall survival, independent of other staging factors[194]. Venous invasion is particularly relevant in stage II CRC, where it serves as an indication for adjuvant chemotherapy despite the absence of lymph node involvement[106]. Detection can be challenging on routine histology, but enhanced staining techniques such as elastin stains improve diagnostic accuracy[195]. Both intramural and extramural venous invasion are recognised, with the latter having greater prognostic impact[194].

1.9.1.6 Lymphatic invasion

Invasion of tumour cells into lymphatics, capillaries and post capillary venules are all considered to be lymphatic invasion and are associated with increased likelihood of regional lymph node involvement and distant metastasis, contributing to poorer disease-free and overall survival[176,196,197]. Lymphatic invasion is associated with poor prognosis across all stages of colorectal cancer[196,197]. Immunohistochemical staining with D2-40 may be used to enhance lymphatic endothelium aiding accurate identification of lymphatic invasion[198].

1.9.1.7 Perineural invasion

Perineural invasion (PNI) in CRC refers to the infiltration of tumour cells into or around nerves and is recognised as an adverse prognostic factor. Its presence indicates aggressive tumour biology and is associated with increased local recurrence, distant metastasis, and reduced overall survival, independent of tumour stage[197,199]. PNI is more frequently observed in high-grade, advanced-stage, and rectal tumours, and it often coexists with other high-risk features such as lymphovascular invasion and positive margins[199]. The importance of PNI has been recognised in recent years and since 2018 has been included in the RCPath core dataset for reporting of CRCs[200].

1.9.1.8 Total Mesorectal Excision quality

Pathological grading of the TME specimen is the standard way to appraise the technical quality of rectal cancer surgery. On macroscopic review, specimens are classified by the plane of excision reflecting the integrity and smoothness of the mesorectal envelope: mesorectal (complete), intramesorectal (nearly complete), or muscularis propria (incomplete)[201]. This grading correlates with key oncologic outcomes: better planes are associated with lower circumferential margin involvement, reduced local recurrence, and improved survival; conversely, muscularis propria plane carries the worst prognosis[202,203]. TME specimen quality is the only routinely reported pathological measure of surgical quality in rectal cancer and is widely used for audit, feedback, and service improvement.

1.9.1.9 Other factors

Features describing the tumour microenvironment and cellular composition of the invasive edge of the tumour are not currently part of the core reporting dataset. These include factors such as tumour budding, peritumoral inflammation, tumoral infiltrating lymphocytes and tumour stromal percentage.

Tumour budding refers to the presence of single cells or small clusters of up to four tumour cells at the invasive front of the tumour. It is considered a marker of epithelial–mesenchymal transition and tumour aggressiveness[204]. High-grade tumour budding is strongly associated with adverse outcomes, including increased risk of lymph node metastasis, local recurrence, and reduced disease-free and overall survival[204,205]. Due to issues with reproducibility of assessment is it not currently within the RCPath core dataset[176].

Peritumoural inflammation refers to the immune and inflammatory response occurring in the stroma immediately surrounding the tumour. This localised reaction plays a significant role in modulating tumour progression, immune surveillance, and ultimately patient outcomes[206,207]. The degree and quality of peritumoral inflammation can be assessed histologically using scoring systems such as the Klintrup–Mäkinen (KM) grade, which evaluates the density and intensity of inflammatory cell infiltrates at the invasive margin. High KM scores, indicative of high numbers of infiltrating immune cells at the invasive margin of tumours are associated with improved survival and lower rates of recurrence, independent of TNM stage[206]. This beneficial effect is thought to reflect active anti-tumour immunity, particularly the presence of cytotoxic T lymphocytes[208]. Conversely, a weak or absent peritumoral inflammatory response may allow tumour cells to evade immune detection and facilitate local invasion and metastasis.

Assessment of the host immune response within the tumour microenvironment can be quantified with a classification system called Immunoscore[209]. The number of tumour infiltrating lymphocytes, specifically $CD3^+$ and $CD8^+$ T cells, in the tumour core and invasive margin, used to calculate the Immunoscore, have been demonstrated to influence outcomes in colorectal cancer[210]. Quantification of these tumour infiltrating lymphocytes using the Immunoscore has been demonstrated to outperform TNM staging in predicting recurrence risk in colorectal cancer[211,212]. Its application in rectal cancer has gained increasing interest, especially in the context of neoadjuvant chemoradiotherapy. Several studies demonstrate that a high Immunoscore correlates with improved disease-free survival and reduced local and distant recurrence[211,213]. Moreover, higher pre-treatment immune infiltration has been associated with increased rates of pathological complete response following neoadjuvant chemoradiotherapy[211] .

Tumour stromal percentage (TSP) refers to the proportion of tumour tissue composed of stromal (non-epithelial) components, including fibroblasts, immune cells, blood vessels, and extracellular matrix. In CRC TSP has emerged as a simple yet powerful histopathological biomarker with significant prognostic value[214,215]. A high TSP, defined as >50% stromal content, has been consistently associated with poorer outcomes, including reduced overall and disease-free survival, independent of tumour stage[216,217]. The poor prognosis associated with high TSP is believed to stem from the pro-tumorigenic activity of the stromal component, primarily composed of cancer-associated fibroblasts (CAFs). These cells contribute to tumour progression by promoting growth, invasion, angiogenesis, and therapy resistance through the

secretion of cytokines, growth factors, and enzymes that remodel the extracellular matrix[218]. In contrast, tumours with a low stromal component (TSP ≤50%) generally exhibit more favourable biological behaviour and better survival outcomes[216,217]. Both TSP and KM scores can be assessed on standard haematoxylin and eosin (H&E) stained sections.

1.9.2 Host factors

Host-related factors exert a major influence on colorectal cancer outcomes, shaping tumour biology, treatment tolerance, and survival. Key determinants include comorbidity burden, nutritional status, body composition, and systemic inflammation. These variables also govern treatment eligibility and access, often determining whether patients can receive intensive multimodality therapy. In LARC/LRRC, where perioperative morbidity and treatment-related adverse events are common, adequate physiological reserve and careful prehabilitation/optimisation are essential to enable safe delivery of therapy and maximise benefit.

1.9.2.1 Comorbidity and age

Comorbidity significantly influences prognosis, treatment selection, and clinical outcomes in patients with CRC. Given that CRC predominantly affects older adults, a substantial proportion of patients present with one or more pre-existing medical conditions, including cardiovascular disease, diabetes, chronic respiratory disorders, and renal impairment[219,220]. These comorbidities can impact both short- and long-term outcomes by limiting the feasibility of curative treatment approaches and increasing the risk of postoperative complication[220]. From a prognostic standpoint, comorbidity has been identified as an independent predictor of survival in CRC[219,221]. In particular, both advancing age and the presence of comorbid conditions have been shown to adversely affect outcomes following major abdominal surgery [222–224]. To assist in preoperative risk stratification and treatment planning, several scoring systems and predictive models have been developed. Among the most widely used are the American Society of Anesthesiologists (ASA) physical status classification and the Charlson Comorbidity Index (CCI), both of which help quantify the effect the likely impact of comorbidity on surgical outcomes [223,225].

Comorbidity also interacts with cancer biology and systemic inflammation. Conditions like obesity, diabetes, and chronic inflammatory diseases are associated with altered immune

function and pro-inflammatory states, which may influence tumour progression and metastasis as previously discussed.

1.9.2.2 Nutrition and body composition

Nutritional status and body composition are important but often under-recognised factors influencing outcomes in CRC. Malnutrition is prevalent in patients with CRC, driven by tumour-related factors such as anorexia, altered metabolism, bowel dysfunction, and systemic inflammation[226]. Malnutrition is associated with impaired immune function, reduced tolerance to treatment, delayed wound healing, and increased morbidity and mortality[226–228]. Body composition analysis offers a more nuanced understanding of nutritional status than body mass index (BMI) alone. Sarcopenia, defined as the loss of skeletal muscle mass and function, is particularly important in CRC and may exist even in patients with normal or elevated BMI, referred to as sarcopenic obesity[229]. Sarcopenia has been associated with increased chemotherapy toxicity, postoperative complications, longer hospital stays, and poorer overall survival in patients with CRC[230–232]. CT imaging at the L3 vertebral level is commonly used to quantify skeletal muscle mass and visceral adiposity in research and increasingly in clinical practice[231,233]. Cachexia, a multifactorial syndrome characterised by weight loss, muscle wasting, and systemic inflammation, is also prevalent in advanced CRC and contributes to physical decline and reduced quality of life[234,235]. In contrast, excess visceral adipose tissue has been linked to worse oncological outcomes, including higher recurrence rates and reduced survival, possibly through metabolic and inflammatory pathways[231,236].

Multimodal prehabilitation may help to address malnutrition and adverse body composition profiles in patients with CRC and this has received increasing attention over the last decade. Evidence for its effectiveness is fairly weak with improvements in functional outcomes not necessarily translating into reduced complications or reduced length of stay in a recent meta-analysis and Cochrane review[237,238].

1.9.2.3 Systemic inflammation

Systemic inflammation is increasingly recognised as a critical determinant of prognosis in CRC. Inflammation plays a central role in the pathogenesis and progression of malignancy by modulating the tumour microenvironment, influencing tumour growth, invasion, and metastasis[60,239,240]. Systemic inflammatory responses, measurable through various haematological and biochemical markers, have been demonstrated to influence survival in

patients with operable malignancy[241]. Several biomarkers have been studied in this context, with the neutrophil-to-lymphocyte ratio (NLR), C-reactive protein (CRP), platelet-to-lymphocyte ratio (PLR), and the modified Glasgow Prognostic Score (mGPS) among the most widely validated [242–245]. These markers are inexpensive, readily available, and reproducible. High CRP and mGPS scores have consistently been associated with poorer overall survival and cancer-specific survival across all stages of CRC, including in patients undergoing curative surgery and those with metastatic disease[246–249]. Importantly, these markers are also associated with cancer cachexia, sarcopenia, and treatment-related complications, highlighting their relevance in treatment planning and supportive care[250,251]. Mechanistically, systemic inflammation promotes tumour progression through several pathways, including the secretion of pro-inflammatory cytokines such as IL-6 and TNF-α, which drive angiogenesis, immune evasion, and resistance to apoptosis[60]. It is this inflammatory milieu that also influences the systemic metabolic response, which likely contributes to adverse changes in body composition[252,253].

1.9.3 Treatment factors

Many treatment-related factors influence both short- and long-term outcomes following colorectal cancer resection. The nature and quality of surgery play a pivotal role not only in determining oncological outcomes such as margin status and recurrence risk, but also in shaping the long-term functional sequelae experienced by patients.

1.9.3.1 Surgical Magnitude

The magnitude of surgery in colorectal cancer significantly influences postoperative outcomes, oncological results, and quality of life. Surgical magnitude refers to the extent and complexity of the procedure, ranging from standard segmental resections to multivisceral resections such as pelvic exenteration for locally advanced or recurrent disease. While extensive surgery may be necessary to achieve clear margins, it often carries higher risks of morbidity and mortality.

In early-stage colorectal cancer, standard resections such as right or left hemicolectomy with adequate lymphadenectomy offer excellent oncological outcomes with relatively low complication rates[254,255]. However, in cases of locally advanced or recurrent disease, more extensive procedures may be required which are associated with longer operative times, greater blood loss, and longer hospital stays and potentially greater associated morbidity and mortality[256].

Studies have shown that the extent of surgery correlates with short-term outcomes such as complication rates, length of hospital stay, and need for intensive care. High-magnitude surgery is also associated with increased risk of a positive resection margin, and longer-term functional impairment[142,257]. We will discuss this further in chapters 3 to 8.

Importantly, the ability to tolerate high-magnitude surgery depends not only on tumour biology but also on patient-related factors such as comorbidities, nutritional status, and systemic inflammation as previously discussed. Enhanced recovery after surgery (ERAS) protocols and multidisciplinary prehabilitation can mitigate some of the risks associated with extensive surgery[258].

1.9.3.2 Colorectal cancer survivorship

Survivorship in CRC encompasses the physical, psychological, and social challenges faced by individuals after completion of primary treatment. With improvements in early detection and advances in surgery, chemotherapy, and radiotherapy, the number of long-term survivors is increasing, particularly in high-income countries[259].

A central component of CRC survivorship is the management of long-term and late effects of treatment. Evidence shows that treatment-related morbidity can persist for up to a decade following diagnosis, with the burden most pronounced among rectal cancer survivors [260]. Common long-term effects include bowel dysfunction, urinary and sexual dysfunction (especially after rectal surgery), cancer-related fatigue, and peripheral neuropathy resulting from chemotherapy[260,261]. Psychological distress, including fear of recurrence, is also prevalent. The presence of a permanent stoma can further impact body image and significantly reduce quality of life [262]. Younger patients, in particular, are more likely to report a sustained decline in quality-of-life following treatment[261,263].

Survivors of pelvic exenteration often experience an even greater burden of long-term sequelae compared with those undergoing standard segmental resections. This is especially true for patients who require extended posterior or lateral resections, or those necessitating complex urological or perineal reconstruction[143,150,264]. The specific long-term outcomes will be discussed in detail in Chapters 5 and 6.

Surveillance is essential in detecting recurrence at a potentially curable stage. Current guidelines recommend regular clinical reviews, carcinoembryonic antigen (CEA) monitoring, periodic colonoscopy, and imaging in the first 3–5 years post-treatment[265]. However, optimal surveillance strategies should be tailored to individual risk profiles.

Lifestyle modification is another critical component. Evidence suggests that physical activity, a healthy diet, smoking cessation, and maintaining a healthy weight can reduce the risk of recurrence and improve overall survival[266]. Holistic survivorship care should also include psychosocial support, access to counselling services, and rehabilitation for functional deficits[266].

2 Summary

Colorectal cancer is a major global health concern, with incidence rising steadily, particularly in high-income countries. While screening and improvements in treatment have reduced overall mortality, an increasing number of cases are being diagnosed in younger adults. The development of CRC is complex, involving both genetic and environmental factors. Most cases are sporadic, arising from stepwise genetic mutations, but a minority result from inherited syndromes.

Advances in molecular oncology have refined the classification and management of colorectal cancer, with tumour stage and validated biomarkers now central to prognosis and treatment selection. Surgical resection remains the cornerstone of therapy, integrated with chemotherapy and/or radiotherapy according to risk. In selected patients with advanced pelvic disease, extended procedures such as pelvic exenteration can offer the possibility of cure. As techniques and technology have evolved, increasingly complex resections are feasible, expanding curative options for LARC and LRRC. Nonetheless, the prevailing paradigm is invasive, and a meaningful subset of patients experience poor outcomes, driven by postoperative complications, early recurrence, or treatment intolerance. Improving prediction of short- and long-term risk, and embedding this in shared decision-making, is essential to optimise patient selection, personalise perioperative optimisation and adjuvant strategies, and ultimately improve survival and quality of life.

Host-related factors play a significant role in outcomes by influencing tumour behaviour, treatment tolerance, and survival. Comorbidities, particularly in older adults, affect treatment

selection and increase the risk of postoperative complications. Nutritional status and body composition are also important predictors of outcome. Adverse body composition profiles are associated with poorer tolerance to treatment, higher complication rates, and worse survival. Elevated systemic inflammation is associated with poor survival in patients with CRC, with numerous different scoring systems used to quantify it. The influence of these host factors is well described in patients with primary operable CRC but less well in those with locally advanced or recurrent disease.

Key tumour characteristics have been shown to adversely affect survival and are associated with tumour recurrence. These high-risk characteristics, in addition to TNM stage, guide oncological treatment and surveillance and include features such as venous, lymphatic and perineural invasion and histological grade and stage. Other factors that are not currently included in the reported core histopathological data set of resected specimens, such as tumour budding and the tumour microenvironment may in future be used to further stratify high-risk patients. Assessment of the impact that these factors have in LARC and LRRC is limited in the literature.

Survivorship is increasingly recognised as a key phase in cancer care, with growing attention to long-term side effects, quality of life, and cancer recurrence. This is of particular importance in patients with locally advanced disease. While numerous prognostic factors influencing outcomes in patients undergoing standard resection for primary rectal cancer are now well established, the factors affecting outcomes in those with locally advanced and locally recurrent rectal cancer remain less well understood. This thesis sets out to explore the role host, clinical and tumour characteristics have on outcome in patients undergoing exenteration surgery for LARC or LRRC.

Chapter 2: Thesis hypothesis

'Short- and long-term outcomes of patients undergoing pelvic exenteration for locally advanced and recurrent rectal cancer are significantly influenced by clinical factors of the host and pathological features of the tumour"

2.1 Thesis Aims:

- To describe the evolution of the complex pelvic cancer service provided by the Complex Cancer Clinic at St Mark's Hospital, a high volume pelvic exenteration unit, to ascertain the inherent challenges of managing this complex patient group and describe the development of a tertiary service in order to benchmark existing standards and provide a basis for QI and ongoing innovation.
- To describe the outcomes for patients with LARC and LRRC who receive non-operative management, and to provide insights into the outcomes in those who do not proceed with surgical intervention.
- To examine the relationship between key patient factors and their influence on postoperative morbidity and long-term survival outcomes.
- To analyse the influence of systemic inflammation on outcomes for patients with LARC and LRRC.
- To explore and examine the relationship between pathological features of the disease and their effect on postoperative morbidity and long-term survival outcomes
- To analyse the tumour microenvironment and circulating and microenvironmental immune status in patients with locally recurrent rectal cancer to identify potential novel prognostic markers.

In order to address these aims within this thesis it is necessary to:

- Systematically review the current literature to identify published clinical and pathological determinants of outcome following pelvic exenteration for locally advanced rectal cancer or locally recurrent rectal cancer

- Present the unique cohort of patients undergoing pelvic exenteration at a UK tertiary referral centre and assess local practice
- Describe the surgical challenges and complications of treating patients with locally advanced rectal cancer or locally recurrent rectal cancer and sacral disease and those requiring perineal flap reconstruction.
- Examine the clinical and pathological factors that influence postoperative morbidity and mortality in patients with locally advanced rectal cancer or locally recurrent rectal cancer undergoing pelvic exenteration
- Examine the clinical and pathological factors that influence long term survival in patients with locally advanced rectal cancer or locally recurrent rectal cancer undergoing pelvic exenteration
- Interrogate the relationship between inflammation and CT body composition and outcomes following pelvic exenteration
- Perform a detailed histological assessment and analysis of the tumour microenvironment in patients with LRRC who have undergone pelvic exenteration to identify potential prognostic markers

Chapter 3: A systematic review of the clinicopathological determinants of outcome following resection by pelvic exenteration of locally advanced and locally recurrent rectal cancer

3.1 Introduction

This thesis sets out to investigate the relationship between host factors and pathological features of disease that influence both short- and long-term outcomes following pelvic exenteration. In order to place these aims in the context of the present thesis, a systematic review of the current literature was conducted.

LARC and LRRC are complex clinical entities that often require extensive intervention beyond conventional treatment strategies. Standard treatment protocols typically involve preoperative radiotherapy, with or without chemotherapy, followed by radical surgical excision. The primary goal of this approach is to maximise the likelihood of a complete pathological resection (R0) and achieve sustained local disease control[126,267].

Over the past two decades, the surgical approach to LARC has broadened considerably. Techniques such as en-bloc removal of adjacent pelvic organs and dissection of extramesorectal lymph nodes have become integral to modern management and are now performed routinely in expert centres[268]. Despite these developments, systemic metastases remain the leading cause of disease relapse in LARC, occurring in roughly one-fifth to one-third of cases[269]. However, overall survival for patients with LARC has improved, likely due to the use of total neoadjuvant therapy and ranges from 61- 75% in the literature[127–129,270]. For patients with LRRC, there are high rates of both local and systemic recurrence despite modern exenteration techniques, with a 5-year overall survival of 25-50%[131–133].

Several variables have been associated with recurrence risk and survival in primary colorectal cancer, including the quality of the original surgery, particularly whether margins were clear, as well as tumour-specific pathological features and the application of perioperative

chemoradiotherapy[128]. Pathological parameters such as tumour stage, differentiation, and lymphovascular invasion are consistently recognised as indicators of prognosis[101]. These factors are assessed as part of routine histological analysis and form the basis of standardised reporting frameworks for primary rectal cancer in the UK [201]

In contrast, there is currently no universally accepted pathology reporting standard for LRRC, resulting in variation in reporting quality and completeness[177]. Moreover, emerging tumour features such as histological growth patterns, molecular alterations, and transcriptomic profiles may provide additional prognostic insight, though these remain unexplored in clinical practice and the subject of research. Disparities in outcomes among patients with similar traditional (TNM) pathology reports suggest that consideration of novel features may in the future help refine risk stratification[86]. Earlier identification of patients with high-risk tumour biology may allow more tailored and intensive treatment strategies, particularly in the neoadjuvant setting. Similarly, better risk prediction following resection may support personalised follow-up strategies, enabling timely intervention should recurrence occur.

Clinical factors strongly influence outcomes following rectal cancer surgery. Older age and medical comorbidities increase the risk of postoperative complications and mortality, with ASA grade providing a validated predictor of perioperative risk[271]. Nutritional status is equally important; malnutrition is linked to longer hospital stay, higher complication rates, and reduced survival[272]. Systemic inflammation, captured by indices such as the neutrophil-to-lymphocyte ratio (NLR) and modified Glasgow Prognostic Score (mGPS), predicts both short- and long-term outcomes by reflecting tumour-associated inflammation[243,273]. Despite these factors being well-reported in standard primary rectal cancer resection, there is little data regarding their influence in the highly select group of patients with LARC and LRRC who undergo PE.

To address these questions, a comprehensive review of the literature was conducted, examining clinical and pathological determinants of outcome, specifically recurrence and survival, in patients undergoing pelvic exenteration for LARC and LRRC.

3.2 Methods

3.2.1 Search strategy

This systematic review was performed following the methodology set out by the Cochrane Prognosis Methods Group for prognostic factor systematic reviews[274]. A predesigned review protocol was used, and the results are reported in accordance with the Preferred Reporting Items for Systematic reviews and Meta-analyses (PRISMA) statement and has been registered on PROPSERO prior to data extraction and analysis of results (PROSPERO 2020 CRD42020223641)[275].

A comprehensive literature search was performed in July 2021 on the following databases: EMBASE, MEDLINE, NICE Evidence Search and Cochrane Central Register of Controlled Trials (CENTRAL) in The Cochrane Library. An online search using Goggle Scholar was also performed. MESH and keyword search terms were used to cover the following: "pelvic exenteration", "multi-visceral resection" and "abdomino-sacral resection" combined with "locally advanced rectal cancer" and "recurrent rectal cancer". An evidence support manager at the Royal College of Surgeons of England helped conduct the search strategy. All studies involving pelvic exenteration were included in the search strategy to identify any reported clinicopathological outcomes. The search maintained breadth to ensure all reported outcomes of interest were captured. The full search strategy is shown in Appendix 1. The search was limited to studies published between January 2001 and July 2021 with no language restriction imposed at the search stage. Search records were downloaded to a citation manager program (*Covidence, Veritas Health Innovation, Melbourne, Australia*) and duplicates removed automatically. Additional papers were identified by hand screening of reference lists of reviewed articles [Prisma Diagram Fig 3.1].

Prior to this review, the most recent systematic review of outcomes following pelvic exenteration for rectal cancer was published in 2018 with a focus on both short and long-term outcomes[276]. Since this time, a number of studies have been published in this field, including large numbers of patients from the collaborative multicentre cohorts. As with this most recent review, a limit to papers published after 2001 was made. The rationale for this is that from 2001 widespread use of MRI in preoperative diagnosis and planning would largely alter the identification and accurate staging of patients. There has also been a significant change in practice and operative equipment used in pelvic exenteration surgery over the last two decades.

3.2.2 Eligibility criteria

The following studies were considered for inclusion in this review: Randomised controlled trials, prospective and retrospective observational trials. Studies had to report on at least one pathological or clinical outcome influencing survival following pelvic exenteration for either LARC or LRRC for them to be included. Studies that included other pathologies such as advanced gynaecological malignancies or anal cancers were only included if the outcomes for rectal cancer were reported separately.

Studies were excluded for the following reasons: (1) no extractable data or outcomes of interest not clearly reported, (2) inclusion of resections other than pelvic exenteration (e.g. abdominoperineal resection) without results reported separately. (3) reporting the outcomes for other pathologies was not reported separately, (4) case series including ten or fewer patients. Conference abstracts, letters, commentaries and review articles were excluded.

To minimise the risk of data duplication, authorship lists from large multicentre studies were systematically cross-referenced with individual publications. Studies were excluded if they recruited participants during overlapping time periods and did not provide additional prognostic data.

3.2.3 Study selection

Titles and abstracts of all studies identified by the search strategy were screened. Full paper screening was performed, and papers were assessed for eligibility based on the predefined inclusion criteria.

3.2.4 Data extraction and assessment of bias

Data was extracted onto a predesigned database spreadsheet including the following data fields: first author, year of publication, journal, country of origin, study type, dates of included cases, number of patients and basic demographics including age and sex, length of follow up, cancer type, procedure type, margin status, clinical and pathological reported factors associated with either recurrence or survival, five-year survival (or the reported survival statistics available). The risk of bias for each included study was evaluated using the Quality in Prognostic Factors Studies (QUIPS) tool. This framework assigns a rating of low, moderate, or high risk of bias

across six domains: study participation, study attrition, prognostic factor measurement, outcome measurement, study confounding, and statistical analysis [277]

3.2.5 Statistical analysis

Due to the use of multiple different definitions for operative type, recurrence and survival, and different end points, direct comparison of the data across studies was not possible. The significant heterogeneity of the studies included meant that meta-analysis was not feasible. Consequently, a narrative review of outcomes was completed.

3.3 Results

The initial search strategy identified 1649 studies after duplicates were removed. 1594 studies were excluded after title and abstract screening, leaving 55 papers for full text review. 32 studies were excluded for the following reasons: 13 did not separately report pelvic exenteration outcomes from other procedures, 8 included non-rectal cancer malignancies without separate analysis of outcomes based on pathology, 5 studies were published in duplicate with different journals, and 6 studies did not have any extractable data relating to the outcomes of interest. 23 studies met the full inclusion criteria and were included in this review as shown in the PRISMA Diagram (Figure 1).

Twenty-three studies met the eligibility criteria and included a total of 4071 patients and were published between 2002 and 2021[141,142,192,278–297]. These are shown in Table 3.1. There were no randomised controlled trials. Of the cohort studies included, 6 presented prospectively collected data, and the remaining 17 studies were retrospective. Each study reported on cases spanning a wide number of years, ranging from 6 to 30 years. Risk of bias was assessed to be low in most studies (Table 3.2). The cohort sizes ranged from 13 to 1291 patients. There were two large multicentre international cohort studies included that account for the large overall patient number[141,142].

Figure 3.1: PRISMA diagram for systematic review

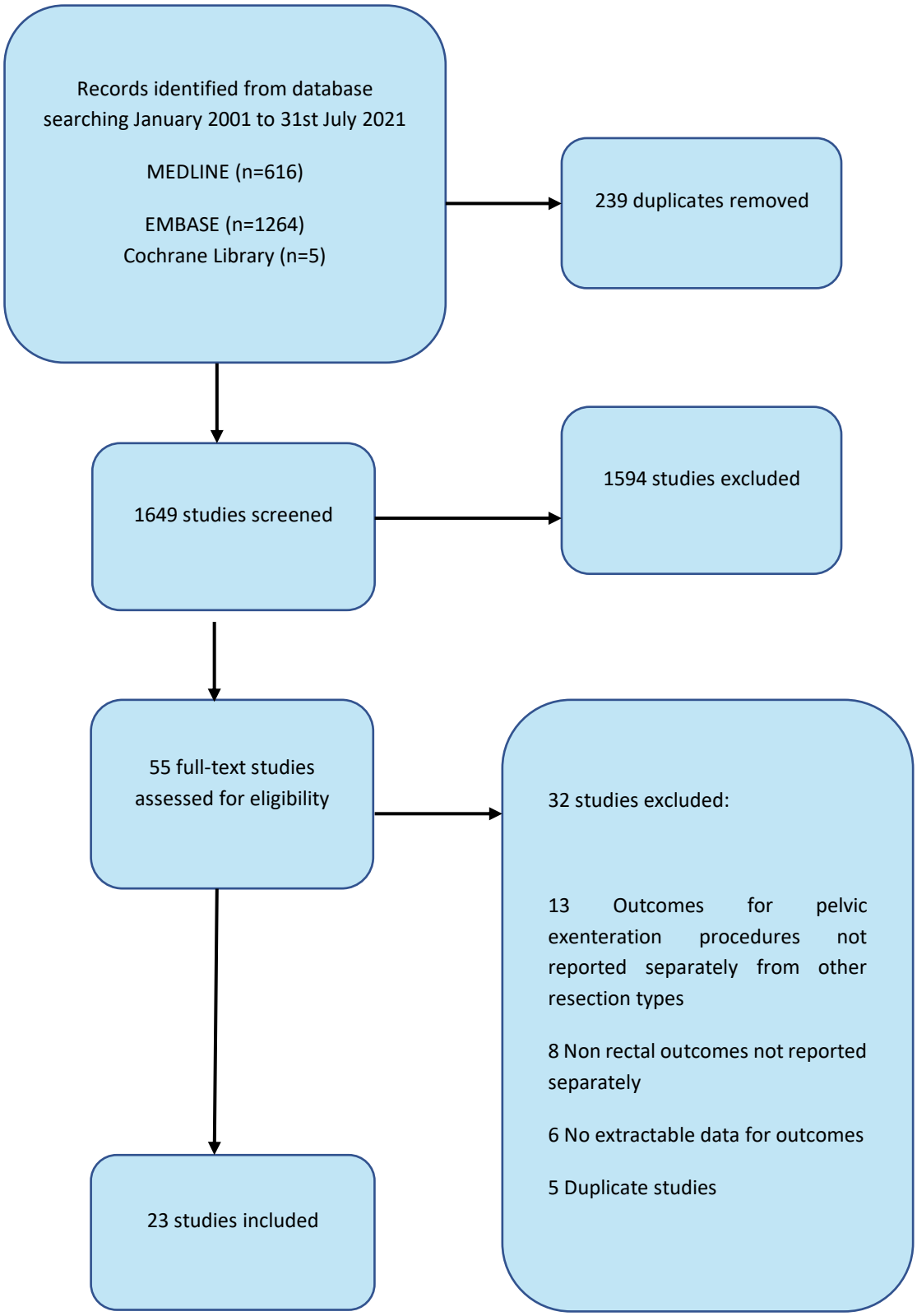


Table 3.1: Summary table of all included studies in the systematic review

								Demographics		Cancer type		Exenteration type						Neoadjuvant oncological treatment			Adjuvant oncological treatment				Resection Margin				Survival	
First Author	**Year**	**Publication**	**Country**	**Single/ multi centre**	**Study type**	**Dates of included cases**	**Total patient number**	**Male**	**Median age**	**LARC**	**LRRC**	**TPE**	**PPE**	**APE**	**MPE**	**Other/ NS**	**Bony resection**	**Any**	**RT or CRT**	**Ct**	**Any**	**RT**	**Ct**	**IORT**	**R0 (%)**	**R1 (%)**	**R2 (%)**	**Follow up**	**Median overall survival**	**5-year Overall Survival**
Wiig[278]	2002	Eur J Surg	Norway	Single	PC	1991-2001	47	89%	64	25	22	47	0	0	0	0	0	NS	47	NS	NS	NS	NS	19	57.4	34.0	8.5	Mean 60 months	NS	28% (36% LARC vs 18% LRRC)
Jimenez[279]	2002	DCR	USA	Single	RC	1991-2000	55	53%	62	16	39	55	0	0	0		11 sacrectomy	NS	NS	NS	NS	33	31	27	72.7	27.3		Median 26 months	NS	40%
Ike[284]	2003	DCR	Japan	Single	RC	1976-1997	71	96%	56	71	0	71	0	0	0	0	0	NS	13	NS	NS	NS	NS	0	NS	NS		NS	NS	54.10%
Moriya[294]	2004	DCR	Japan	Single	RC	1993-2001	57	100%	55	0	57	57	0	0	0	0	57 distal sacrectomy	NS	28	NS	NS	NS	NS	NS	84.2	15.8		NS	NS	NS
Vermaas[296]	2006	EJSO	The Netherlands	Single	RC	1994-2004	35	94%	58	23	12	35	0	0	0	0	4 sacrectomy, 2 coccygectomy	NS	34	NS	NS	NS	NS	13	74.3	14.3	11.4	Mean 28m months	NS	LARC 50%, LRRC 16%
Ishiguro[288]	2009	Surgery	Japan	Single	RC	1975-2005	93	86%	55	93	0	83	1	9	0	0	6 distal sacrectomy	NS	17	0	NS	4	25	2	97.8	2.2		Minimum 36 months	NS	51%
Nielsen[297]	2011	Colorectal Disease	Denmark	Single	PC	2001-2010	90	92%	63	50	40	40	0	0	0	0	20 sacrectomy	NS	65	5	NS	12	NS	33	53.3	41.1	5.6	Median 12 months	39.6 months LARC, 28.8 months LRRC	NS
Domes[291]	2011	Can Surg	Canada	Single	RC	1997-2007	28	89%	61	24	2	28	0	0	0	0	0	NS	23	0	NS	0	19	0	67.9	25.0		Median 35 months	NS	75.1% (3 year)
Hsu[286]	2011	Asian J Surg	Taiwan	Single	RC	1991-2007	23	100%	58	13	10	18	0	0	0	5 Supralevator	0	NS	NS	NS	NS	9	14	0	60.9	13.0		NS	NS	20%
Kuhrt[295]	2012	WJSO	USA	Single	RC	2004-2010	36	44%	59	9	27	27	0	0	0	0	0	NS	28	20	NS	NS	NS	16	41.7	27.8	16.7	NS	21.4 months	NS
Bhangu[283]	2014	Annals of Surgery	UK	Single	PC	2006-2001	100	70%	60.3	55	45	0	0	0	0	100 described by compartment resected	30 sacrectomy	NS	75	70	NS	NS	NS	0	78	15	7	NS	R0 85%, R1 46%, R2 0% (3 year)	R0 67%, R1 49%, R2 0% (3 year)
Ghouti[289]	2015	Am J Surg	France	Single	RC	2004-2013	27	67%	58	0	27	14	13	0	0	0	0	NS	7	21	19	NS	NS	0	63.0	18.5		Median 33 months	NS	75.5% (3 year)

Kusters[290]	2015	BJS	The Netherlands/ Australia	Multiple- 2 hospitals	PC	1997-2013	95	100%	63	95	0	23	53	0		20 Supralevator	30 sacrectomy or coccygectomy	NS	91	0	NS	NS	31	49	87.4	12.6		Median 62 months	NS	62%
Yang[293]	2015	Ann Surg Treat Res	Korea	Single	RC	2001-2010	40	80%	59	23	17	19	0	0	21	0	14 sacrectomy	NS	8	12	NS	0	31	0	67.5	32.5	15.0	Median 25 months	80 months LARC, 15 months LRRC	28.10%
Radwan[287]	2015	BJS	Wales	Single	RC	1992-2014	174	48%	65	174	0	78	96	0	0	0	0	103	NS	NS	NS	NS	31	0	90.2	9.8		NS	NS	59.3% for R0, 23% R1
Koda[280]	2016	Int J Colorectal Dis	Japan	Single	RC	1986-2013	54	88.9%	64	54	0	54	0	0	0	0	0	NS	11	NS	27	0	27	0	90.7	8.3		NS	23 months and 41 months based on operative group	30.4% and 71.8% based on operative group
Quyn[285]	2016	EJSO	Australia	Single	PC	1994-2014	104	52%	62	104	0	39	0	0	0	65	42 NOS	NS	85	81	NS	NS	NS	0	85.6	14.4		Median 52 months	91 months	62%
Pellino[292]	2018	World J Gastroenterol	Spain	Multiple - 33 hospitals	PC	2006-2017	82	66%	62	82	0	0	0	0	0	82 TPE/PPE	0	59	55	11	54	6	48	0	76.8	23.2		>5 years	43.8 months	67.2%
PelvEx[141]	2018	BJS	International	Multiple - 27 hospitals	RC	2004-2014	1184	64%	63	0	1184	418	395	80	91	200	240	614	517	61	NS	NS	NS	0	59.2	32.9	7.9	NS	30 months	R0 28.2%, R1 17.3%, R2 3% (3 year)
PelvEx[142]	2019	Annals of Surgery	International	Multiple - 27 hospitals	RC	2004-2014	1291	60%	63	1291	0	551	529	30	139	42	106	1008	968	40	NS	NS	NS	0	83.7	14.0	2.4	Median 48 months	37 months	R0 56.4%, R1 29.6%, R2 8.1% (3 year)
Koh[192]	2020	Annals of Surgery	Australia	Single	RC	1994-2018	210	67%	62	0	210	101		0		106 partial PE	122 sacrectomy	NS	95	102	NS	NS	NS	0	78.6	16.7	4.8	Median 29 months	46 months (95% CI 37.1-54.9)	NS
Culcu[282]	2021	Turk J Colorectal Dis	Turkey	Single	RC	2015-2019	17	47%	53	0	17	17	0	0	0	0	0	7	7	0	NS	NS	NS	0	76.5	23.5	0	Median 16 months	NS	26% (2year)
Kazi[281]	2021	BJS	India	Single	RC	2013-2020	158	55%	44	158	0	96	62	0	0	0	0	147	147	103	127	NS	NS	0	90.5	8.9	0.6	Median 29 months	NS	64% (3year)
Total							**4071**	**74%**	59	**2360**	**1709**	**1817**	**1149**	**119**	**251**	**131**	**704**	**1938**	**2321**	**526**	**100**	**65**	**257**	**111**	**74.5 %**	**19.6 %**	**7.3%**			

PC- Prospective cohort, RC- retrospective cohort, LARC- Locally advanced rectal cancer, LRRC- Locally recurrent rectal cancer, TPE- Total pelvic exenteration, PPE- Posterior pelvic exenteration, APE- Anterior pelvic exenteration, MPE- Modified pelvic exenteration, RT- radiotherapy, CRT- Chemoradiotherapy, Ct- Chemotherapy, IORT- Intraoperative radiotherapy, NS- Not stated

Table 3.2: The risk of bias assessment of included studies using QUIPS tool [277]

Study	Study population	Study attrition	Prognostic factor measurement	Outcome measurement	Adjustment for other prognostic factors	Statistical analysis and reporting
Wiig 2002	Low	Low	Low	Low	Low	Low
Jimenez 2002	Low	Low	Low	Low	Low	Low
Ike 2003	Low	Low	Low	Low	Low	Low
Moriya 2004	Low	Moderate	Low	Low	Low	Low
Vermaas 2006	Low	Low	Low	Low	Low	Low
Ishiguro 2009	Low	Low	Low	Low	Low	Low
Nielsen 2011	Low	Moderate	Low	Low	Low	Low
Domes 2011	Low	Low	Low	Low	Low	Low
Hsu 2011	Low	Low	Low	Low	Low	Low
Kuhrt 2012	Low	Low	Low	Low	Moderate	Moderate
Bhangu 2014	Low	Low	Low	Low	Low	Low
Ghouti 2015	Low	Low	Low	Low	Moderate	Moderate
Kusters 2015	Low	Low	Low	Low	Low	Low
Yang 2015	Low	Low	Low	Low	Low	Low
Radwan 2015	Low	Low	Low	Low	Low	Low
Koda 2016	Low	Low	Low	Low	Low	Moderate
Quyn 2016	Low	Low	Low	Low	Low	Low
Pellino 2018	Low	Low	Low	Low	Low	Low
PelvEx Collaborative 2018	Low	Moderate	Low	Low	Low	Low
PelvEx Collaborative 2019	Low	Moderate	Low	Low	Low	Low
Koh 2020	Low	Low	Low	Low	Low	Low
Culcu 2021	Low	Low	Low	Moderate	Moderate	Moderate
Kazi 2021	Low	Low	Low	Low	Low	Low

74% of patients were males (n=3013) with a median age of 59 years (range 55-65years). There were 2360 cases of LARC and 1709 patients with LRRC. The predominant procedure type was total pelvic exenteration (TPE) with 1817 cases, 1149 posterior pelvic exenterations (PPE), 119 anterior pelvic exenterations (APE), 251 'modified 'pelvic exenterations (MPE) (defined by Yang et al. as a resection above the anus or lower rectum allowing for intestinal continuity to be restored[293] or otherwise not defined by the PelvEx collaborative papers[141,142]), 106 partial pelvic exenterations, 25 supra-levator exenterations and in 142 cases the type of procedure was not stated. Extended bony resection was completed in 704 cases including 660 sacrectomies. Twenty studies (87%) reported the use of neoadjuvant oncological therapies and twelve (52%) reported adjuvant treatment. Seven studies (30%) reported the use of intra-operative radiotherapy. Overall median follow-up was thirty-six months, eight papers (35%) did not comment on length of follow up.

Table 3.3 demonstrates the clinical and pathological outcomes that each study assessed in relation to its impact on survival.

Table 3.3. Clinicopathological factors assessed in each study

	Clinical features assessed				**Tumour pathological factors assessed**					
First author	Age	Sex	BMI	other	Resection margin	Nodal status	Vascular invasion	Tumour stage	Differentiation	Other
Wiig[278]	N	N	N	0	Y	N	N	N	N	N
Jimenez[279]	Y	Y*	N	Preoperative pain	Y	Y	N	Y	N	N
Ike[284]	Y*	Y	N	0	N	Y*	N	Y*	Y	N
Moriya[294]	N	N	N	Preoperative pain	Y*	Y	N	N	N	Tumour size
Vermaas[296]	N	N	N	Preoperative pain*	Y*	N	N	Y*	N	N
Ishiguro[288]	Y	Y	N	0	Y	Y*	Y*	Y	Y	N
Nielsen[297]	N	N	N	0	Y	N	N	N	N	N
Domes[291]	N	N	Y	0	Y	Y	N	Y	N	N
Hsu[286]	Y	N	N	0	Y*	N	N	N	N	N
Kuhrt[295]	N	N	N	0	Y*	N	N	N	N	N
Bhangu[283]	Y	Y	N	0	Y*	Y*	N	Y	N	N
Ghouti[289]	Y	Y	N	0	Y*	Y	N	Y	Y	N
Kusters[290]	Y	Y	N	0	Y	Y*	N	N	N	N
Yang[293]	Y	Y	N	0	Y*	N	N	N	N	N
Radwan[287]	Y*	Y	N	0	Y*	Y*	N	N	N	N
Koda[280]	Y	Y	N	N	N	Y*	N	N	N	N
Quyn[285]	N	N	N	0	Y*	N	N	N	N	N
Pellino[292]	N	N	N	ASA	Y	N	N	Y	N	N
PelvEx[141]	N	N	N	0	Y*	Y*	N	N	N	N
PelvEx[142]	N	N	N	0	Y*	Y*	N	N	N	N
Koh[192]	N	N	N	0	Y*	N	Y*	N	N	Resection margin size*
Culcu[282]	N	Y	N	N	Y	Y	Y*	Y	N	Perineural invasion
Kazi[281]	Y	N	Y	Preoperative bowel obstruction, anaemia, hypoalbuminaemia	Y*	Y*	Y*	N	Y*	Perineural invasion, Tumour Regression Grade

Y, yes; N, no; *= statistically significant effect on survival

3.3.1 Clinical outcomes

In terms of the relationships between clinical and patient factors, and disease outcome a number of publications were identified in which patient age, sex, presence of symptoms, ASA grading and BMI have previously been reported within the LARC/LRRC population. No studies were identified in which the roles of the pre-treatment systemic inflammatory response, body composition parameters, ethnicity or deprivation have been assessed in LARC/ LRRC.

Age

Eleven studies (48%) assessed the impact of age using a range of cut-off values. Nine of the eleven studies found no significant association between increasing age and survival. Interestingly, the two studies using the cut-off age of fifty years identified a significant association between age and outcome. In the paper by Radwan *et al.* however, there was only significance when the overall survival of octogenarians was compared with that of patients under the age of 50 years[287]. Although this remained significant on multivariate analysis (OR 1.57, p=0.0001), other factors such as ASA and performance status were not commented on that may influence these data. The effect of age on cancer-specific survival was not reported. Ike *et al.* also used the cut off of fifty years, demonstrated a relatively modest, significant impact on survival on multivariate analysis when tumour stage and lymph node metastasis were also considered, with a HR of 1.054 (95% CI 1.0139-1.0966, p=0.008)[284]. The authors did not state whether this was disease-free survival (DFS) or overall survival (OS).

Sex

Ten studies (43%) assessed the influence of sex on survival. A total of 242 females and 532 males were included in these studies. Jiminez *et al.* did identify a potential survival benefit for females on univariate analysis, but this did not remain following multivariate modelling, including history of previous abdominoperineal resection, resection margin status and use of IORT[279]. The remaining studies found no significant influence of sex on survival outcomes.

Presenting symptoms

Four studies (20%) looked at the influence of pain at presentation and its effect on survival. In the small study by Vermass *et al.,* eight of thirty-five (23%) patients presented with pain and this was significantly correlated with reduced OS ($p<0.01$) and DFS ($p<0.01$)[296]. However, this was not replicated in a slightly larger study by Jimenez *et al.,* where sixteen of thirty-five (46%)

patients presented with pain (p=0.84)[279]. The definition of the presenting symptom in terms of grading of severity or analgesic use was not commented on in these studies. In patients with rectal tumours extending towards the sacrum requiring TPE with distal sacrectomy Moriya *et al.* found no significance in those patients presenting with severe pain radiating to the buttocks or thigh compared with those with more limited pain[294]. Ghouti *et al.* compared patients diagnosed with recurrence on standard follow-up imaging with those patients presenting with pain or other symptoms and found no survival difference[289]. Kazi et al. analysed whether preoperative bowel obstruction influenced recurrence-free survival (RFS) but found no significant difference[281].

ASA grade

Only one paper commented on the influence of ASA on outcomes. No significant difference was identified in this study; however, the majority of patients were ASA II (51.2%)[292]. This may represent the rigorous selection of suitable patients to undergo such invasive procedures, who are therefore unlikely to have a high ASA.

Body Mass Index

The influence of body mass index (BMI) on survival outcomes was reported by two studies. Domes *et al.* demonstrated in their series of 28 patients that a BMI greater than 30 was associated with reduced DFS but not OS on univariate analysis; however, significance was not reached on multivariate analysis[291]. Kazi et al. used a cut-off of BMI 25 and found no association with RFS[281]. The effect of body composition was not commented on in any other studies.

Other clinical factors

Kazi et al. were the only group to study the influence of anaemia (defined as Hb <12g/dL) and hypoalbuminaemia (defined as Albumin <3.5g/dL). They found neither factor to influence RFS[281]. No papers reported on the influence of systemic inflammation as measured by indices such as NLR or the modified Glasgow Prognostic score.

3.3.3 Pathological outcomes

When assessing the relationships between pathological factors and disease outcome a number of studies were found in which resection margin status, tumour stage, lymph node involvement, lymphovascular invasion, tumour differentiation, tumour size and margin size were reported

in patients undergoing exenteration for LARC or LRRC. No other adverse tumour features other than those in standard reporting datasets for rectal cancer resections were assessed in relation to their impact on survival and recurrence. No papers were identified that looked at tumour morphology, tumour epigenetics, tumour immunohistochemistry phenotypes or the tumour microenvironment. Additionally, molecular tumour characteristics and their influence on outcome in patients undergoing exenteration for LARC or LRRC have not been considered to date.

Resection margin

Twenty-one studies (91%) reported on resection margin status, however, only eighteen commented (86%) on its impact on survival. Across all studies clear resection margins (R0), defined as a clear margin of >1mm, were reported in 2849 of 3946 patients (72%) with a range in R0 of 48-98% between studies. The remaining 28% of patients had a positive margin; the distinction between R1 (tumour <1mm from margin edge) and R2 resections (macroscopically involved margin) was not made clear in all studies. Eighteen studies reported margins separately for primary and recurrent rectal cancer. In patients with LARC the overall R0 rate was 84.2% (1844/2191 patients) with a range of 48-98% and median of 76.8% across fifteen studies. For LRRC the overall R0 rate was 61.9% (965/1559 patients) with a range and median respectively of 25-84% and 58.7% across the eleven studies.

Twelve studies reported that a positive resection margin was a negative prognostic marker for overall. Most studies compared negative and positive resection margins, where a positive margin may include both R1 and R2 resections. The greatest magnitude of effect on outcomes were noted when comparing survival of patients with an R0 margin compared with an R2 margin for both LARC and LRRC (HR 3.01 95% CI 1.97-4.87, p<0.001 and HR 4.84 95% CI 2.77-8.46, p<0.001, respectively)[141,142]. When R0 resections were compared with positive margins, both microscopic and macroscopic (R1 or R2) the effect was more modest, with hazard ratios ranging from 1.8 to 2.6[281,282,286,289]. Of the remaining studies reporting resection margins, four found no significant difference in overall survival, and the remaining two did not comment on it. Seven studies assessed the impact of the resection margin on disease-free survival. Six of these found that a positive margin significantly reduced DFS, with only the study by Bhangu *et al.* quoting hazard ratios (HR 4.04 95%CI 1.87-8.71, p<0.001)[283]. Four studies commented on the effect of the surgical margin on local recurrence. Three studies looked at patients with LARC only. Pellino *et al.* and Kazi *et al.* found that a positive margin

greatly increased the risk of local recurrence (HR 5.58, 95% CI 1.04-30.07, p=0.04, HR 3.00 95% CI 1.59-5.65, p=0.0007) but Kusters *et al.* demonstrated no significant difference (HR 1.6, 95% CI 0.6-4.26, p=0.464)[281,290,292]. When looking at LARC and LRRC cases combined Bhangu *et al.* demonstrated a significant negative impact on local recurrence free survival (HR 5.48, 95%CI 1.83-16.39, p=0.002)[283].

In addition to assessing the impact of a positive or negative resection margin on survival, one study assessed this further by looking at the influence of margin size on outcomes for patients with LRRC. No difference in OS was seen by increasing the clear margin size from 0.5mm to 1mm or 2mm, which had not been previously reported in the literature. However, a clear margin greater than 0.5mm was associated with increased local disease-free survival (p=0.005) when compared with less than 0.5mm[192].

Tumour stage

Eight papers (35%) commented on the impact of tumour (T) stage on survival. Only two studies found advancing T stage to influence outcomes. Ike *et al.* assessed the effect of advancing T stage in patients with LARC. They found a significant difference in OS at 5 and 10 years for patients with stage 3 disease compared with stage 4 on univariate analysis (p=0.00185)[284]. However, when assessed with patient age and lymph node metastasis upon multivariate analysis, this significance was lost. The second study looked at patients with LRRC and found that increasing Wanebo stage (five stages of tumour invasiveness are classified from limited invasion TR1 to TR5 where there is invasion into the bones or ligaments in the pelvis[152]) was associated with reduced five year survival with 38% OS for stage 0-3 compared with no surviving patients with stage 4 tumours (p=0.003) and DFS (p=0.05)[296].

Tumour differentiation

The effect of tumour differentiation on outcomes was explored by four studies[281]. Two studies compared well to moderately differentiated lesions[279,289], the third paper compared poor or mucinous tumours to well or moderately differentiated cancers and the last compared well/moderately differentiated to poorly differentiated or signet ring tumours. Poorly differentiated or signet ring tumours were found to be a negative prognostic marker with reduced 3-year OS in patients with LARC: HR 2.10 (95%CI 1.061-4.643, p=0.031) on multivariate analysis[281]. However, no significant effect was noted for 1 year OS (83% vs 80%,

p=0.902) in patients with LRRC when comparing well differentiated to moderately differentiated lesions[281].

Tumour size

Tumour size and its impact on survival was examined in one study (5%) where tumours less than or greater than 5cm were compared in patients undergoing TPE with distal sacrectomy[294]. No significant difference in survival was noted.

Nodal disease

The influence of nodal disease on outcomes was reported in thirteen studies (57%), seven of which were in patients with LARC, four in patients with LRRC and two studies including both groups of patients. Some studies looked at overall nodal positivity whilst others commented particularly on lateral lymph node involvement. In patients with LARC all seven studies found that positive lymph nodes were a negative prognostic marker. Radwan *et al.* found that node positivity was associated with reduced five-year OS (OR 2.18, p=0.004) when compared across all stages of tumour[287]. However, when the effect of lymph node positivity was looked at in patients with T4 tumours only, no effect was seen on survival. In the study by Kusters *et al.* positive lymph nodes were associated with reduced DFS but not OS (HR 2.59, 95% CI 1.0-6.7, p=0.05)[290]. Ishiguro *et al.* demonstrated on multivariate analysis that lateral lymph node involvement (nodes along the internal iliac artery system), but not upper lymph node involvement (defined as nodes along the inferior mesenteric artery territory), was associated with reduced OS and DFS (HR 2.09, 95% CI 1.06-4.1, p=0.03 and HR 2.1 95 % CI 1.38-4.92, p=0.01, respectively).[288] However, this influence of lateral nodes was not replicated by Kazi et al.[281]. A similar magnitude of impact on survival was demonstrated by Ike *et al.* when comparing N2 to N1 and N0 disease and five-year survival (HR 2.23, 95% CI 1.42-3.51, p=0.0005)[284]. In the PelvEx Collaborative study for LARC the hazard ratio was more modest although still showing a negative prognostic influence of lymph node involvement (HR 1.27 95% CI 1.06-1.52, p=0.009)[142]. This significant effect was not seen in the PelvEx cohort in LRRC where the significance of nodal involvement was present on univariate analysis but lost in the multivariate analysis[141]. The other three studies in patients with LRRC also showed no influence of nodal status on survival. In the two studies that analysed the impact of node positivity on a combined cohort of LARC and LRRC patients only one found a significant association with outcome. Bhangu *et al.* demonstrated an association between positive nodes

and reduced three-year DFS (HR 2.43 95%CI 1.14-5.18, p=0.022) but not local recurrence free survival (p=0.7)[283].

Lymphovascular invasion

Four studies discussed the effect of lymphovascular invasion (LVI) on outcomes. All found a significant association between its presence and outcomes. In the recent study by Koh *et al.,* the authors comment that lymphovascular invasion was associated with systemic recurrence for patients with LRRC (p=0.032), but no other data or effect on survival was provided[192]. Ishiguro *et al.* demonstrated a negative impact of lymphovascular invasion on OS (HR 2.0, 95% CI 1.05-3.82, p=0.04) in LARC, but the significant impact on DFS was lost on multivariate analysis[288]. Kazi et al. reported a significant impact of 3-year RFS in LARC (HR 2.84, 95% CI 1.64-4.92, p=0.0002)[281]. Culcu et al. showed a significant reduction in 2-year OS in the presence LRRC with LVI (16.7% vs 80%, p=0.038)[282].

Perineural invasion

Two studies assess the impact of perineural invasion (PNI) on outcomes. Kazi et al. did not demonstrate a significant effect of PNI on 3-year RFS in LARC (p=0.073)[281]. However, in a small study of patients with LRRC, PNI was associated with a significantly reduced 2-year OS (15.2% v 83.3%, p=0.022)[282].

Tumour regression

Kazi *et al.* assessed the influence of tumour regression, scored using Mandard's classification, following neoadjuvant therapy in patients with LARC. This histological scoring system is used to grade tumour response to neoadjuvant therapy by evaluating the proportion of residual viable tumour cells relative to fibrotic (regressed) tissue on a 5-point scale from TRG 1 (complete regression) to TRG 5 (no evidence of regressive changes[298]. They demonstrated that a score of three or greater, indicating an incomplete or poor pathological response to neoadjuvant therapy, was associated with a reduced 3-year RFS (HR 2.21, 95% CI 1.12-4.36, p=0.02) on multivariate analysis[281,298].

3.4 Discussion

This review highlights pelvic exenteration as a rapidly evolving subspecialist field, with continued advances anticipated. However, studies conducted over the past 18 years often demonstrate non-standardised reporting, with the majority of data collected retrospectively.

These methodological limitations restrict one's ability to draw robust conclusions and introduce the inherent risk of bias. In recent years, this has been partly addressed with large multicentre cohort studies such as those coordinated by the PelvEx collaborative[141,142]. The substantial contribution of these multinational studies lends greater strength and credibility to the evidence base within the published literature.

This review has highlighted a number of pathological factors that are considered to influence outcome, including resection margin status and lymph node involvement. The majority of studies demonstrate a significant association between an incomplete excision and reduced survival. It is, however, difficult to assess if there has been an improvement in R0 rates over time due to the large range of dates over which patients included in studies had their surgery. This ranged from six to thirty years in this review. It may be anticipated that R0 resection margin status would have improved over the last two decades through the use of improved preoperative scanning, increasingly rigorous multidisciplinary decision making in relation to operative planning, and advances in operative equipment and technique, but this is difficult to prove from the available literature. A recent multicentre study found no significant increase in R0 resection rates over time, but this is in the context of increasingly radical resections[299]. T stage and N stage appear to be of lesser importance.

No specific clinical features have been identified that impact independently on survival although this may reflect the rigorous preoperative selection of patients who are suitably fit enough, without significant comorbidity, to undergo such major surgery. Increasing age may be a negative factor, as demonstrated by two studies in this review; however, other important confounders were not controlled for. There is a paucity of evidence of the impact of physical fitness and frailty on outcomes for patients undergoing pelvic exenteration. In the era of prehabilitation it is likely that evidence will accrue in the future. Pilot studies have demonstrated promising initial results for reducing post-operative complications and have even influenced tumour regression in patients with advanced rectal cancer[300,301].

As knowledge of tumour biology and host response continues to expand, there is increasing emphasis on the development of novel prognostic markers in rectal cancer. Locally advanced and recurrent rectal cancers are biologically aggressive, with a recognised propensity for local invasion and recurrence. Tumour genotyping and epigenetic signatures are emerging as potential determinants of survival, while systemic inflammatory markers, such as the

neutrophil-to-lymphocyte ratio and the modified Glasgow Prognostic Score, have demonstrated prognostic value in primary colorectal cancer[248,302]. Local tumour immune features, including stromal inflammatory infiltration, and CT-derived measures of sarcopenia and myosteatosis have also been identified as relevant biomarkers, particularly in advanced disease where tumour perforation or invasion of adjacent structures provokes a pronounced inflammatory response[216,235]. Additional tumour-based biomarkers, including those predictive of response to neoadjuvant chemoradiotherapy, show promise in LARC, but their role in outcomes after exenteration remains unexplored[303]. A deeper understanding of the biology of recurrent rectal cancer is also required, including whether adverse features can be identified in the original primary tumour specimen. Such factors will be considered further in this thesis.

Despite progress in prognostication for primary rectal cancer, comparable advances have not been achieved in patients with LARC or LRRC undergoing pelvic exenteration. To address this gap, robust prospective case-controlled studies are needed to validate novel biomarkers and integrate them into prognostic models for overall and disease-free survival. Such tools would improve patient selection, support more accurate preoperative counselling, and guide treatment allocation in a group where surgery carries substantial risk. Ultimately, incorporating tumour- and host-related biomarkers into clinical pathways has the potential to personalise oncological care, facilitate earlier detection of recurrence, and identify those patients who may safely coexist with their disease for prolonged periods.

Study limitations

This chapter is subject to several limitations. First, all included studies were observational, with the majority being retrospective single-centre cohorts, introducing significant risk of selection and reporting bias. The wide timeframes over which patients were treated (spanning up to three decades) limit comparability, particularly given substantial evolution in imaging, surgical techniques, perioperative care, and oncological strategies. Reporting was inconsistent, with variable definitions of outcomes such as recurrence and survival, and non-standardised pathology reporting, especially in LRRC. Importantly, few studies adjusted for key confounders, and the prognostic role of clinical factors such as frailty, systemic inflammation, or body composition was not explored. The inability to perform meta-analysis due to heterogeneity further restricts the strength of conclusions. Lastly, publication bias cannot be excluded, as studies with negative or non-significant findings may remain underreported.

Collectively, these limitations emphasise the need for high-quality, prospective, multicentre studies with standardised reporting frameworks.

3.5 Conclusions

In conclusion, this systematic review of the literature demonstrates that pathological resection margin status remains the most consistent prognostic determinant of outcome following pelvic exenteration for LARC and LRRC, while the impact of other conventional pathological factors appears less certain. Clinical characteristics such as age, comorbidity, and presenting symptoms have not been shown to independently influence long-term survival, though this may reflect the selective nature of candidates deemed fit for exenteration. The current literature is limited by retrospective design, non-standardised reporting, limited focus on the influence of factors on operative morbidity and incomplete evaluation of emerging prognostic metrics. With rising R0 rates, future work must focus on identifying additional tumour- and host-related biomarkers that can refine risk stratification, inform patient selection, and guide adjuvant strategies. This will be explored in the coming chapters.

A modified version of this review focusing solely on the pathological factors influencing outcomes has been published in the International Journal of Surgery.

- Gould LE, Pring ET, Drami I, Moorghen M, Naghibi M, Jenkins JT, Steele CW, Roxburgh CS. A systematic review of the pathological determinants of outcome following resection by pelvic exenteration of locally advanced and locally recurrent rectal cancer. Int J Surg. 2022 Aug;104:106738. PMID: 35781038

Chapter 4: The Complex Cancer Clinic - A Unique Cohort

4.1 Introduction

St Mark's Complex Cancer Clinic (CCC) is a nationally and internationally recognised tertiary and quaternary referral centre specialising in the management of advanced and recurrent rectal cancer. As a high-volume institution with a dedicated multidisciplinary team (MDT), it provides specialist opinion and care for patients with complex pelvic disease, including those requiring exenteration surgery, and extensive reconstructive procedures. The extensive experience with resections at St Mark's offers a distinctive opportunity to study this comparatively uncommon patient population.

To investigate the prognostic factors that influence oncological and functional outcomes in this highly selected patient group, a comprehensive database was established. This includes detailed clinicopathological, operative, and follow-up data for all patients referred to the Complex Cancer Clinic with locally advanced or recurrent rectal cancer.

This chapter will describe the St Mark's Complex Cancer cohort and outline the structure and function of the multidisciplinary team responsible for managing these challenging cases. It will also describe the basic demographics of this unique cohort and look at the outcomes for both patients who proceed with pelvic exenteration and those who receive non-operative management for LARC and LRRC.

St Mark's Complex Cancer Clinic

The Complex Cancer Clinic at St Mark's Hospital was established in 2008 and has evolved into the large tertiary referral unit it is today receiving hundreds of referrals each year from across the United Kingdom and internationally. The team perform more than one hundred complex cancer resections per annum. Over the last decade the MDT has expanded to manage demand and now includes three complex cancer surgeons, three specialist GI radiologists, two plastic surgeons, two urologists, two orthopaedic surgeons, a Macmillan nurse consultant, a colorectal cancer nurse specialist, a Macmillian physiotherapist and an MDT coordinator. Each patient is reviewed and assessed in a systematic manner as described here.

Referral criteria

The CCC accepts referrals for patients with locally advanced rectal cancers, locally recurrent rectal cancers, locally advanced colon cancers, locally advanced anal cancers, extensive recurrent anal cancers and colorectal cancers with peritoneal disease. This is in addition to other cancers, including neuroendocrine tumours and other rarer pelvic masses such as retrorectal cyst and tumours (both benign and malignant). All referrals are made through an online portal from the referring institution, where comprehensive details regarding the patient's diagnosis, radiology, previous treatment and oncological therapy are provided.

Patient selection and optimisation

Patients are assessed for physical fitness and comorbidities during their initial consultation. The requirement for preoperative Cardiopulmonary Exercise Tolerance (CPET) testing is based on specialist anaesthetic opinion. There are currently no set criteria for CPET testing in this institution, but the anaesthetists select patients they feel require a more in-depth assessment of their physiological risk. For patients with malnutrition (often assessed using the Malnutrition Universal Screening Tool- MUST) or significant cachexia, a review by a consultant gastroenterologist occurs and nutritional optimisation is performed[304]. Prehabilitation is initiated by the complex cancer team physiotherapist with an individualised plan offered to each patient.

Disease assessment

For both patients with LARC and LRRC, the extent of tumour infiltration is assessed using MRI T2 weighted imaging with an antispasmodic, unless contraindicated, and reported by a GI radiologist with special interest in complex cancer. CT scanning of the chest, abdomen and pelvis is completed to assess for metastatic disease, which, if present, may not preclude surgery. Additional imaging, such as PET CT, may be requested in equivocal cases. Liver MRI is requested for patients with extensive extramural venous invasion to assess for metastases. This is based on local preference and supported by the literature, where EMVI is associated with increased risk of liver metastasis. In one study by Bugg *et al.,* the incidence of liver metastasis at 1 year was 25% in patients with EMVI and 7% in those without EMVI, and in a meta-analysis of 804 patients with rectal cancer, those with EMVI were five times more likely to have metastasis at presentation compared to those without.[305,306]

Neoadjuvant therapy

Neoadjuvant therapy is provided by the referring centres and is based on local and national guidelines. Patients with LRRC will undergo radiotherapy if not previously received during treatment of their primary cancer. Re-irradiation and intraoperative radiotherapy (IORT) are not employed as part of the treatment strategy at St Mark's Hospital.

Radiological roadmap and operative planning

The operative approach is devised during the Complex Cancer MDT where each patient's scans are reviewed by a panel including complex cancer surgeons and radiologists with a special interest in advanced colorectal cancer. The operative plan is based on the maximal disease extent that is present on pre-treatment imaging if neoadjuvant therapy has been delivered due to concerns regarding tumour fragmentation. Following neoadjuvant therapy, tumour regression does not always produce concentric "shrinkage." In a fragmentation pattern viable tumour breaks into scattered nests within the fibrotic regression bed and may persist at the periphery of the original tumour contour, therefore potentially abutting a previously threatened circumferential resection margin. The consequence of this is that the tumour retains its original depth of infiltration despite a seemingly favourable tumour regression and can lead to a positive margin[307]. Imaging within 6 weeks of resection is performed and reviewed to confirm the operative plan and ensure there has not been disease progression that would preclude curative resection. For each patient, a systematic approach to the resection plan is followed with consideration given to each of the following components of the resection using the BONVUE method (Figure 4.1)[146]. This is in addition to consideration of any required major vascular, perineal and urological reconstruction[148].

Figure 4.1 The BONVUE checklist for structured reporting in beyond-TME rectal cancer. (Reproduced with permission[146])

B	Bones	Including, but not limited to, sacrum, ilium, acetabulum, ischial spines, and pubic rami
O	Organs	Urinary organs: urinary bladder, prostate, seminal vesicles, vasa deferens, urethra, and penis Gynaecological organs: vagina, cervix, uterus, salpinges, and ovaries Muscles: piriformis, obturator internus, gluteus, and iliopsoas Sacral ligamentous and muscle complexes ('SLAMs')
N	Nerves	L4/5 nerves (lumbosacral trunk), sacral nerves (S1–4), and femoral and obturator nerves
V	Vessels	Common, external, and internal iliac arteries, with particular reference to the superior gluteal artery Common femoral vessels Aorta/inferior vena cava
U	Ureters	Ureters
E	Extra sites	Including pelvic sidewall, inguinal, and iliac/para-aortic/aortocaval nodes extending cranially to the level of the renal vessels Pelvic peritoneal disease Other distant metastatic disease (including surgically inaccessible nodes above the level of the renal vessels)

Standardised approach to surgery

Each key component of the resection is carried out using a standardised technique. Descriptions of these techniques have been previously published[308–310]. Minimally invasive approaches are employed in appropriate cases.

Postoperative care

Dependant on the extent of resection and patient comorbidities patients will be admitted to the high dependency unit or intensive care postoperatively for at least 24 hours. Modified ERAS principles are observed with oral intake resumed from day 0, and patients are mobilised on the

first postoperative day unless contraindicated. Patients who have undergone perineal flap reconstruction are nursed on their side for the first seven days postoperatively. Patients are reviewed daily by the surgical team and physiotherapist.

Follow up

All patients are offered at least one follow-up appointment with the Complex Cancer Clinic following discharge, then patients can choose to continue with follow-up locally thereafter or continue to attend St Mark's Hospital. The referring unit is requested to maintain correspondence regarding postoperative complications and surveillance imaging with St Marks for 5 years. Follow-up correspondence is scanned into the patients' online records. Surveillance CT and pelvic MRI scans are carried out at 6, 12, 18 and 24 months with annual CTs thereafter until 5 years. Patients who have undergone formation of a urostomy are also advised to have a CT urogram at the time of surveillance CT imaging. Serial CEA monitoring is recommended at the same intervals as imaging and a colonoscopy at 12 months postoperatively.

4.2 Assessment of practice - The CCC Cohort

A retrospective analysis of prospectively collected data of consecutive complex cancer operations undertaken through the tertiary referral Complex Cancer Clinic at St Mark's Hospital, London, UK from January 2008 to July 2021 was performed. All patients undergoing curative resection for locally advanced primary rectal cancer that extend beyond the total mesorectal excision plane (PR-bTME[126]) or LRRC by pelvic exenteration were included. Palliative or abandoned resections or those performed for a diagnosis other than rectal adenocarcinoma were excluded.

Data were compiled using electronic clinical records and laboratory reporting systems. Demographic data and use of neoadjuvant oncological treatments were recorded. Neoadjuvant treatment for LRRC was defined as oncological treatment given after the confirmation of recurrence and prior to resection of the recurrent tumour. Survival and recurrence data were validated with Cancer Registry data, (Office for Data Release, Public Health England).

Demographic data included gender, age, ASA, comorbidity and body mass index (BMI). Reported comorbidities prior to surgery were recorded and categorised using NICE

definitions[311–313]. A Charlson Combined Comorbidity Index (CCI) score was calculated using all recorded comorbidities (except rectal cancer)[223].

Preoperative blood results from within two weeks prior to resection were collected and values for haemoglobin, platelets, neutrophils, lymphocytes, albumin and C-reactive protein (CRP) recorded. Median values of haemoglobin and albumin are presented and standard cut of values for anaemia and hypoalbuminaemia used (Hb: 130g/L in males, 120g/L in females, albumin <35g/dL)[312]. NLR and PLR were calculated and cut-off values of 3.0 and 150 were used as deemed clinically relevant in similar populations[302,314]. Platelet counts are presented as median values for the cohort and patients identified with counts greater than 400, a clinically significant threshold for outcomes in colorectal cancer[315]. The modified Glasgow Prognostic score was calculated for all patients with available blood results[242].

Operative records were scrutinised and coded according to the extent and complexity of the procedure with high complexity procedures recorded as those including sacral or pubic bone resection and/or extensive pelvic side wall resections[148]. Total pelvic exenteration (TPE) was defined as resection of the rectum with en bloc removal of the urinary bladder, proximal urethra with either prostate and seminal vesicles in males or urinary bladder, proximal urethra, uterus, ovaries and salpinges in females. A partial exenteration (PPE) was defined as resection of the rectum with en bloc removal of pelvic side wall structures, or pelvic floor (including posterior vagina/uterus or part of prostate and/or seminal vesicles), and/or extended posterior resection to include at least a subperiosteal sacral resection, with or without restoration of GI continuity. These definitions align with those adopted in recent international collaborative research on pelvic exenteration [141,299].

Resected specimens were reported in line with the recommended Royal College of Pathologists guidelines and histopathological reports of the resected tumours were added to the database [316]. This included use of the AJCC 7th edition TNM staging prior to 2017 and the updated 8th addition thereafter[87]. An R0 resection was defined as the absence of viable tumour within 1mm of the resection margin, an R1 margin as microscopic tumour infiltration within 1mm of the margin and an R2 resection as a macroscopically involved margin.

Overall survival (OS) was calculated from the month of resection to the month of death or the censor date (5th May 2022). Disease-free survival (DFS) was calculated from the date of

resection to the date of radiological or histopathological diagnosis of distant metastasis or local recurrence (LR), death or the censor date. Local recurrence-free survival (LRFS) was calculated from the date of resection to the month of death, LR or the censor date. For LRRC, the date of the resection of the recurrent tumour was used to calculate these figures.

Ethics

Approval was obtained for use of the prospective database in research by the NHS Health Research Authority, UK, with ethical approval from the South East London NHS Research Ethics Committee (reference number: 12/LO/1556).

Statistics

Continuous variables are presented with median and interquartile range (IQR), and categorical data with frequency and percentage. To detect differences between the groups the Mann–Whitney U-test was used for continuous data and Fisher's Exact test or Pearson's chi-square test for categorical data. Survival plots were performed using the Kaplan-Meier method with differences between groups assessed using a log rank test. Multivariate analysis was performed by backwards stepwise cox regression using only variables that were statistically significant ($p<0.05$) on univariate analysis. This was only performed when there were at least 10 events per factor in the model. A p-value of less than 0.05 was considered significant. Data were analysed using SPSS software (version 24) (IBM, Armonk, New York, USA).

Description of the cohort

Between January 2008 and July 2021 506 resections were performed. Of which, 388 were curative resections performed for LARC or LRRC and therefore included in this analysis. Demographics and baseline characteristics are shown in Table 4.1. There was a marked male preponderance with 62% of the cohort male with a median age of 59 years (IQR 43-67). Significantly more patients aged 55-74 were treated for LRRC compared with LARC ($p=0.041$). Most patients were ASA 2, with 16-18% ASA 3. The median BMI was higher for those with LRRC (27 vs 25 kg/m^2), but the total number of patients with a BMI greater than thirty was not significantly different between LARC and LRRC.

Table 4.1: Baseline demographics and neoadjuvant therapy for CCC cohort

	TOTAL (n=388)	LARC (n=256)	LRRC (n=132)	
	N (%)	N (%)	N (%)	p value
DEMOGRAPHICS				
Male	234 (62.4)	159 (62.1)	83 (62.9)	0.912
Age (median years, IQR)	59 (49.3, 67.0)	57 (47, 67)	61 (51,66)	0.320
>55years	154 (39.7)	108 (42.2)	46 (34.8)	0.189
55-75 years	209 (53.9)	128 (50.0)	81 (61.4)	**0.041**
>75 years	25 (6.4)	20 (7.8)	5 (3.8)	0.135
ASA				
2	323 (83.2)	215 (84.0)	108 (81.8)	0.667
3	65 (16.8)	41 (16.0)	24 (18.2)	
BMI (n=278)				
Median BMI (kg/m^2,IQR)	26 (22, 30)	25 (22,30)	27 (24, 31)	**0.019**
BMI>30	75 (19.3)	45 (17.6)	30 (22.7)	0.060
NEOADJUVANT THERAPY (within 6 months of surgery)				
Chemotherapy only	45 (11.6)	14 (5.5)	31 (23.5)	**<0.001**
Chemoradiotherapy	139 (35.8)	112 (43.8)	27 (20.5)	**<0.001**
Short course Radiotherapy	17 (4.4)	9 (3.5)	8 (6.1)	0.397
Total neoadjuvant therapy	115 (29.6)	95 (37.1)	20 (15.2)	**<0.001**
No therapy	72 (18.6)	26 (10.1)	46 (34.8)	**<0.001**

As expected, the use of neoadjuvant treatment differed between primary and recurrent disease. 89.1% of patients with LARC received neoadjuvant therapy, with 43.8% receiving chemoradiotherapy alone, 37.1% receiving total neoadjuvant therapy, 5.5% had chemotherapy only, and 3.5% had only short-course radiotherapy. More patients with LRRC received preoperative chemotherapy alone (23.5 vs 5.5%, p<0.001), likely reflecting previous radiotherapy use for their primary disease and 34.8% went straight to resection without oncological treatment.

A partial pelvic exenteration was performed in 247 (63.7%) of cases, with the remaining patients undergoing a TPE (Table 4.2). The majority of cases were performed with an open approach, and this was significantly more likely in patients with LRRC compared with LARC (93.9% vs 69.5%, p<0.001). Patients with LRRC were much more likely to require high complexity resections as evidenced by the statistically significant incidence in need for vascular resections (14.4% vs 1.6%, p<0.001), pelvic side wall resections (63.6% vs 46.5%, p=0.002) and extended posterior resections (47% vs 35.2%, p=0.028). Consequently, patients with LRRC were more likely to have an increased median length of stay (23 days vs 17 days,

p=0.001) and a need for rehabilitation prior to discharge home (23.5% vs 10.9%, p=0.001). There was also higher inpatient mortality following resection for LRRC compared to LARC (6.8% vs 1.6%, p=0.001). These results will be investigated in further detail in chapters 5 and 7.

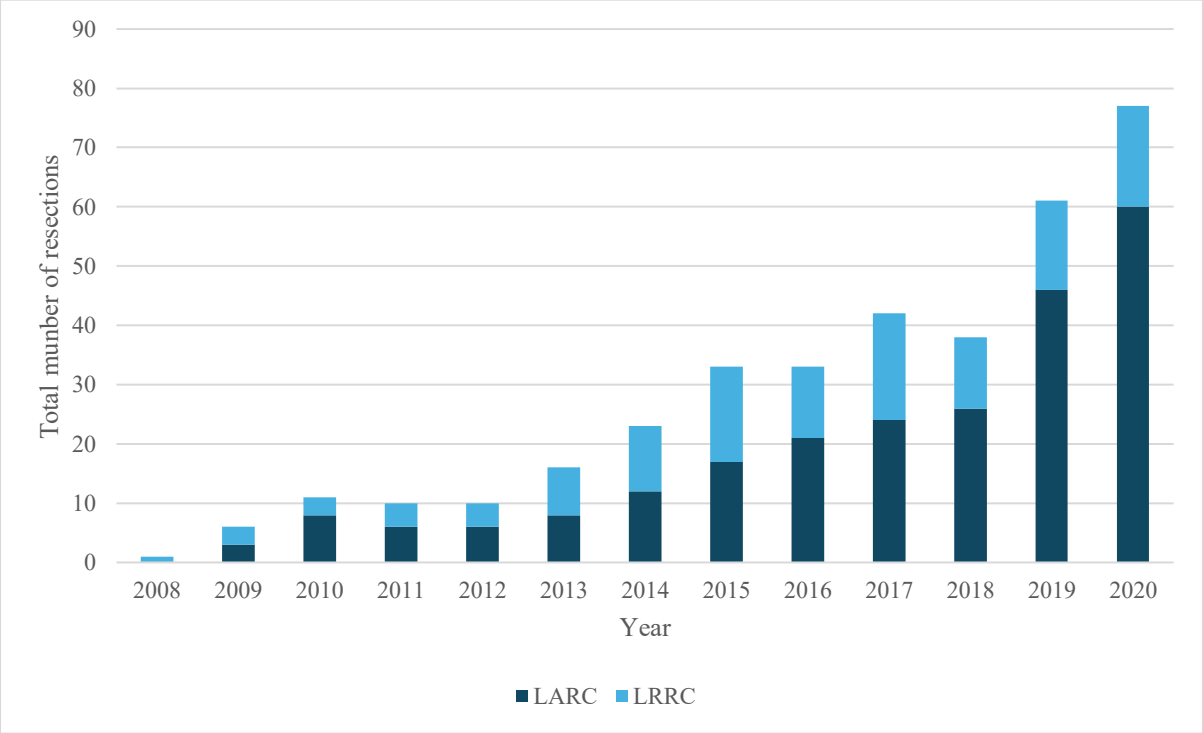
Table 4.2: Operative details and postoperative outcomes for the CCC cohort

OPERATIVE DETAILS	**TOTAL (n=388)**	**LARC (n=256)**	**LRRC (n=132)**	
Operation				
Partial pelvic exenteration	247 (63.7)	171 (66.8)	76 (57.6)	0.076
Total pelvic exenteration	141 (36.3)	85 (33.2)	56 (42.4)	
Surgical approach				
Laparoscopic	79 (20.4)	72 (28.1)	7 (5.3)	**<0.001**
Open	302 (77.9)	178 (69.5)	124 (93.9)	
Lap converted to open	7 (1.8)	6 (2.3)	1 (0.8)	
Urological resection				
Ileal conduit	143 (36.9)	86 (33.6)	57 (43.2)	0.075
Boari/ureteric reimplantation	24 (6.2)	10 (3.9)	14 (10.6)	**0.010**
Vascular resection	23 (6.0)	4 (1.6)	19 (14.4)	**<0.001**
Lateral pelvic resection				
Side wall resection (any)	203 (52.3)	119 (46.5)	84 (63.6)	**0.002**
ELSiE	117 (30.2)	55 (21.5)	62 (47.0)	**<0.001**
Posterior resection				
Extended posterior resection (any)	152 (39.2)	90 (35.2)	62 (47.0)	**0.028**
High sacrectomy	49 (12.6)	20 (7.8)	29 (22.0)	**<0.001**
Distal sacrectomy	46 (11.9)	28 (10.9)	18 (13.6)	0.508
HiSS	24 (6.2)	15 (5.9)	9 (6.8)	0.824
Subperiosteal resection	33 (8.5)	27 (10.5)	6 (4.5)	0.054
Perineal reconstruction				
Flap reconstruction	175 (45.1)	112 (43.8)	63 (47.7)	0.518
Length of stay (median, IQR)	20 (11,35)	17 (9, 30)	23 (14, 45)	**0.001**
Complications				
30 day (C-V III+)	118 (30.4)	71 (27.7)	47 (35.6)	0.140
90 day (C-V III+)	128 (33.0)	75 (29.3)	53 (40.2)	0.065
Mortality				
30 day	10 (2.6)	5 (2.0)	5 (3.8)	0.318
90 day	19 (4.9)	9 (3.5)	10 (7.6)	0.087
Readmission				
Within 30 days	58 (14.9)	39 (15.2)	19 (14.4)	0.881
Discharge destination				
Home	316 (81.4)	224 (87.5)	92 (69.7)	**<0.001**
Local hospital/rehab unit	59 (15.2)	28 (10.9)	31 (23.5)	
Inpatient death	13 (3.4)	4 (1.6)	9 (6.8)	

Changes during service development

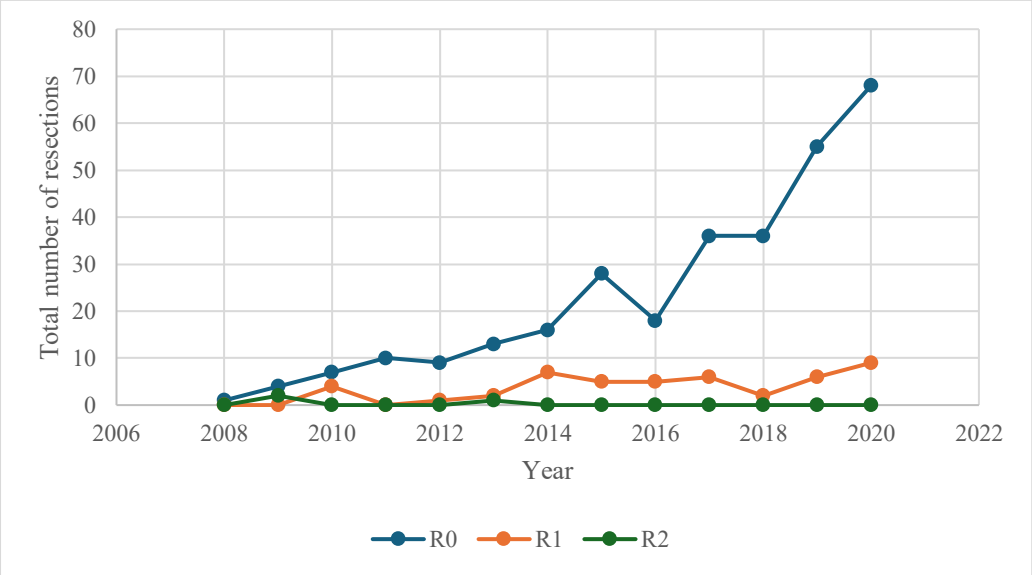
During the study period there was a significant increase in annual volume of resections with 76 resections performed in the first 7 years (2008-2014) compared with 312 performed in the second 7 years (2015-2021), p=0.003 (Figure 4.2). 87 resections alone were performed in the last 12 months of the database records despite the global pandemic.

Figure 4.2: Volume of pelvic exenterations for LARC and LRRC per year



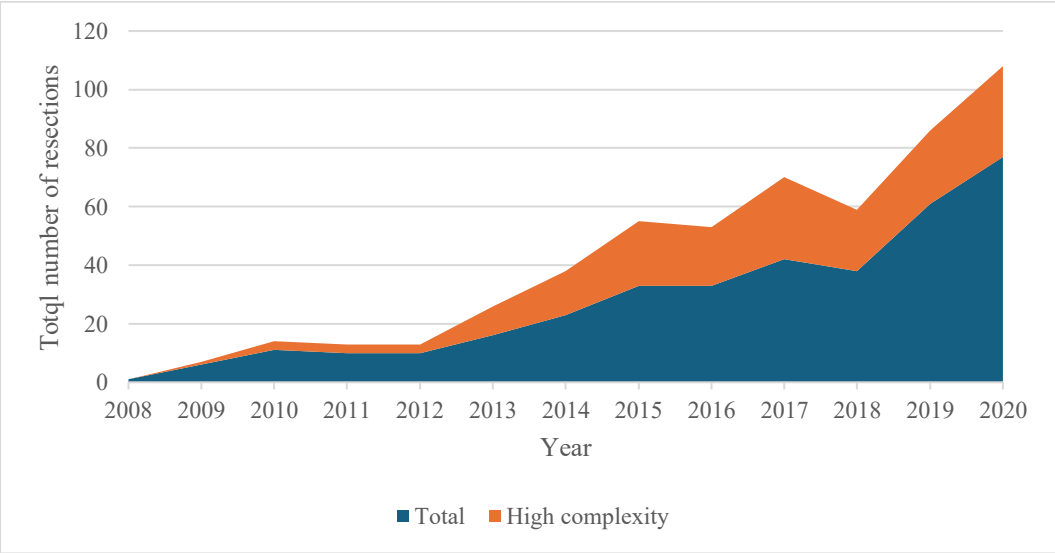
The rate of R0 resections increased significantly over time; In 2008-2015 there were 58 (76.3%) R0 resections, 15 (19.7%) R1 resections and 3 (3.9%) R2 resections. In 2015-2021 the rates of R0, R1 and R2 resections were 280 (89.7%), 32 (10.3%) and 0, respectively (figure 4.3).

Figure 4.3: Resection Margin status per year for the CCC cohort



This was accompanied by increasingly radical procedures with 24 patients (31.6%) undergoing extended lateral/pelvic side wall resections in the early study period compared to 179 (57.4%), in the later period, p<0.001. There was a non-significant increase in extended posterior resections (32.9% vs 40.7%, p=0.239). The total number of high complexity procedures performed per year is demonstrated in Figure 4.4. Increasing use of neoadjuvant therapy was noted when comparing these time periods; LARC 73.8% vs 93%, p<0.001 and LRRC 47.1% vs 71.4%, p 0.013.

Figure 4.4: Resection type per year for the CCC cohort



4.3 Non-operative outcomes

Despite its curative potential, pelvic exenteration is a highly complex procedure. Its feasibility depends on factors such as tumour extent, patient comorbidities, and individual preference. Patients who are not candidates for surgery may receive alternative treatments, including radiotherapy, chemotherapy, or palliative care[106]. However, several studies have shown markedly reduced survival among non-operatively managed patients compared to those who undergo surgery with curative intent with three-year survival ranging from 19-35%[317,318].

In addition to reporting the outcomes of the patients who have undergone pelvic exenteration at St Mark's it is vital to also report the outcomes of those who, for a variety of reasons, had non operative management of their disease after the CCC and MDT decision making. The aim of assessing this cohort was to stratify the non-operative cohort into clinically relevant subgroups to better understand survival outcomes and guide clinical decision-making and patient counselling. Additionally, by comparing this cohort to the cohort who underwent pelvic exenteration, a direct assessment of the survival benefit conferred by surgery was possible. The non-operative data was collected by Baha Siam (Consultant General Surgeon, Beilinson Hospital, Rabin Medical Centre, Petah Tikva, Israel) who consented to its use in this thesis. It is currently unpublished but under review at Annals of Surgery.

Methods

All consecutive referrals to the CCC between January 2014 and December 2022 were included. All patients were assessed for suitability for surgery as outlined at the start of this chapter. Patients who had non-operative management were classified into five categories based on the reason for surgical exclusion: medically unfit for surgery, refusal of surgery despite resectable disease, presence of unresectable metastases, disease progression during neoadjuvant treatment leading to irresectable disease, and extensive local disease beyond surgical salvage. Survival data for each patient were cross-referenced with the NHS Spine portal to provide verified survival status for each patient and date of death, where applicable.

Results

During the time period, 1032 patients were diagnosed with LARC or LRCC (including both adenocarcinoma and squamous cell carcinoma). 579 patients (56.1%) underwent resection by pelvic exenteration, and 453 (43.9%) had non-operative management.

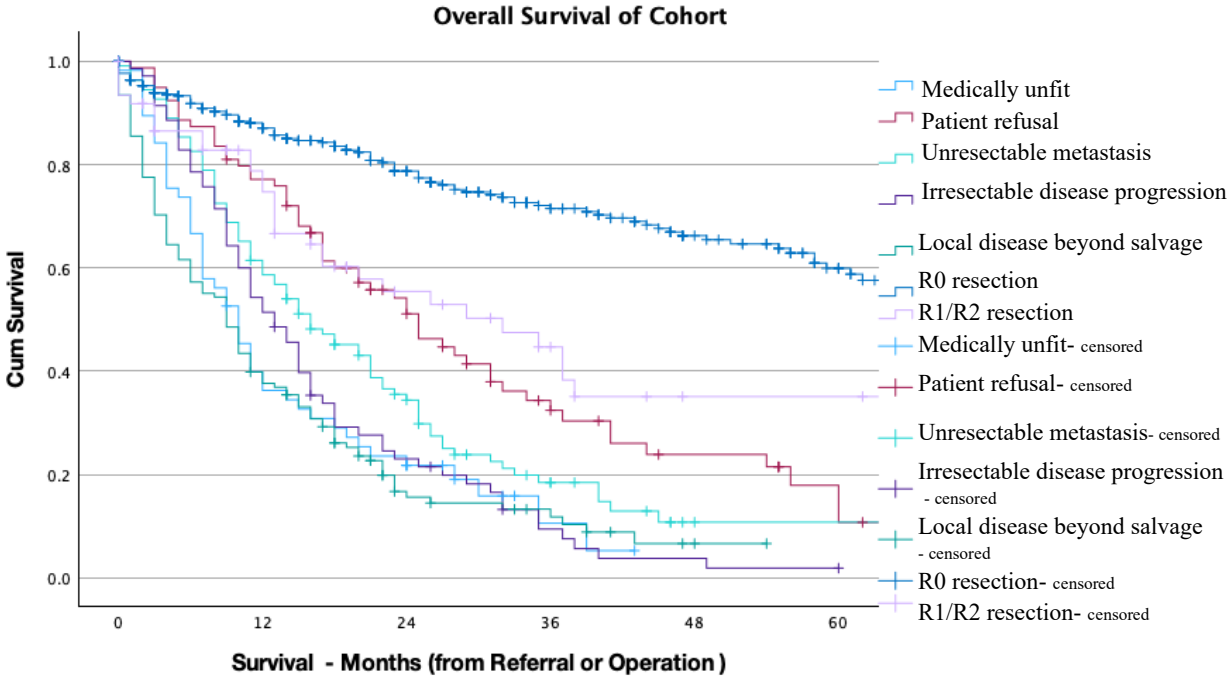
In the non-operative cohort, the median age was 65 years (range 17-86), with a male preponderance (60.1%). 60% (n=272) had LARC and 40% (n=181) had LRRC, with the majority of patients having rectal adenocarcinoma (437 patients, 96.5%), and 33 patients (3.5%) had squamous cell carcinoma.

Overall, the median survival for non-operative patients was 14 months (95% CI 12.2-15.7) compared to 83.2 months (95% CI 75.8-90.8) for those who underwent pelvic exenteration. However, survival varied significantly between subgroups (Table 4.3). Medically unfit patients (n=57, 12.6%) had a median survival of 10 months (95% CI 7.5-12.4). Patients who declined surgery despite having resectable disease (n=79, 17.4%) had the longest median survival of 25 months (95% CI 18.7-31.2), while those with unresectable local disease (n=138, 30.5%) fared the worst with a median survival of 9 months (95% CI 6.8-11.1). Patients with unresectable distant metastases (n=109, 24%) had intermediate outcomes with a median survival of 16 months (95% CI 11.1-20.8). Patients whose disease progressed following their initial assessment to become unresectable (n=70, 15.5%) had a median survival of 13 months (95% CI 10.1-15.9). Figure 4.4 demonstrates the differences in survival between the operative cohort, subdivided into R0 and R1/R2 resections and the non-operative cohort.

Table 4.3. Non-operative outcomes

Reason for non operative management	**n=453 (%)**	**Median overall survival [95%CI]**
Medically unfit	57 (12.6)	10 months [95%CI 7.5-12.4]
Patient refusal of surgery despite resectable disease	79 (17.4)	25 months [95%CI 18.7-31.2]
Presence of unresectable metastases	109 (24)	16 months [95%CI 11.1-20.8
Disease progression leading to irresectable disease	70 (15.5)	13 months [95%CI 10.1-15.9]
Local disease beyond surgical salvage	138 (30.5)	9 months [95%CI 6.8-11.1]

Figure 4.4 Overall survival comparing patients who have undergone pelvic exenteration and those who received non-operative management



These results highlight the heterogeneity within non-operative patients, a group often considered uniform in prior research. Additionally, patients who decline surgery despite its feasibility represent a unique subgroup where more intensive counselling may be warranted, given the clear survival disadvantage.

Limitations of this dataset are that specific details of oncological treatment for the patients having non-operative management were not consistently available, as these patients were managed by their referring institution and not through the CCC. However, these data provide greater insight into the natural history of advanced rectal cancer in the absence of surgical intervention and quantify the life-prolonging impact of pelvic exenteration. It provides evidence that pelvic exenteration offers substantial survival benefits for appropriately selected patients. Non-operative patients, particularly those with inoperable disease or poor performance status, have dismal outcomes. These findings can inform shared decision-making and help tailor management strategies for patients with LARC or LRRC, especially when surgery is being considered or declined.

This chapter has outlined the management of patients referred to the CCC and the outcomes of those who do not proceed with pelvic exenteration. This unique cohort will form the basis for the investigation of prognostic factors in the rest of this thesis.

Chapter 5: Management of advanced disease involving the upper sacrum and pelvic sidewalls in patients with locally advanced and locally recurrent rectal cancer

This chapter examines the challenges of managing a select group of patients with LARC and LRRC whose disease is so extensive that it would once have been considered irresectable. In particular, the role of radical exenteration surgery for tumours extending to the upper sacrum and pelvic sidewall which remains highly contentious.

5.1 Introduction

As outlined in Chapter 3, complete pathological resection (R0) is the single most important determinant of oncological outcome, with reported 5-year survival rates approaching 65%; in contrast, prognosis following incomplete resection (R1/R2) is significantly poorer[141,142,283,319–322]. Despite the considerable risks, en bloc sacrectomy undertaken as part of pelvic exenteration currently represents a chance of durable cure in patients with direct sacral involvement. For tumours extending below the S2/3 junction, distal sacrectomy can provide the opportunity for local control and is now widely performed in specialist centres[323]. However, the value of attempting resection for more proximal or high sacral invasion and in the presence of pelvic sidewall extension, remains far less certain. Traditionally, such involvement was viewed as an absolute contraindication to surgery, given the associated morbidity, functional compromise, and potential impact on quality of life, which may outweigh any survival benefit. However, tumours previously regarded as irresectable have been rendered amenable to R0 resections by technical adaptations such as extended lateral pelvic sidewall excision (ELSiE) for pelvic sidewall disease involving the greater sciatic notch, and penile base excision with or without partial pubic bone resection for anterior disease extension [149,324–326]. These previously "inoperable" cases are increasingly managed with curative intent in expert units.

Anatomically, the posterior pelvic compartment comprises the retrorectal space, including the presacral fascia, sacrum, and associated neurovascular structures such as the S1–S2 roots[327]. When tumour spread is confined to the fascia or periosteum, subperiosteal dissection can achieve clear margins and avoid the morbidity of sacrectomy[328]. In contrast, cortical invasion or deeper sacral involvement generally necessitates sacral resection to secure an R0

margin and achieve durable local control. The required level of sacrectomy is dictated by the cranio-caudal extent of disease. Examples of LARC with sacral and pelvic side wall involvement are demonstrated in figures 5.1 and 5.2.

Figure 5.1: Sagittal MRI of a large mucinous rectal tumour abutting the anterior cortex of S2 up to the level of the S1/2 disc. Fistulation anteriorly into the catheterised urinary bladder

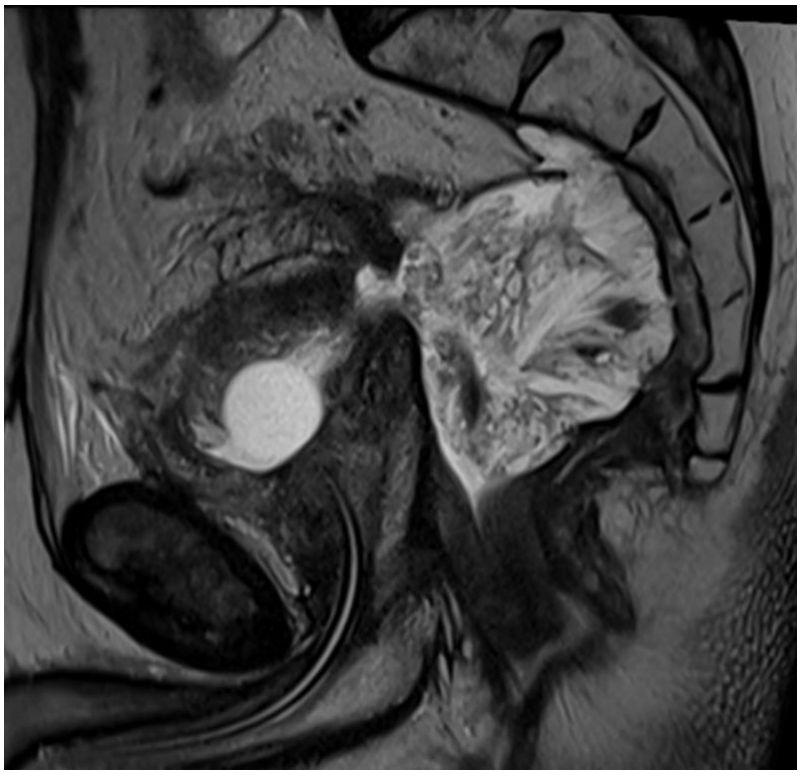
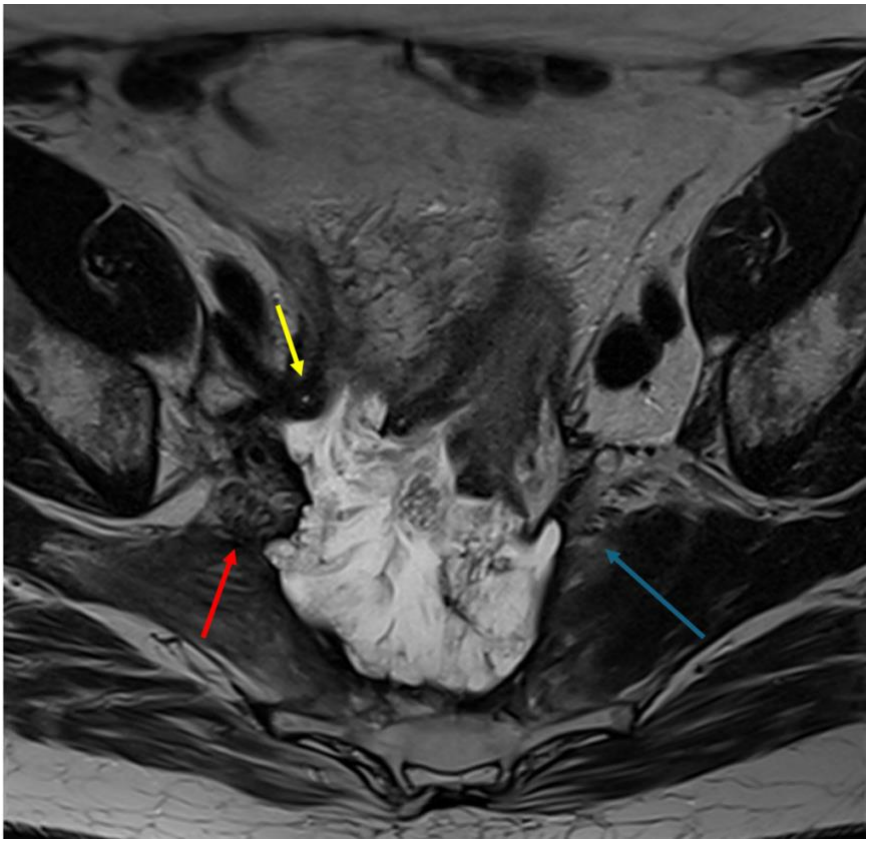


Figure 5.2: Axial MRI of large mucinous tumour encasing the right mid ureter (yellow arrow) and right sciatic nerve (red arrow). The right SGA is also involved (not shown). The right external iliac vein is threatened. Tumour involves the left internal iliac artery below SGA and threatens the left S1 nerve (blue arrow).



The tertiary referral CCC, as previously described, has developed a multi-specialty approach to maximise R0 resection rates whilst aiming to limit intra-operative and postoperative morbidity. This chapter will describe their standardised approach to patients with tumours that extend high on the sacrum but also extend into the pelvic sidewalls. The captured outcomes in this study aim to demonstrate not only the feasibility but also the oncological and treatment-related outcomes associated with pelvic exenteration with en bloc high sacrectomy with unilateral or bilateral extended lateral pelvic sidewall excisions; so called “high and wide” resections. No other UK surgical centre has reported on this type of case series previously. The CCC with multidisciplinary team working facilitates this type of surgery and as a result more cases are increasingly being referred and taken on from secondary and tertiary colorectal units around the UK. We hypothesised that successful R0 resections would offer improvements in overall and recurrence-free survival with acceptable morbidity compared to the alternatives in the existing literature.

5.2 Methods

Study design

All patients in the CCC cohort (as described in Chapter 4) who underwent a high sacrectomy (defined as sacral transection at or above the level of the S2/3 junction) for from January 2008 to July 2021 were identified and included in the analysis. Demographic and operative data were collected; histopathological reports of surgical specimens were used to confirm data on resection margin status. Cancer registry data was used to confirm previous oncological therapy and patient mortality and corroborate outcomes recorded in the patient records available at St Mark's.

Primary endpoints for this study were the resection margin status and oncological outcome (overall and local recurrence-free survival). Secondary endpoints were postoperative mortality, major morbidity (defined as Clavien-Dindo grade III and IV complications), long-term complications and long-term mobility. Patient mobility was recorded in relation to their level of independence with activities of daily living. No other validated mobility metric was available to us during the period of study. Self-reported level of mobility (independently mobile, use of walking aid for >50% time, immobile/dependent on wheelchair) was reported and recorded prospectively by specialist nursing staff.

Pre-operative assessment and patient selection

Each patient is assessed in the structured way described in Chapter 4. The team considers the disease extent and the involvement of pelvic structures and formulates a precise anatomical plan aimed at achieving an R0 resection. MRI is the main modality of investigation determining the anatomical boundaries and resectability of pelvic tumours; specifically, sagittal images are used to accurately measure the distance from the sacral promontory to the planned level of sacral transection, while axial images are used to delineate the lateral borders of dissection into the pelvic sidewall [329]. A detailed review of available imaging is performed to construct the surgical "roadmap" and delineate precise resection planes in order to achieve R0 resection. This is then communicated to the patient in clinic with the colorectal surgeon, radiologist and specialist nurse present to help illustrate the magnitude of surgery, using the patient's own scans, and possible sequelae of the operation to help improve informed consent.

Operative technique

The operative procedure is standardised and subdivided into abdominal-supine, perineal and posterior/prone (extrapelvic) phases, depending on disease extent and extent of pelvic involvement and the need for additional extended procedures.

Statistical analysis

Continuous variables are presented with median and interquartile range (IQR), and categorical data with frequency and percentage. The Mann–Whitney U-test was used for continuous data and Pearson's chi-square test for categorical data was used to detect differences between the groups where applicable. Statistical significance of the survival was analysed with the log-rank (Mantel-Cox) test and Kaplan-Meier curves. Multivariate analysis was performed with the Cox proportional hazards model. A p-value of less than 0.05 was considered significant. Data were analysed using SPSS software (version 24) (IBM, Armonk, New York, USA).

5.3 Results

Study population

Of the 388 patients included in the CCC cohort during the study period, 47 patients underwent high sacrectomy with pelvic sidewall resection.

Demographic, clinical, and operative characteristics of patients who had sacrectomy are shown in Table 5.1. As shown, median age was 57 years (IQR 48, 64 years) and 34 (72.3%) patients were male. Thirty-eight (80.9%) patients had been treated with chemoradiotherapy at some point during their disease course and 18 (38.3%) had undergone further systemic chemotherapy as well. Five (10.6%) had distant oligometastatic disease either treated during the course of their disease or still in situ at the time of exenteration surgery with plans for later intervention as required.

Surgical outcomes

Thirty-five (75.4%) patients underwent a total pelvic exenteration, while the remaining 12 (25.5%) underwent a bladder-preserving posterior exenteration. All patients underwent excision of one or both pelvic sidewalls, 42 (89.4%) of whom underwent en bloc extended lateral pelvic sidewall excision (ELSiE). Nineteen (39.5%) underwent a partial or complete excision of the sciatic nerve. One patient required an extended acetabular resection. All patients underwent flap reconstruction of the perineal defect, with an SGAP flap performed in 43 cases (91.5%). R0 resection margin status was achieved in 45 cases (95.7%), with the remaining two

(5%) having an R1 resection with positive anterior specimen margins.

Table 5.1: Study demographics, operative and postoperative outcomes

Patient characteristics		**Operative characteristics**	
Age (median, years)	57 (IQR 48,64)	Posterior exenteration Total pelvic exenteration	12 (25.5%) 35 (74.5%)
Gender Male Female	 34 (72.3%) 13 (27.7%)	**Sacral level** S1 S1/2 S2 S2/3	 3 (6.4%) 17 (36.2%) 14 (29.9%) 13 (27.7%)
Cancer type LARC LRRC	 19 (40.4%) 28 (59.6%)	**Pelvic side wall** Pelvic side wall excision (any) ELSiE	 47 (100%) 42 (89.4%)
Comorbidity ASA 2 3 WHO performance status 0 1 Body Mass Index Median BMI <30	 42 (89.4%) 5 (10.6%) 46 (97.9%) 1 (2.1%) 25 (IQR 22,28) 5 (10.6%)	**Flap reconstruction** SGAP DIEP SGAP + thigh advancement	 44 (91.5%) 1 (2.1%) 3 (6.4%)
		Postoperative Median length of stay (days)	 35 (IQR 23,63)
		Complications Major complication (Clavien Dindo III+) 30 day mortality 90 day mortality	 20 (42.6%) 3 (6.4%) 5 (10.6%)
		Tumour Characteristics Nodal involvement EMVI Resection margin R0 R1	 3 (6.4%) 18 (38.3%) 45 (95.7%) 2 (4.3%)

Morbidity

Major postoperative morbidity (Clavien-Dindo III or IV) occurred in 20 (42.6%) patients. Eleven (23.4%) patients developed pelvic fluid collections requiring percutaneous drain insertion. Seven (14.9%) developed osteomyelitis, either based on imaging results or proven by bone biopsy, all of which were managed successfully with long-term antibiotic therapy.

Five patients (10.6%) developed a pelvic or sacral fracture detected coincidentally on MRI surveillance imaging. Only one patient required delayed operative fixation at over 12 months postoperatively (previous upper/mid S1 sacrectomy); the rest were managed conservatively and did not require fixation or orthopaedic surgical intervention.

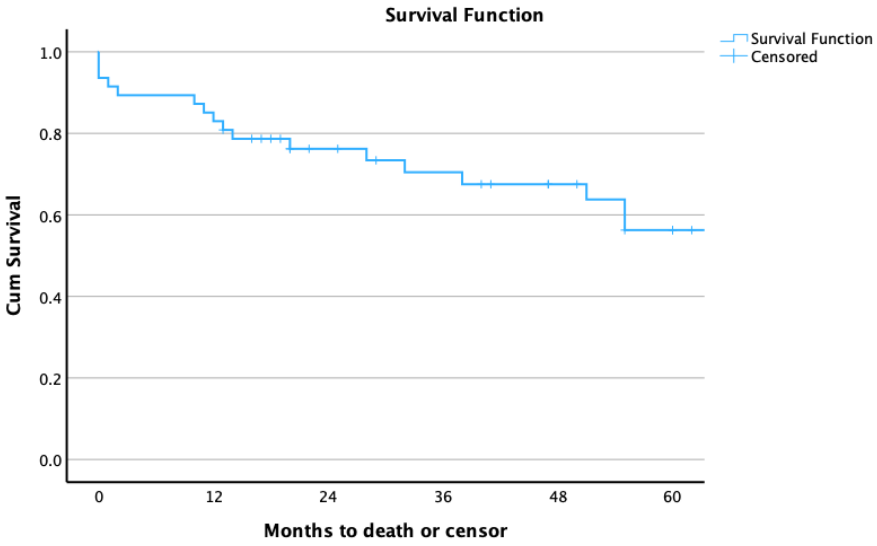
Postoperative mortality within 90 days occurred in five (10.6%) patients, three (6.4%) of whom died within 30 days after surgery. Major haemorrhage was the cause of death in 3 (60%) of these cases from false aneurysm formation.

Long-term mobility outcomes for those surviving beyond 90 days showed that the majority of patients maintained or regained lower limb function, either fully independent in 30 (71.4%) patients or with a walking aid in 8 (19%). Four patients (9.5%) required a wheelchair to mobilise outdoors.

Survival outcomes

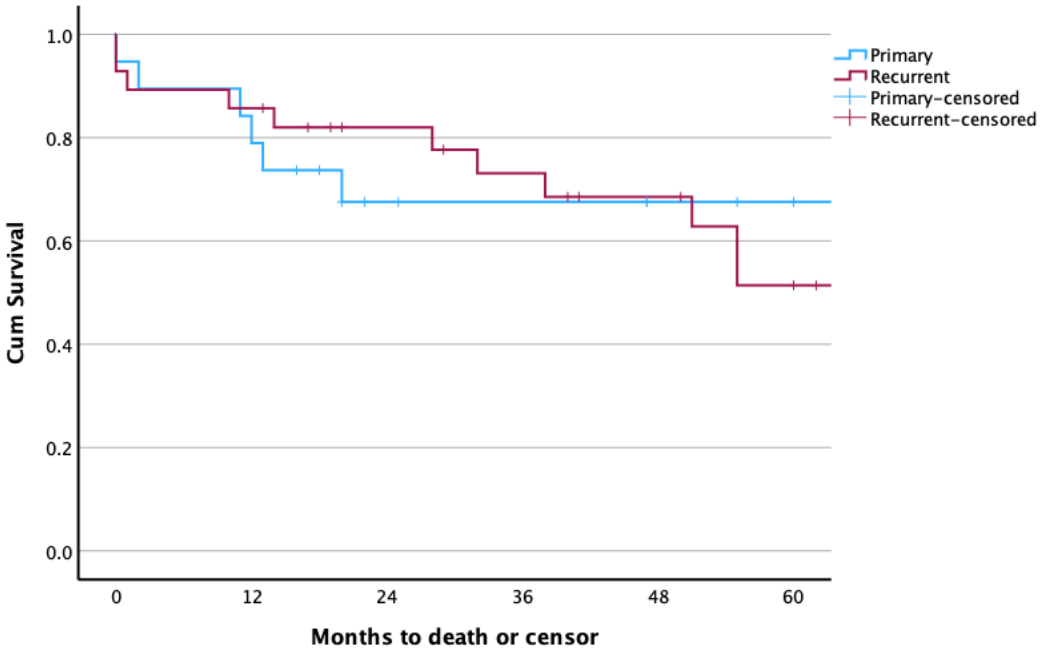
Median follow-up was 24 months (IQR 13-51). During the follow-up period, eight (19%) developed a local recurrence and 15 (35.7%) developed either new or progressive distant metastatic disease. As shown in Figure 5.1, mean overall survival (OS) was 71 months (95% CI 57.9 – 85.1), with 1-, 3- and 5-year OS of 82%, 68% and 56.5%, respectively. The median OS was not reached. Excluding those patients who died within 90 days of surgery the 5-year OS increases to 63%. Median recurrence-free survival (RFS) was 25 months (95% CI 14.8-35.1), with 1-, 3- and 5-year RFS of 72%, 38% and 34%, respectively.

Figure 5.1: Overall survival for all patients undergoing resection



As shown in Figure 5.2, survival outcomes for recurrent disease were not significantly different to those with primary cancer with mean OS of 72.8 months (95% CI 52.8 – 92.7) in LARC patients and 70.0 months (95% CI 53.1 – 86.9) in LRRC patients (P=0.85).

Figure 5.2: Overall survival outcomes for patients based on primary or recurrent disease



Survival outcomes were not significantly associated with pre-operative chemoradiotherapy: mean OS in patients who had been treated with chemoradiotherapy prior to exenteration surgery versus those who had not was 74.5 months (95% CI 57.9 – 91.2) and 63.3 months (95% CI 41.5 – 84.9), respectively (P=0.56). Many other factors influence overall survival, and these will be discussed in greater detail in subsequent chapters.

5.4 Discussion

This study demonstrates that pelvic exenteration incorporating high sacrectomy and extended lateral pelvic sidewall excision ("high and wide" resections) can achieve excellent oncological outcomes in selected patients with locally advanced and recurrent rectal cancer. Historically, tumour invasion above the S2/3 junction was considered a relative contraindication to abdominosacral resection due to the risks of major blood loss, neurological injury, pelvic sepsis, bladder and sexual dysfunction, gait disturbance, pelvic instability, and cerebrospinal fluid leak[330–332]. For example, biomechanical studies demonstrate that resection at the mid-S1 level significantly compromises pelvic stability, sometimes necessitating implant-based reconstruction[333]. Where regarded as operable, disease extension into S1 or S2 will often require a total or subtotal sacrectomy, with associated risk of pelvic instability and major surgical morbidity, potentially negating the oncological advantages of achieving a R0 resection[151,334]. Techniques such as High Subcortical Sacral resection (HiSS), involving resection of the anterior upper sacral cortex and underlying cancellous bone, offer alternatives, preserving pelvic stability in patients with S1 or S2 periosteal or cortical involvement[153].

Despite these concerns, our series shows that very high R0 resection rates (95%) are achievable, translating into 5-year overall survival of 56.5% (63% when perioperative mortality is excluded). These findings far exceed published R0 rates of 62–78% in comparable cohorts[151,323,334,335]. The patients in this cohort appear similar to other patient series assessing the outcomes of high sacrectomy in terms of age and sex, but limited comment is made regarding patient comorbidity in these other studies[334,335].

A systematic review reported that, in patients undergoing sacrectomy for LRRC, R0 resection margin status is associated with long-term disease-free survival (55% at median follow-up of 33 months); moreover, it was demonstrated that distal sacral resections are associated with higher R1 resections than high sacrectomies, suggesting that, in a proportion of patients, oncological outcomes may be compromised by not performing high sacrectomy[323]. This has

been more recently confirmed in a multicentre retrospective study of 1184 patients undergoing exenteration surgery for LRRC; amongst 825 with (potential) bone involvement, en bloc bone resection was an independent predictor of overall survival after surgery[336]. However, these results were not replicated in another large multicentre study comparing high and distal sacrectomies in patients with both LARC and LRRC, where no difference was observed in overall or disease-free survival or major post-operative complications[334]. Together, these data highlight the complexity of interpreting outcomes across heterogeneous series, where patient selection, surgical expertise, and definitions of "high" sacrectomy vary considerably.

Morbidity in our series was substantial, with 42.6% experiencing Clavien-Dindo grade III–IV complications and 30-day perioperative mortality of 6.4%. These figures are at the upper end of the range reported in the literature (major morbidity 35–50%, mortality 0–10%)[323,326,334,337]. The higher early mortality observed in our series may reflect the technical complexity of "high and wide" resections and the small cohort size. Most other series include results following high sacrectomy but do not include extended lateral pelvic side wall excisions. Nonetheless, these results emphasise that surgery should only be attempted in specialist centres with access to advanced perioperative support. Common complications included fluid collections and osteomyelitis, both of which were manageable with interventional radiology or prolonged antibiotics, while pelvic and sacral fractures were observed radiologically in 10% of patients but rarely required operative fixation.

The balance between oncological clearance and morbidity is central to interpreting these results. While our R0 rates and survival outcomes are excellent, the significant risk of perioperative mortality prompts the question of where the threshold lies between curative surgery and unacceptable harm. International consensus is needed to better define patient selection criteria, incorporating not only anatomical resectability but also comorbidity, frailty, and baseline functional status.

Functional outcomes are of equal importance. Despite undergoing high sacrectomy with extended lateral pelvic sidewall excision, over 90% of our long-term survivors were independently mobile or required only a walking aid. This compares favourably with published series, though it is acknowledged that high sacrectomy is associated with reduced lower limb function and impaired quality of life compared to pelvic exenteration alone [338]. Rehabilitation plays a pivotal role in optimising outcomes. The dedicated specialist physiotherapy support

provided within our centre facilitated functional recovery and safe discharge, despite prolonged inpatient stays. Prospective evaluation of patient-reported outcomes and satisfaction is ongoing, as further work is needed to understand how patients perceive the trade-off between morbidity and survival. Evidence suggests that quality of life may take up to six months to return to preoperative levels; with mean overall survival in our series exceeding 70 months, this recovery period may be acceptable for many patients, though formal patient-centred evaluation is essential[339].

This chapter has limitations. It is a single-centre series from a tertiary referral unit and therefore may not be generalisable to all practice settings. The cohort is relatively small, reflecting the rarity of this presentation, and outcomes may be influenced by referral bias and case selection. Although follow-up was adequate to report medium-term survival, longer follow-up is required to confirm durability of local control. Finally, functional outcomes were recorded using pragmatic rather than validated measures, limiting comparison with quality-of-life studies.

5.5 Conclusion

This study provides prospective evidence that "high and wide" pelvic exenteration, including high sacrectomy and extended lateral pelvic sidewall excision, is feasible and can yield excellent oncological outcomes in selected patients. While morbidity remains high and perioperative mortality significant, most long-term survivors retain mobility and independence. These results challenge the traditional view that high sacral or sidewall involvement represents an absolute contraindication to surgery and highlights the importance of centralisation to expert multidisciplinary teams. Future work should focus on international consensus regarding patient selection, standardised reporting of outcomes, and incorporation of patient-reported metrics to ensure that surgical advances translate into meaningful benefit for patients. The next chapter will look at the impact of these extensive resections on perineal reconstruction.

Chapter 6: The impact of perineal reconstruction on outcomes following pelvic exenteration for locally advanced or locally recurrent rectal cancer

This chapter has been reproduced in part from a publication that is currently accepted for publication and in press in the Journal of Surgical Oncology (JSO):

Gluteal Flap Reconstruction Following Complex Rectal Cancer Surgery: A Large Consecutive Series of Perineal Wounds Exploring Risk Factors For Complications. Laura E. Gould, Edward. T. Pring, Ioanna Drami, Joannis Constantinides, Nicola Hodges, Colin W. Steele, Campbell S.D. Roxburgh, Elaine M. Burns, John T. Jenkins

6.1 Introduction

As discussed in chapter 5 recent advancements in surgical approaches have significantly expanded curative options for patients with locally advanced or recurrent rectal cancer. Previously considered inoperable, cases involving sacral or pelvic sidewall invasion are now amenable to radical resection, with reported three-year survival rates ranging from 48% to 56% in select cohorts[141,142,299]. Nevertheless, such extensive operations are associated with substantial morbidity, and approximately 40% of patients experience major complications postoperatively [141,142,326].

Among these, perineal wound complications are particularly burdensome. Pelvic exenterations typically result in large perineal defects that cannot be closed primarily, necessitating plastic surgical input and often flap-based reconstruction. The main goals of reconstruction are to achieve durable wound closure and to eliminate pelvic dead space using well-vascularised tissue, often in previously irradiated fields[340].

A wide array of flap types have been described for this purpose, including musculocutaneous options like the vertical rectus abdominis myocutaneous (VRAM) and gracilis flaps, fasciocutaneous flaps such as the superior and inferior gluteal artery perforator (SGAP/IGAP), anterolateral thigh, and posterior thigh flaps, as well as regional fasciocutaneous options like the Singapore or Lotus pedal flaps[340,341]. Reported flap usage rates following exenteration

range from 22.6% to 40%, and although various algorithms exist to guide flap selection, no clear consensus has emerged[141,142,169,342].

The incidence of perineal wound complications is influenced by both patient-specific and surgical factors and can delay recovery, prolong hospitalisation, defer adjuvant therapies, and increase healthcare costs[343]. Identifying modifiable and non-modifiable risk factors is therefore essential to improve surgical outcomes.

In this chapter is presented a large, single-centre experience with gluteal flap reconstruction following resection of locally advanced or recurrent rectal cancer. It aims to determine whether procedures classified as high complexity are associated with increased perineal wound morbidity and to evaluate risk factors for flap-related complications.

6.2 Methods

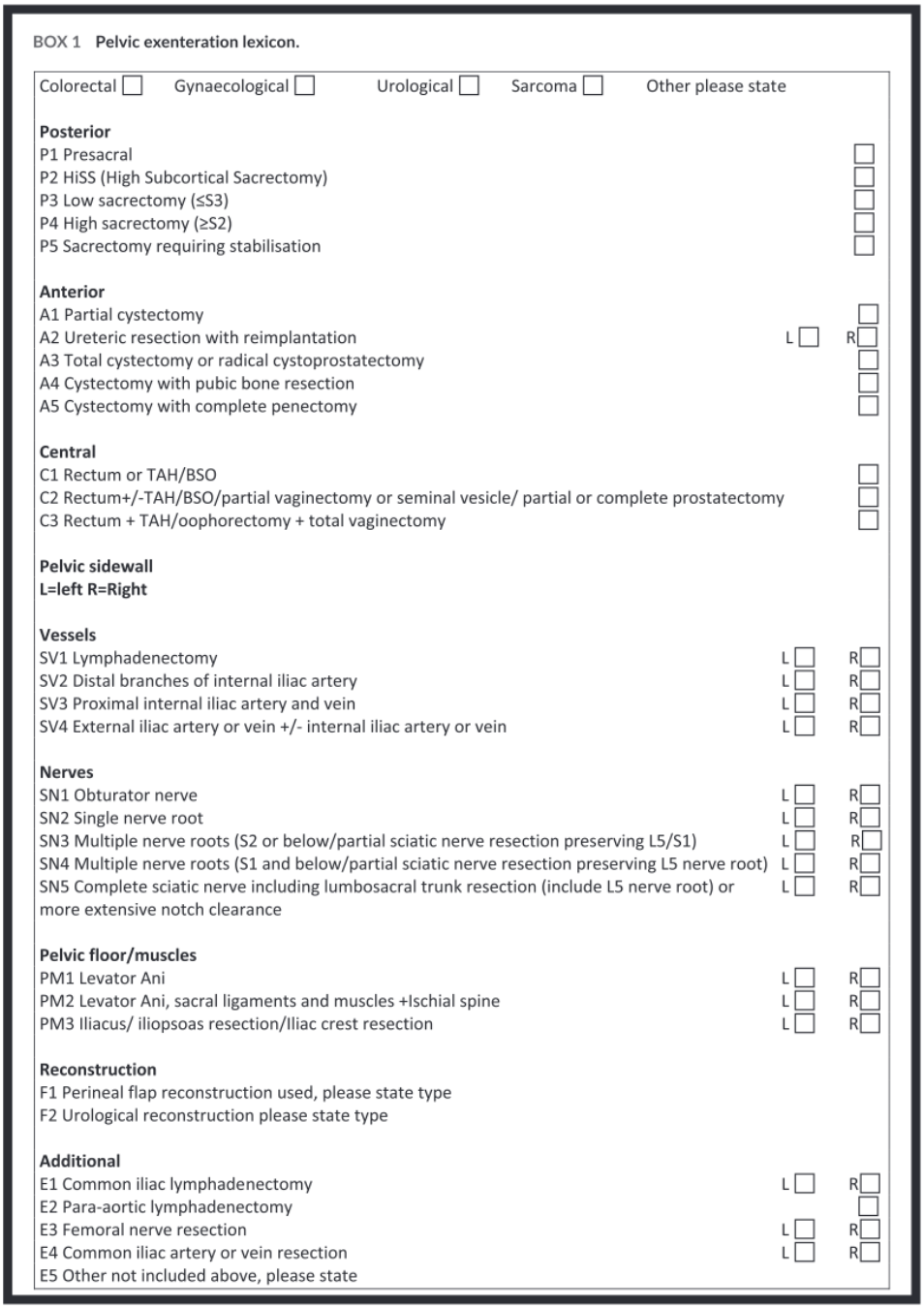
This was a retrospective cohort study based on prospectively maintained data from St Mark's Hospital, London, covering the period from January 2013 to July 2021. In addition to the CCC cohort described in Chapter 4 all adults who underwent an extended extralevator abdominoperineal excision (ELAPE) for rectal malignancy and patients undergoing pelvic exenteration for resection of anorectal squamous cell carcinoma were included. The reason for including this wider patient group was to maximise the number of patients included to allow for sufficient assessment of the factors influencing outcome following flap reconstruction. Cases deemed palliative or where surgery was abandoned were excluded from analysis.
Clinical data were collated and cross-verified using electronic patient records, multidisciplinary team (MDT) reports, clinic letters, operative documentation, and laboratory systems.

Baseline variables included demographics (age, sex), comorbidity status (ASA classification, BMI, smoking history, diabetes), malignancy subtype, and history of neoadjuvant radiotherapy (both short- and long-course protocols were included). All cancer diagnoses were validated using the Cancer Registry maintained by Public Health England.

Surgical records were reviewed to determine operative complexity, flap type, extent of soft tissue or bony resection, and whether vascular or urological reconstruction was performed. Procedures were stratified into two categories based on complexity. High complexity

resections involved any of the following: en bloc sacrectomy, high sacral transection, extended lateral pelvic side wall excision (ELSiE), or high subcortical sacrectomy (HiSS), pubic bone resection, as defined by the ACPGBI/UKPEN Pelvic Exenteration Lexicon (Figure 1)[148,153,156,344]. These were compared with conventional (soft tissue) exenterations and extended ELAPE not involving extensive bony or neurovascular dissection.

Figure 6.1: Pelvic exenteration Lexicon (Reproduced with permission- appendix 2)[148]



BOX 1 **Pelvic exenteration lexicon.**

Colorectal ☐ Gynaecological ☐ Urological ☐ Sarcoma ☐ Other please state

Posterior		
P1 Presacral		☐
P2 HiSS (High Subcortical Sacrectomy)		☐
P3 Low sacrectomy (≤S3)		☐
P4 High sacrectomy (≥S2)		☐
P5 Sacrectomy requiring stabilisation		☐
Anterior		
A1 Partial cystectomy		☐
A2 Ureteric resection with reimplantation	L ☐	R ☐
A3 Total cystectomy or radical cystoprostatectomy		☐
A4 Cystectomy with pubic bone resection		☐
A5 Cystectomy with complete penectomy		☐
Central		
C1 Rectum or TAH/BSO		☐
C2 Rectum+/-TAH/BSO/partial vaginectomy or seminal vesicle/ partial or complete prostatectomy		☐
C3 Rectum + TAH/oophorectomy + total vaginectomy		☐
Pelvic sidewall **L=left R=Right**		
Vessels		
SV1 Lymphadenectomy	L ☐	R ☐
SV2 Distal branches of internal iliac artery	L ☐	R ☐
SV3 Proximal internal iliac artery and vein	L ☐	R ☐
SV4 External iliac artery or vein +/- internal iliac artery or vein	L ☐	R ☐
Nerves		
SN1 Obturator nerve	L ☐	R ☐
SN2 Single nerve root	L ☐	R ☐
SN3 Multiple nerve roots (S2 or below/partial sciatic nerve resection preserving L5/S1)	L ☐	R ☐
SN4 Multiple nerve roots (S1 and below/partial sciatic nerve resection preserving L5 nerve root)	L ☐	R ☐
SN5 Complete sciatic nerve including lumbosacral trunk resection (include L5 nerve root) or more extensive notch clearance	L ☐	R ☐
Pelvic floor/muscles		
PM1 Levator Ani	L ☐	R ☐
PM2 Levator Ani, sacral ligaments and muscles +Ischial spine	L ☐	R ☐
PM3 Iliacus/ iliopsoas resection/Iliac crest resection	L ☐	R ☐
Reconstruction		
F1 Perineal flap reconstruction used, please state type		
F2 Urological reconstruction please state type		
Additional		
E1 Common iliac lymphadenectomy	L ☐	R ☐
E2 Para-aortic lymphadenectomy		☐
E3 Femoral nerve resection	L ☐	R ☐
E4 Common iliac artery or vein resection	L ☐	R ☐
E5 Other not included above, please state		

Primary and Secondary Outcomes

The main outcomes assessed were perineal wound complications. These were categorised into:

- Short-term (within 90 days): surgical site infection (defined as clinical infection with or without microbiological confirmation requiring antibiotics), flap necrosis (requiring surgical debridement), and wound dehiscence (requiring packing or negative pressure therapy).
- Long-term (beyond 90 days): persistent sinus or fistula formation, and perineal hernia.

Secondary endpoints included duration of hospitalisation, 30-day mortality, major postoperative complications (Clavien–Dindo grade ≥3), and reoperation or readmission within 90 days due to wound-related issues[345]. A "major flap complication" was defined as either reoperation within 90 days or readmission within 30 days directly attributed to perineal wound problems- an endpoint used in similar case series[346].

Operative Technique and Postoperative Protocol

Surgical planning was guided by pre-operative MRI reviewed in a specialist MDT setting. The extent of resection was tailored to the maximal anatomical spread of disease as described in Chapter 4. Flap selection was guided by defect size, vascular anatomy, and anticipated resection of pelvic sidewall or sacral vasculature.

Following surgery, patients were nursed in the lateral decubitus position for seven days. Mobilisation in the standing position was permitted from postoperative day one. If the flap appeared viable, sitting was reintroduced on day seven in five-minute increments until day ten, after which unrestricted sitting was allowed on pressure-relieving support. Flap assessments were conducted by the plastic surgery team and tissue viability nurses. Superficial wound issues were managed with appropriate dressings or vacuum-assisted closure (VAC) systems where necessary.

Statistical Analysis

Continuous variables were summarised as medians with interquartile ranges (IQRs), while categorical variables were reported as counts and percentages. Group comparisons were performed using the Mann–Whitney U test for non-parametric continuous data, and Pearson's chi-square or Fisher's exact test for categorical variables, as appropriate.

Multivariate analysis was conducted using binary logistic regression models, including only variables found to be significant on univariate analysis. Hazard ratios (HRs) and 95% confidence intervals (CIs) were reported. Kaplan–Meier survival analysis was used to assess outcomes over time, and differences between survival curves were tested using the log-rank test. Statistical significance was set at $p<0.05$. Analyses were conducted using SPSS version 24 (IBM Corp., Armonk, NY, USA).

6.3 Results

Between January 2013 and July 2021, a total of 453 patients underwent complex rectal cancer surgery through the CCC. Of these, 194 patients received immediate flap reconstruction for perineal defects and were included in the analysis.

The median age of the cohort was 56 years (IQR 48–66), with a predominance of male patients (60.5%). The majority were classified as ASA grade 2 (n=155, 80%), reflecting a relatively fit surgical population, while 20% (n=39) were ASA grade 3 (Table 6.1).

Comparison Between Surgical Groups

Patients were categorised according to surgical complexity. Baseline characteristics including age, sex, and presence of major cardiovascular comorbidities, did not differ significantly between the conventional and high-complexity groups (Table 6.1). However, inflammatory bowel disease and current smoking were more common in those undergoing standard exenteration procedures, (18.3% vs 8%, p=0.046 and 11% vs 2.7%, p=0.031, respectively). Most surgeries (84%, n=163) were performed for primary or locally recurrent rectal cancer, with recurrent disease more frequently requiring high-complexity resections ($p<0.001$).

Total pelvic exenteration (TPE) was performed in approximately 50% of the entire cohort. Patients in the high-complexity group (bony posterior resection or pelvic side wall resection) were significantly more likely to undergo TPE rather than extended ELAPE (0% vs 61.6%, $p<0.001$). Notably, 71.4% (n=80) of high-complexity procedures involved combined posterior and lateral compartment resections, including en bloc sacrectomy and extended lateral side wall excision.

Table 6.1: Patient demographics and operative details

	Conventional Complex resection n=82 [%]	High Complexity resection n=112 [%]	P value		Conventional Complex resection n=82 [%]	High Complexity resection n=112 [%]	P value
Age, Median years (IQR)	56 (50-67.25)	57 (47-65)	0.626	**Surgical resection**			
Sex Male	46 (56.1)	71 (63.4)	0.373	Extended APER	20 (24.4)	0	**<0.001**
Female	36 (43.9)	41 (36.6)		Anterior pelvic exenteration	1 (1.2)	1 (0.9)	1.00
Comorbidity				Posterior pelvic exenteration	34 (41.5)	42 (37.5)	0.655
IHD	4 (4.9)	4 (3.6)	0.651	Total pelvic exenteration	27 (32.9)	69 (61.6)	**<0.001**
Type 2 diabetes	3 (3.7)	8 (7.1)	0.361	Oncovascular resection	0	8 (7.1)	**<0.001**
HTN	14 (17.1)	12 (10.7)	0.209	Ileal conduit	28 (34.1)	70 (62.5)	**<0.001**
IBD	15 (18.3)	9 (8.0)	**0.046**	Boari or ureteric reimplantation	1 (1.2)	8 (7.1)	0.081
Current smoker	9 (11)	3 (2.7)	**0.031**	**High Complexity resections**			
BMI (n=157)				Sacrectomy/HiSS	0	89 (79.5)	
Median, IQR	25.9 (23.4- 30.6)	25.0 (22.5- 30.4)	0.458	ELSiE	0	97 (86.6)	
Over 30 kg/m^2	17 (20.7)	20 (17.9)	0.709	**Perineal flap reconstruction type** (Note combined flaps used in selected cases)			
Cancer type				IGAP	69 (84.1)	42 (37.5)	**<0.001**
Locally advanced rectal cancer	55 (67.1)	43 (38.4)	**<0.001**	SGAP	4 (4.9)	61 (54.5)	**<0.001**
Recurrent rectal cancer	12 (14.6)	53 (47.3)	**<0.001**	ALT	1 (1.2)	2 (1.8)	1.00
Anal SCC	3 (3.7)	5 (4.5)	1.00	VRAM	1 (1.2)	1 (0.9)	1.00
Recurrent anal SCC	3 (3.7)	6 (5.4)	0.736	Gracilis	6 (7.3)	7 (6.3)	0.779
Ileoanal pouch rectal cuff cancer	6 (7.3)	3 (2.7)	0.652	Medial thigh	3 (3.7)	6 (5.4)	0.736
Other *	3 (3.7)	2 (1.8)	0.171	Other**	1 (1.2)	4 (3.6)	0.399
History of pelvic radiotherapy				Two flap types combined	3 (3.6)	11 (9.8)	0.150
Yes	58 (70.7)	82 (73.5)	0.747	Vaginal reconstruction	27 (32.9)	21 (18.8)	**0.029**
No	24 (29.3)	30 (26.5)					

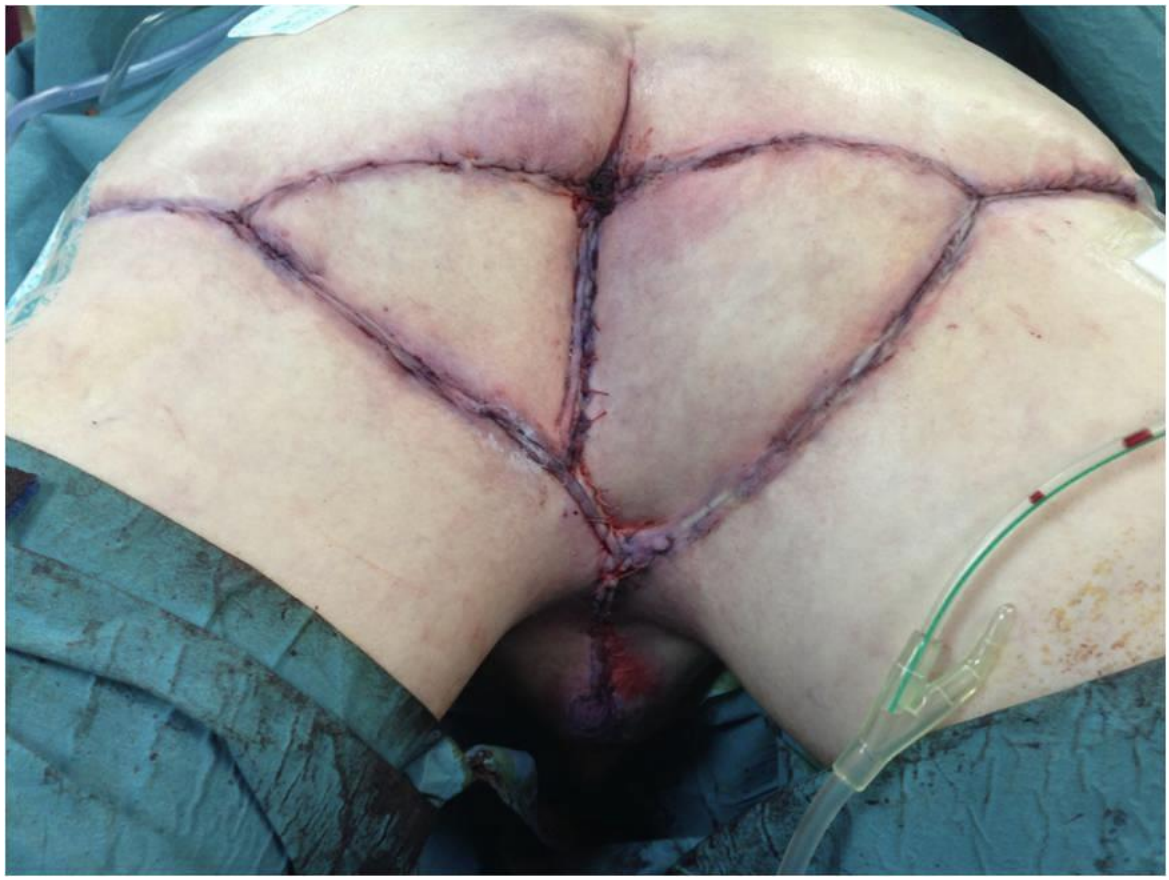
IHD: Ischaemic Heart Disease, HTN: Hypertension, IBD: Inflammatory Bowel Disease, SCC: Squamous Cell Carcinoma, ELSiE: Extended Lateral Sidewall Excision, IGAP: Inferior gluteal artery perforator, SGAP: Superior Gluteal Artery Perforator, ALT: Anterolateral Thigh, VRAM: Vertical Rectus Abdominis Musculocutaneous

*1 re-recurrent appendiceal cancer, 1 mucinous pelvic tumour on a background of Crohn's disease, 1 malignant duplication cyst, 2 anal adenocarcinoma

** Included 2 Singapore, 1 Deep inferior epigastric perforator, 2 rotational buttock flap

All operations were undertaken with curative intent. Gluteal artery perforator flaps were the most common reconstructive approach across both groups. SGAP flaps were significantly more prevalent in the high-complexity group (54.5% vs 4.9%, p<0.001), in keeping with internal iliac vessel resection limiting the use of inferior gluteal vessels in these cases. Conversely, IGAP flaps (Figure 6.2) were more commonly used in the conventional resection group (84.1% vs 37.5%, p<0.001). A greater proportion of vaginal resections was observed in the standard group, corresponding to a higher proportion of female patients in that cohort (32.9% vs 18.8%, p=0.029).

Figure 6.2: Bilateral IGAP flap reconstruction (image reproduced with patient's consent)



Postoperative Outcomes

The overall median postoperative length of stay was 27 days (IQR 18–49), with significantly longer admissions observed following high-complexity procedures (20.5 days vs 32.5 days, $p<0.001$) (Table 6.2). Major complications (Clavien-Dindo ≥ grade 3) occurred in 34.4% of patients. The most frequent serious complications were pelvic collections requiring drainage (11.3%) and urinary leaks (9.7%). Four postoperative deaths (2%) were recorded, all in patients undergoing high-complexity resection. Overall survival (OS) at 5 years was significantly lower in the high-complexity group compared with the conventional group (52% vs 78%, $p=0.015$).

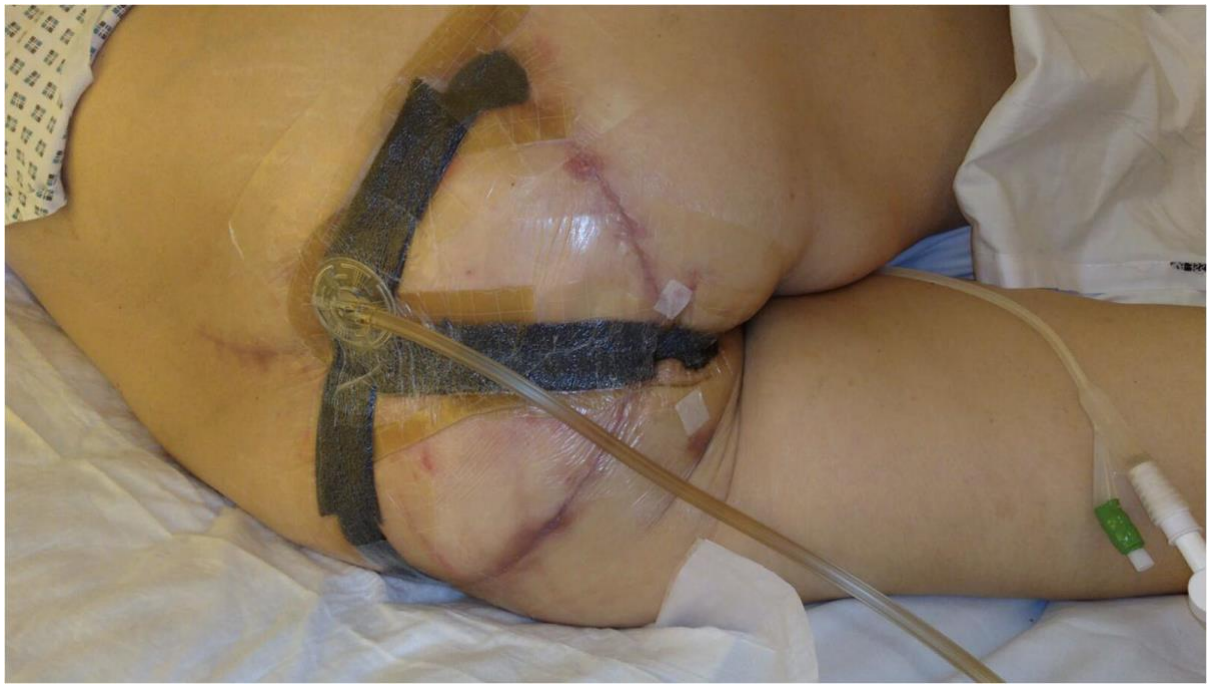
Table 6.2: Postoperative outcomes

	Conventional Complex resection (n=82)	High Complexity resection (n=112)	P value
Postoperative length of stay, median days (IQR)	20.5 (13-29.5)	32.5 (23-57)	**<0.001**
Overall major complication	22 (26.8%)	48 (42.8%	**<0.001**
30 day mortality	0	4 (3.6)	0.139
Perineal wound complications			
Early wound complication			
Simple wound dehiscence requiring packing	9 (11.0)	9 (8.0)	0.618
Superficial dehiscence requiring VAC therapy	20 (24.3)	40 (35.7)	0.116
Full thickness dehiscence	2 (2.4)	1 (0.9)	0.572
Wound infection	19 (23.2)	7 (6.3)	**0.001**
Necrosis	3 (3.7)	7 (6.3)	0.524
Major flap complications			
Return to theatre for plastics revision within 90 days	4 (4.9)	10 (9.1)	0.402
Readmission with wound complication within 30 days	5 (6.1)	6 (5.4)	1.00
Delayed/late wound complication			
Sinus or fistula formation	5 (6.1)	12 (10.7)	0.312
Enteroperineal fistula	4 (4.9)	8 (7.1)	0.564
Symptomatic perineal hernia	5 (6.1)	3 (2.7)	0.286
Flap Revision	6 (7.3)	13 (11.6)	0.464

Wound-related complications of any type were seen in 104 patients (53.3%). Distribution between groups was similar (40.4% conventional vs 59.6% high complexity, p=0.664). The most prevalent complication was superficial wound dehiscence necessitating VAC therapy (figure 6.3), reported in 20 patients (24.3%) following standard resection and 40 (35.7%) in the high-complexity group (p=0.116). The only statistically significant difference was the rate of wound infection requiring antibiotics, which was more frequent in the conventional group (23.2% vs 6.3%, p=0.001).

Ten patients (5.1%) developed partial flap necrosis necessitating debridement under general anaesthesia. Rates were similar across both surgical groups (6.3% vs 3.7%, p=0.524). Return to theatre within 90 days for wound-related issues occurred in 10 patients (9.1%) in the high-complexity group and in 4 (4.9%) patients undergoing conventional resection (p=0.402). Eleven patients (5.6%) required readmission within 30 days for wound complications, with no significant difference between groups (6.1% vs 5.4%, p=1.00). Importantly, there were no cases of total flap failure in the entire cohort.

Figure 6.3: Use of VAC dressing for superficial flap dehiscence (image used with patient's permission)



The median follow-up duration was 26 months (IQR 9–42). Twelve patients (6%) were lost to follow-up within the first six months postoperatively. Chronic wound complications (persistent sinus or fistula) developed in 17 patients (8.8%), with a higher incidence observed in the high-complexity group (10.7% vs 6.1%, p=0.312). Four cases were attributable to urinary leaks. Enteroperineal fistulae were recorded in four patients (4.9%) after conventional resection and eight (7.1%) following high-complexity procedures (p=0.564). This complication significantly impaired long-term survival (mean OS 42.3 months vs 74.0 months, p=0.023). Perineal hernia developed in eight patients (4.1%), more frequently in the conventional group (6.1% vs 2.7%, p=0.286), although this difference was not statistically significant.

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Univariate analysis identified several variables linked to increased risk of short-term perineal wound complications. These included patient age >65 years, BMI >30 kg/m², type 2 diabetes, and undergoing TPE (Table 6.3). However, in multivariate regression, only elevated BMI (HR 2.70, 95% CI 1.22–5.97, p=0.014) and TPE (HR 2.13, 95% CI 1.07–4.23, p=0.031) remained independently associated with short-term wound events.

Table 6.3: Cox regression analysis of the risk factors for perineal wound complications

	Univariate analysis		Multivariate analysis	
Risk Factors	OR (95%CI)	P value	OR (95%CI)	P value
Early wound complication				
Age >65 years	2.13 (1.11-4.13)	**0.023**	1.73 (0.79-3.79)	0.164
Sex	1.28 (0.72-2.28)	0.464		
BMI>30 kg/m^2	2.95 (1.36-6.40)	**0.008**	2.70 (1.22-5.97)	**0.014**
Smoker	1.03 (0.32-3.32)	1.000		
History of RT	0.70 (0.38-1.32)	0.337		
Diabetes Mellitus	12.68 (1.60-100.27)	**0.002**	7.47 (0.88-63.07)	0.065
IHD	1.03 (0.25-4.25)	1.000		
High Complexity Resection	1.10 (0.62-1.95)	0.772		
TPE	1.87 (1.06-3.30)	**0.044**	2.13 (1.07-4.23)	**0.031**
Ureteric/ileal conduit leak	1.16 (0.45-3.00)	0.812		
Late wound complication				
Age >65 years	1.27 (0.56-2.90)	0.664		
Sex	1.17 (0.54-2.55)	0.845		
BMI>30kg/m^2	1.39 (0.55-3.49)	0.469		
Smoker	0.43 (0.05-3.44)	0.695		
History of RT	0.86 (0.38-1.95)	0.677		
Diabetes Mellitus	2.65 (0.75-9.40)	0.124		
IHD	0.82 (0.77-0.88)	0.356		
Complex resection	1.49 (0.67-3.29)	0.434		
TPE	1.00 (0.47-2.14)	1.000		
Ureteric/ileal conduit leak	3.37 (1.21-9.34)	**0.024**		
Readmission <30days or reoperation <90days				
Age >65 years	2.66 (1.07- 6.6)	**0.040**		
Sex	1.46 (0.57-3.76)	0.495		
BMI>30 kg/m^2	1.27 (0.37-4.3)	0.746		
Smoker	0.88 (0.83-0.93)	0.367		
History of RT	1.83 (0.59-5.68)	0.448		
Diabetes Mellitus	1.63 (0.33-7.97)	0.630		
IHD	1.13 (0.13-9.64)	1.000		
Complex resection	1.07 (0.43-2.63)	1.000		
TPE	0.43 (0.17-1.10)	0.111		
Ureteric/ileal conduit leak	1.55 (0.41-5.81)	0.456		

Patients who developed early flap complications had significantly longer hospital stays (median 30 days, IQR 22–59) compared to those without such issues (median 23 days, IQR 15–38; p=0.001).

Long-term wound-related morbidity, including chronic sinus, fistula, or perineal hernia, was independently associated with urinary tract leakage (either uretero-ileal anastomotic or conduit-related), with a hazard ratio of 3.37 (95% CI 1.21–9.34, p=0.024). Additionally, patient age over 65 years was significantly associated with a higher likelihood of readmission or need for reoperation within 90 days post-surgery (HR 2.66, 95% CI 1.07–6.60, p=0.040).

Interestingly, despite the well-established impact of smoking on wound healing, no significant association with flap complications was observed in our cohort, likely reflecting the low proportion of active smokers. Previous exposure to pelvic radiotherapy, although nearly universal in this population, was not linked to increased wound morbidity in this analysis.

6.4 Discussion

This study presents a large series evaluating perineal reconstruction following complex rectal cancer surgery with predominant use of gluteal artery perforator flaps. The findings indicate that while perineal wound complications remain common, particularly in the short term, their incidence is not significantly affected by the complexity of pelvic resection. This challenges prevailing assumptions that larger perineal defects, as seen with high complexity exenterations, inherently result in higher wound morbidity.

Complication rates observed in this cohort align with those reported in other series (range 9.5-55%), with short-term perineal wound events affecting just over one-third of patients[347,348]. However, drawing comparisons across studies is challenging. Recent systematic reviews and meta-analyses on perineal reconstruction report significant study heterogeneity, with significant variability in flap choice, extent of resection, outcome definitions, and follow-up durations[347,349].

Many prior studies have focused on VRAM flaps, which, while effective, are associated with donor site morbidity and abdominal wall complications[171]. Recent comparative analyses suggest that gluteal flaps may offer reduced donor site morbidity and better preserve abdominal wall integrity[350]. Data from this study support this, particularly in high-complexity settings where abdominal access may be compromised or contraindicated.

Although patients undergoing high-complexity resections experienced longer hospital stays and greater overall complication rates, these were not attributable to increased rates of perineal wound breakdown. Instead, the results reinforce the suitability of gluteal perforator flaps as a durable reconstruction option across a broad range of surgical extents, including resections requiring sacrectomy or lateral pelvic sidewall clearance. Flap survival rate in this series was excellent, with no complete flap losses recorded, underscoring the robustness of gluteal artery perforator flaps in the setting of irradiated, high-risk fields.

Obesity emerged as a key modifiable predictor of short-term flap complications. This aligns with prior data from VRAM flap studies, reinforcing the importance of preoperative optimisation[171,172]. Similarly, the association between TPE and early wound complications likely reflects the increased surgical insult, rather than perineal defect size alone.

A novel and important observation from this data was the significant association between urinary leaks (particularly from uretero-ileal conduits) and late-onset perineal wound complications. These findings highlight the critical role of meticulous urological reconstruction and suggest a potential benefit in closer surveillance of urinary drainage systems postoperatively. Enteroperineal fistulation, though relatively uncommon, was associated with markedly reduced long-term survival. Whether this reflects ongoing pelvic sepsis, anastomotic failure, or an underlying aggressive tumour phenotype warrants further investigation. These findings also support the notion that age over 65 years predicts early readmission or reoperation, which may inform discharge planning and patient counselling.

The economic burden of wound complications is well documented. For instance, a New Zealand study reported an average cost of NZ$25,911 (~£13,200) for managing wound complications following abdominoperineal resection[343]. Avoiding such morbidity is particularly relevant in patients undergoing extensive, resource-intensive cancer surgery.

In an era of increasing emphasis on survivorship and quality of life (QoL), these findings provide a foundation for future work assessing functional and QoL outcomes following perineal reconstruction. Prior studies suggest that VRAM flap-related complications can negatively impact QoL up to 18 months postoperatively[172]. Prospective evaluation of QoL in patients undergoing gluteal flap reconstruction is now warranted.

This study has several strengths. It uses a standardised surgical classification system, incorporates a large and consecutive patient cohort, and provides robust follow-up data. The standardised classification of resection complexity using the ACPGBI/UKPEN Pelvic Exenteration Lexicon allowed for more nuanced comparisons across subgroups, something lacking in many previously published reports[148]. However, limitations include its retrospective nature and potential under-reporting of complications managed at local institutions,

particularly in patients referred from distant centres. Despite this, the majority of patients received medium- to long-term follow-up within the CCC service.

6.5 Conclusions

Gluteal fasciocutaneous perforator flaps offer a reliable and versatile option for perineal reconstruction following complex rectal cancer surgery, including in the context of high-complexity pelvic exenteration. In this large single-centre series, increased surgical extent and larger perineal defects did not translate into higher rates of wound-related complications.
Obesity and total pelvic exenteration were independently associated with short-term wound morbidity, while urinary tract leaks emerged as a significant driver of long-term complications. These findings underscore the importance of preoperative risk stratification, multidisciplinary surgical planning, and meticulous intraoperative technique.

The absence of flap loss across the cohort highlights the durability of gluteal perforator flaps, even in irradiated or anatomically complex fields. As pelvic cancer surgery becomes increasingly aggressive in pursuit of oncological cure, ensuring robust reconstructive strategies that minimise complications and preserve patient function is essential. Future studies should further investigate the impact of perineal wound complications on quality of life and explore strategies to reduce risk in high-risk subgroups, including targeted perioperative optimisation.
Taken together, these results demonstrate that reconstructive success is achievable even in the most challenging scenarios, providing a platform for evaluating how broader surgical, clinical, and pathological factors contribute to overall postoperative morbidity and mortality, which will be the focus of the next chapter.

Chapter 7: The Influence of Clinical, Surgical and Pathological Factors on Short-Term Outcomes Following Pelvic Exenteration for Locally Advanced or Locally Recurrent Rectal Cancer

7.1 Introduction

The previous chapter examined outcomes and complications related to perineal reconstruction after pelvic exenteration, with particular attention to the risk factors driving wound-related morbidity. Building on that analysis, this chapter takes a broader perspective, evaluating how patient-related, surgical, and pathological factors collectively influence overall postoperative morbidity and mortality.

Pelvic exenteration is among the most complex procedures in colorectal surgical oncology and is associated with substantial risk as reported in previous chapters. Reported rates of major morbidity approach 40% in many series, reflecting both the technical demands of surgery and the high-risk nature of the patient population[141,142,257]. A clearer understanding of the determinants of short-term outcomes is therefore essential, not only to refine patient selection but also to optimise preoperative preparation where possible, guide intraoperative strategy, and tailor postoperative care to minimise complications and improve recovery.

Clinical factors such as age, sex, comorbidities, and nutritional status play a critical role in determining postoperative outcomes following colorectal surgery[222,223,351]. Older patients and those with significant comorbidities are generally at higher risk for complications and mortality following PE[352,353]. Malnutrition has been consistently associated with poor outcomes, including increased rates of postoperative complications and mortality following colorectal cancer resections[354–356]. Additionally, the presence of anaemia and elevated inflammatory markers, such as the neutrophil-to-lymphocyte ratio and modified Glasgow Prognostic Score (mGPS), have been linked to worse short-term outcomes, highlighting the importance of preoperative optimisation[242,243,245,273,357].

Surgical factors also significantly impact short-term outcomes. The extent of surgery, including whether a total pelvic exenteration (TPE) is performed or whether additional procedures such as sacrectomy or lateral sidewall excision are required, can dictate the risk of adverse outcomes and reduced quality of life[150]. More extensive surgical operations are generally associated with poorer outcomes with higher rates of complications[358,359].

Pathological factors, such as tumour size, stage, and involvement of adjacent structures, further complicate the surgical management and influence outcomes[148,360,361]. Tumours that invade the pelvic sidewall or sacrum are more challenging to resect completely, as highlighted in previous chapters, and are typically associated with increased operative time and greater blood loss[358,359].

The short-term outcomes following pelvic exenteration for LARC and LRRC are influenced by a complex interplay of clinical, surgical, and pathological factors. A thorough understanding of these factors is essential for improving surgical outcomes, minimising complications, and enhancing the overall survival of patients undergoing this high-risk procedure. A detailed analysis of the CCC cohort outcomes was performed to identify prognostic clinical, surgical and pathological factors that influence short-term outcomes following PE in a high-volume, tertiary referral centre.

7.2 Methods

A retrospective review was performed of prospectively collected data for consecutive patients operated on from the Complex Cancer Clinic at St Mark's Hospital, The National Bowel Hospital, London, UK, between January 2008 and July 2021, as described in Chapter 4.

A pre-planned analysis was performed to see how each clinical, surgical and pathological factor influenced postoperative complications. Outcome measures included all postoperative complications within 30 days, defined as Clavien-Dindo grade I-IV, and 30-day major complications, defined as Clavien-Dindo grade III and above[345]. The influence of each factor on 30 and 90-day postoperative mortality was also analysed. Outcomes for patients with LARC and LRRC were analysed separately, and comparisons were made between these two cohorts to ascertain if differences existed in prognostic factors.

Statistical analysis

Continuous variables are presented with median and interquartile range (IQR), and categorical data with frequency and percentage. Differences between groups were detected using Fisher's exact test or Pearson's Chi square test for categorical data and the Mann–Whitney U-test for continuous data. Multivariate analysis was performed by backwards stepwise Cox regression using only variables with a p-value less than 0.05 on univariate analysis ensuring there were at least 10 events per factor in the model. A P-value of less than 0.05 was considered significant. Data were analysed using SPSS software (version 24) (IBM, Armonk, New York, USA).

7.3 Results

388 cases met the inclusion criteria in the CCC cohort. The baseline characteristics for the cohort have previously been discussed and are shown in Table 7.1. The median age was 59 years (IQR 49-67). There were significantly more patients aged 55-75 years undergoing resection of recurrent disease (50% vs 61.4%, p=0.041). A greater number of patients with LARC were smokers (7.8% vs 2.3%, p=0.039) and had inflammatory bowel disease (9% vs 2.3%, p=0.017) when compared with those with LRRC. There were no significant differences in the Charlson Combined Comorbidity Index between groups. Despite a higher median BMI for patients with LRRC (27kg/m^2 vs 25kg/m^2, p=0.019) there was no significant difference in the number of clinically obese (BMI >30kg/m^2) individuals when compared with LARC. As expected, fewer patients with LRRC received any oncological therapy in the six months prior to resection compared with LARC (10.1% vs 34.8%, p<0.001). Patients with LARC were significantly more likely to have undergone total neoadjuvant therapy (37.1% vs 15.2%, p<0.001) or chemoradiotherapy (43.8% vs 20.5%, p<0.001) than patients with LRRC. However, patients with LRRC were more frequently treated with chemotherapy alone (23.5% vs 5.5%, p<0.001).

Table 7.1: Baseline characteristics

Demographics	**Total (n=388)**	**LARC (n=256)**	**LRRC (n=132)**	
	N (%)	N (%)	N (%)	p value
Male sex	234 (62.4)	159 (62.1)	83 (62.9)	0.912
Age, median years (IQR)	59 (49, 67)	57 (47, 67)	61 (51,66)	0.320
<55years	154 (39.7)	108 (42.2)	46 (34.8)	0.189
55-75 years	209 (53.9)	128 (50.0)	81 (61.4)	**0.041**
>75 years	25 (6.4)	20 (7.8)	5 (3.8)	0.135
ASA				
2	323 (83.2)	215 (84.0)	108 (81.8)	0.667
3	65 (16.8)	41 (16.0)	24 (18.2)	
Comorbidity present				
Hypertension	66 (17.0)	44 (17.2)	22 (16.7)	1.00
Cardiovascular	21 (5.4)	15 (5.9)	6 (4.5)	0.645
Diabetes	32 (8.2)	26 (10.2)	6 (4.5)	0.078
Respiratory	18 (4.6)	15 (5.9)	3 (2.3)	0.132
Current smoker	23 (5.9)	20 (7.8)	3 (2.3)	**0.039**
Inflammatory bowel disease	26 (6.7)	23 (9.0)	3 (2.3)	**0.017**
BMI (n=278)				
BMI, median kg/m^2 (IQR)	26 (22, 30)	25 (22,30)	27 (24, 31)	0.019
BMI>30	75 (19.3)	45 (17.6)	30 (22.7)	0.060
Neoadjuvant therapy (within 6 months of surgery)				
Chemotherapy only	45 (11.6)	14 (5.5)	31 (23.5)	**<0.001**
Chemoradiotherapy	139 (35.8)	112 (43.8)	27 (20.5)	**0.007**
Short course Radiotherapy	17 (4.4)	9 (3.5)	8 (6.1)	0.397
Total neoadjuvant therapy	115 (29.6)	95 (37.1)	20 (15.2)	**<0.001**
No therapy	72 (18.6)	26 (10.1)	46 (34.8)	**<0.001**

BMI: Body Mass Index

Preoperative blood results, recorded within two weeks of resection, were broadly similar when comparing patients with primary and recurrent disease (Table 7.2). Preoperative anaemia was prevalent in 40.1% (n=143) overall. Significantly more patients with LARC had an NLR greater than 3.0 (69.5% vs 56.8%, p=0.017) and a platelet count over 400 x 10^9/L (84% vs 70.5%, p=0.001). A small subset of patients were hypoalbuminaemic preoperatively (8%, n=31). Most patients (68.5%, n=213) had a modified Glasgow Prognostic Score of zero, indicating normal levels of albumin and CRP preoperatively.

Table 7.2: Preoperative blood counts and inflammatory markers

	Total (n=388)	**LARC (n=256)**	**LRRC (n=132)**	
	N (%)	N (%)	N (%)	p value
Haemoglobin, median g/L (IQR)	130 (116,140)	128 (114,140)	132 (119,141)	0.158
Anaemia*	155 (40.4)	109 (43.1)	46 (35.1)	0.154
Neutrophils, median $x10^9$/L (IQR)	4.3 (3.3, 5.8)	4.4 (3.3, 6.2)	4.2 (3.2, 5.5)	0.213
Lymphocytes, median $x10^9$/L (IQR)	1.1 (0.81,1.5)	1.0 (0.8, 1.4)	1.2 (0.9, 1.7)	**0.001**
Platelets, median $x10^9$/L (IQR)	263 (218,319)	265 (220,331)	260 (210, 304)	0.146
Platelets >400 $x10^9$/L	32 (8.0)	6 (4.6)	25 (9.9)	0.078
NLR >3.0	253 (65.2)	178 (69.5)	75 (56.8)	**0.017**
PLR >150	308 (79.4)	215 (84.0)	93 (70.5)	**0.001**
Albumin, median g/L (IQR)	43.5 (40,46)	43 (40, 46)	44 (40, 47)	0.232
Hypoalbuminaemia**	31 (8.0)	18 (7)	13 (9.8)	0.431
CRP, median mg/L (IQR)	4.0 (1.8,14.5)	4.0 (1.9, 17.3)	4.0 (1.5, 10.6)	0.313
mGPS				
0	213 (68.5)	139 (67.5)	74 (70.5)	0.608
1	84 (21.6)	54 (26.2)	24 (22.9)	0.581
2	20 (5.2)	13 (6.3)	7 (6.7)	1.000

FBC result available for 384 patients, Albumin for 380 and CRP for 311. *<115g/L for females, <130g/L for males **Albumin <35g/L NLR: Neutrophil to lymphocyte ratio, PLR: Platelet to lymphocyte ratio, CRP: C-reactive protein, mGPS: Modified Glasgow Prognostic score

Operative Outcomes

247 (64%) of patients underwent a partial pelvic exenteration, and the remaining 141 (36%) had total pelvic exenteration (Table 7.3). A Bricker ileal conduit was formed for 143 patients (37%), and 24 patients (6%) underwent a Boari-flap reconstruction or ureteric reimplantation. A lateral pelvic sidewall resection was required for 203 patients (52%), and this was more commonly performed for LRRC (64% vs 47%, p=0.002). In 117 of these cases, an Extended Lateral Side Wall Excision (ELSiE) was performed[156]. An extended posterior resection was performed in 152 cases (39%), with higher rates of en-bloc sacrectomy required in LRRC compared with LARC (42% vs 25%). 175 patients (45.2%) needed a perineal reconstruction with a myocutaneous flap. A clear resection margin (>1mm) was achieved in 86.6% of patients overall; 228 patients (89.1%) with LARC and 109 patients (82.6%) with LRRC (Table 7.4). Operative time and blood loss results were not available.

Table 7.3: Operative approach

Operative details	**Total (n=388)**	**LARC (n=256)**	**LRRC (n=132)**	**p value**
Operation				
Partial pelvic exenteration	247 (63.7)	171 (66.8)	76 (57.6)	0.076
Total pelvic exenteration	141 (36.3)	85 (33.2)	56 (42.4)	
Surgical approach				
Laparoscopic	79 (20.4)	72 (28.1)	7 (5.3)	**<0.001**
Open	302 (77.9)	178 (69.5)	124 (93.9)	
Lap converted to open	7 (1.8)	6 (2.3)	1 (0.8)	
Urological resection				
Ileal conduit	143 (36.9)	86 (33.6)	57 (43.2)	0.075
Boari flap/ureteric reimplantation	24 (6.2)	10 (3.9)	14 (10.6)	**0.010**
Vascular resection	23 (6.0)	4 (1.6)	19 (14.4)	**<0.001**
Lateral pelvic resection				
Side wall resection (any)	203 (52.3)	119 (46.5)	84 (63.6)	**0.002**
ELSiE[156]	117 (30.2)	55 (21.5)	62 (47.0)	**<0.001**
Posterior resection				
Extended posterior resection (any)	152 (39.2)	90 (35.2)	62 (47.0)	**0.028**
High sacrectomy	49 (12.6)	20 (7.8)	29 (22.0)	**<0.001**
Distal sacrectomy	46 (11.9)	28 (10.9)	18 (13.6)	0.508
HiSS[153]	24 (6.2)	15 (5.9)	9 (6.8)	0.824
Subperiosteal resection	33 (8.5)	27 (10.5)	6 (4.5)	0.054
Perineal reconstruction				
Flap reconstruction	175 (45.1)	112 (43.8)	63 (47.7)	0.518

CRS: Cytoreductive surgery ELSiE: Extended Lateral Sidewall Excision, HiSS: High Subcortical Sacrectomy, C-V: Clavien Dindo grade

Table 7.4: Tumour histopathology

Histology	**Total (n=388)**	**LARC (n=256)**	**LRRC (n=132)**	**p value**
Tumour stage				
0		28 (10.9)		
1		10 (3.9)		
2		22 (8.6)		
3		103 (40.2)		
4		89 (34.8)		
Not stated		4 (1.6)		
Nodal status*				
No nodal involvement	290 (74.7)	183 (71.5)	107 (81.7)	**0.035**
Positive nodes	97 (25.0)	73 (28.5)	24 (18.2)	
Total nodes harvested (median)	14 (7, 25)	19 (12, 30)	6 (1,12)	**<0.001**
Lymphatic invasion	84 (21.6)	58 (22.7)	26 (19.7)	0.520
Venous invasion	172 (44.3)	113 (44.1)	59 (44.7)	0.914
EMVI	150 (38.7)	103 (40.2)	47 (35.6)	0.406
PNI	147 (37.9)	94 (36.7)	54 (40.9)	0.441
Resection margin				
R0	336 (86.6)	228 (89.1)	109 (82.6)	0.140
R1	48 (12.4)	28 (10.9)	20 (15.2)	0.081
R2	3 (0.8)	0	3 (2.3)	**0.013**
Histological characteristics**				
Poor	29 (7.5)	19 (7.4)	10 (7.6)	0.835
Moderate/well	298 (76.8)	205 (80.0)	93 (70.5)	
Signet ring features present	8 (2.1)	5 (2.0)	3 (2.3)	1.00
Mucinous features present	55 (14.2)	36 (14.1)	19 (14.4)	0.879
Tumour diameter (median, mm)	40 (29,60)	40 (28.5, 60)	42.5 (30,60)	0.832
MMR testing				
Yes	231 (59.5)	179 (67.2)	52 (39.4)	
MMR deficient	12 (5.2)	11 (6.1)	1 (1.9)	

EMVI: Extramural Venous Invasion, PNI: Perineural Invasion *1 patient missing data **Histological characteristics not reported in 59 (15.2%)

Median length of stay was significantly longer for patients with LRRC (23 days, IQR 14-45) compared with the LARC group (17 days, IQR 9-30, p=0.001) (Table 7.5). Regarding complications within 30 days post-surgery, 66.8% (n=259) of all patients experienced at least one complication with no differences between LARC and LRRC. Minor complications (Clavien-Dindo grade I-II) only occurred in 36.3% (n=141) of all patients, with identical rates in both LARC (36.3%) and LRRC (36.4%) groups (p = 1.000). Major complications (Clavien-Dindo grade III-V) were observed in 30.4% (n=118) of patients overall, with 27.7% in the LARC group and 35.6% in the LRRC group, but this difference was not statistically significant

(p = 0.130). The rate of return to theatre was significantly higher in the LRRC group (25.8%) compared with the LARC group (11.3%), p <0.001. Readmission to an intensive care unit (ICU) occurred in 5.7% of all patients, with no significant difference between the LARC and LRRC groups.

Table 7.5: Postoperative outcomes

	Total	**LARC**	**LRRC**	
	N=388	N=256	N=132	
	N (%)	N (%)	N (%)	P value
Length of postoperative stay, median days (IQR)	20 (11, 35)	17 (9, 30)	23 (14, 45)	**0.001**
No 30 day postoperative complications	129 (33.2)	92 (35.9)	37 (28.0)	0.139
30 day minor complication (CD I-II)	141 (36.3)	93 (36.3)	48 (36.4)	1.000
30 day major complication (CD III+)	118 (30.4)	71 (27.7)	47 (35.6)	0.130
Inpatient death	15 (3.9)	6 (2.3)	9 (6.8)	**0.048**
Return to theatre	63 (16.2)	29 (11.3)	34 (25.8)	**<0.001**
Readmission to ICU	22 (5.7)	12 (4.7)	10 (7.6)	0.254
30 day mortality	10 (2.6)	5 (2.0)	5 (3.8)	0.318
90 day mortality	19 (4.9)	9 (3.5)	10 (7.6)	0.087
Readmission within 30 days	58 (14.9)	39 (15.2)	19 (14.4)	0.881

Inpatient mortality was higher in the LRRC group at 6.8% compared with 2.3% in the LARC group, reaching statistical significance (p = 0.048). The 30-day mortality rate was 2.6% overall, with 2.0% in the LARC group and 3.8% in the LRRC group (p = 0.318). The 90-day mortality rate was higher in the LRRC group at 7.6% compared with 3.5% in the LARC group, though this did not reach statistical significance (p = 0.087). Readmission within 30 days occurred in 14.9% of patients overall, with no significant difference between the LARC (15.2%) and LRRC (14.4%) groups (p = 0.881).

Clinical factors and their association with postoperative outcomes

The clinical factors associated with postoperative complications of any grade (Clavien-Dindo grade 1-4) for patients with LARC were NLR >3, hypertension and ASA grade 3 on univariate analysis with hypertension and ASA 3 retaining significance on multivariate analysis with

hazard ratios of 3.02 (95%CI 1.25-7.28, p = 0.014) and 4.78 (1.61-14.18, p =0.005), respectively (Table 7.6).

The analysis of clinical factors associated with major postoperative complications (Clavien-Dindo grade 3 or above) in patients with LARC revealed several significant predictors (Table 7.7). In univariate analysis factors such as anaemia (HR 1.82, 95% CI 1.04-3.17, p = 0.036), NLR >3.0 (HR 3.31, 95% CI 1.59-6.89, p = 0.001), PLR >150 (HR 2.86, 95% CI 1.07-7.66, p = 0.003), hypoalbuminaemia (HR 2.85, 95% CI 1.08-7.52, p = 0.034), mGPS ≥1 (HR 2.65, 95% CI 1.43-4.92, p = 0.002), hypertension (HR 2.08, 95% CI 1.06-4.09, p = 0.034), diabetes (HR 2.97, 95% CI 1.30-6.76, p = 0.010), and an ASA score of 3 (HR 3.92, 95% CI 1.96-7.83, p < 0.001) were significantly associated with higher complication rates. However, in the multivariate analysis, only NLR >3.0 (HR 2.91, 95% CI 1.23-6.87, p = 0.015), mGPS ≥1 (HR 2.39, 95% CI 1.23-4.66, p = 0.011), diabetes (HR 4.12, 95% CI 1.38-12.23, p = 0.011), and ASA score of 3 (HR 2.21, 95% CI 1.01-4.85, p = 0.048) remained significant.

The analysis of 30-day mortality for patients with LARC demonstrated significant associations with certain clinical factors. In the univariate analysis, hypoalbuminaemia was strongly associated with a significantly increased risk of 30-day mortality (HR 22.9, 95% CI 3.55-147.68, p < 0.001). Additionally, an ASA score of 3 was also associated with a higher risk of mortality (HR 8.41, 95% CI 1.34-52.01, p = 0.022). However, in the multivariate analysis, hypoalbuminaemia remained a significant predictor of 30-day mortality (HR 22.9, 95% CI 3.55-147.68, p < 0.001), while the association with an ASA score of 3 was not statistically significant (HR 4.38, 95% CI 0.60-31.87, p = 0.145). Hypoalbuminaemia was the only significant factors in patients with LARC that was associated with increased 90-day mortality (HR 21.8, 95% CI 5.23-91.09, p=<0.001).

For patients with LRRC, factors associated with complication of any grade were male sex and preoperative anaemia on univariate analysis, with preoperative anaemia retaining significance on multivariate analysis with a HR 4.26 (95% 1.24-10.53, p=0.018). When analysing factors associated with major complications only in LRRC the univariate analysis identified an ASA score of 3 (HR 3.18, 95% CI 1.28-7.90, p = 0.013) as a significant factor. No clinical factors were associated with 30- or 90-day mortality for patients with LRRC.

Table 7.6: Clinical factors associated with any postoperative complications (Clavien-Dindo grade 1-4)

	LARC				**LRRC**			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Sex[+]	1.55 (0.92-2.62)	0.100			3.14 (1.43-6.90)	**0.004**	2.11 (0.92-4.86)	0.078
Age >55y	1.34 (0.80-2.24)	0.270			2.65 (0.76-3.61)	0.208		
BMI >30	1.33 (0.64-2.77)	0.445			1.01 (0.38-2.65)	0.986		
Anaemia	1.55 (0.92-2.53)	0.102			4.95 (1.77-13.83)	**0.002**	4.26 (1.24-10.53)	**0.018**
NLR >3.0	1.91 (1.10-3.31)	**0.022**	1.69 (0.95-3.01)	0.074	0.75 (0.35-1.64)	0.754		
PLR >150	1.36 (0.67-2.74)	0.394			1.05 (0.46-2.42)	0.909		
Hypoalbuminaemia	2.12 (0.68-6.63)	0.199			1.35 (0.35-5.21)	0.664		
mGPS ≥1	1.34 (0.71-2.56)	0.369			2.55 (0.93-7.02)	0.069		
Hypertension	3.54 (1.51-8.30)	**0.004**	3.02 (1.25-7.28)	**0.014**	1.05 (0.38-2.92)	0.931		
Cardiovascular disease	3.87 (0.86-17.56)	0.079			0.77 (0.14-4.39)	0.768		
Diabetes	1.59 (0.64-3.94)	0.316			2.00 (0.23-17.72)	0.533		
Respiratory disease	1.58 (0.49-5.12)	0.444			-	0.999		
Current smoker	2.38 (0.77-7.34)	0.132			0.77 (0.07-8.80)	0.837		
ASA 3	6.41 (2.21-18.63)	**<0.001**	4.48 (1.61-14.19)	**0.005**	2.20 (0.70-6.94)	0.179		
Neoadjuvant therapy	1.91 (0.85-4.32)	0.119			0.54 (0.182-1.57)	0.256		

[+]Females used as reference population

Table 7.7: Clinical factors associated with major postoperative complications (Clavien Dindo grade 3+)

	LARC				**LRRC**	
	Univariate		Multivariate		Univariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Sex[+]	1.28 (0.72-2.27)	0.404			1.23 (0.58-2.59)	0.586
Age >55y	1.38 (0.79-2.42)	0.265			1.42 (0.66-3.06)	0.325
BMI >30	1.33 (0.64-2.77)	0.445			1.01 (0.38-2.65)	0.986
Anaemia	1.82 (1.04-3.17)	**0.036**	0.84 (0.40-1.75)	0.643	1.47 (0.69-3.11)	0.319
NLR >3.0	3.31 (1.59-6.89)	**0.001**	2.91 (1.23-6.87)	**0.015**	1.16 (0.56-2.39)	0.688
PLR >150	2.86 (1.07-7.66)	**0.003**	1.98 (0.56-6.99)	0.288	0.80 (0.37-1.75)	0.584
Hypoalbuminaemia	2.85 (1.08-7.52)	**0.034**	*		1.61 (0.51-5.11)	0.419
mGPS ≥1	2.65 (1.43-4.92)	**0.002**	2.39 (1.23-4.66)	**0.011**	2.11 (0.91-4.89)	0.084
Hypertension	2.08 (1.06-4.09)	**0.034**	1.85 (0.82-4.17)	0.139	0.82 (01-2.17)	0.685
Cardiovascular disease	2.42 (0.84-6.94)	0.100			3.95 (0.70-22.46)	0.121
Diabetes	2.97 (1.30-6.76)	**0.010**	4.12 (1.38-12.23)	**0.011**	3.86 (0.68-21.93)	0.127
Respiratory disease	0.94 (0.29-3.07)	0.924			3.73 (0.33-42.31)	0.288
Current smoker	1.830 (0.72-4.69)	0.207			3.82 (0.34-43.28)	0.279
ASA 3	3.92 (1.96-7.83)	**<0.001**	2.21 (1.01-4.85)	**0.048**	3.18 (1.28-7.90)	**0.013**
Neoadjuvant therapy	1.69 (0.61-4.67)	0.311			0.79 (0.37-1.66)	0.537

[+]Females used as reference population *Hypoalbuminaemia not included in multivariate model as mGPS dependant on result

Surgical factors and their associations with postoperative outcomes

Multiple significant factors were associated with increased total postoperative complications for patients with LARC (Table 7.8). In the univariate analysis, a laparoscopic approach was associated with a lower risk of postoperative complications (HR 0.37, 95% CI 0.21-0.65, $p < 0.001$), though this association was not statistically significant in the multivariate analysis (HR 0.56, 95% CI 0.31-1.03, $p = 0.064$) and likely confounded by a potentially less extensive resection being required. Extended resections involving an ELSiE, sacrectomy or perineal flap reconstruction were significant on univariate analysis but did not retain significance after adjusting for other factors in the multivariate model. TPE was strongly associated with an increased risk of complications in both univariate (HR 4.25, 95% CI 2.23-8.13, $p < 0.001$) and multivariate analyses (HR 3.52, 95% CI 1.77-7.00, $p < 0.001$).

Several significant surgical factors were associated with major postoperative complications in patients with LARC (Table 7.9). In the univariate analysis, a laparoscopic approach was associated with a significantly lower risk of major complications (HR 0.24, 95% CI 0.11-0.53, $p < 0.001$), though this association was not statistically significant in the multivariate analysis (HR 0.44, 95% CI 0.19-1.05, $p = 0.063$). TPE (HR 3.38, 95% CI 1.91-5.99, $p < 0.001$), ELSiE (HR 4.22, 95% CI 2.25-7.92, $p < 0.001$), sacrectomy (HR 2.79, 95% CI 1.53-5.09, $p < 0.001$) and perineal flap reconstruction (HR 2.19, 95% CI 1.26-3.83, $p = 0.006$) were associated with greater major postoperative complications on univariate analysis. On multivariate analysis TPE (HR 2.10, 95% CI 1.10-3.99, $p = 0.024$) and ELSiE (HR 2.76, 95% CI 1.40-5.45, $p = 0.003$) retained significance.

On analysis of the surgical factors associated with increased 30- and 90-day mortality for patients with LARC only sacrectomy was associated with increased deaths at 90 days (HR 4.07, 95%CI 1.06-15.67, p 0.041).

TPE was the only significant predictor of total postoperative complications in patients with LRRC on both univariate (HR 3.70, 95% CI 1.54-8.93, $p = 0.004$) and multivariate analyses (HR 3.70, 95% CI 1.54-8.93, $p = 0.004$). ELSiE showed significance in univariate analysis but not in multivariate analysis. TPE, when compared to PPE, was also the only factor significantly associated with an increased risk of major complications (HR 4.01, 95% CI 1.89-8.50, $p < 0.001$) in LRRC. No surgical factors were found to influence 30- or 90-day mortality for patients with LRRC.

Table 7.8: Surgical factors associated with any postoperative complications (Clavien-Dindo grade 1-4)

	LARC				**LRRC**			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Laparoscopic approach	0.37 (0.21-0.65)	**<0.001**	0.56 (0.31-1.03)	0.064	0.27 (0.06-1.28)	0.099		
TPE	4.25 (2.23-8.13)	**<0.001**	3.52 (1.77-7.00)	**<0.001**	3.70 (1.54-8.93)	**0.004**	3.70 (1.54-8.93)	**0.004**
Pelvic sidewall	1.21 (0.72-2.02)	0.470			1.41 (0.64-3.08)	0.393		
ELSiE	2.7 (1.17-4.76)	**0.016**	1.23 (0.56-2.70)	0.614	2.32 (1.04-5.14)	**0.039**	1.74 (0.75-4.01)	0.198
Sacrectomy	1.91 (1.01-3.61)	**0.047**	1.08 (0.49-2.41)	0.847	2.30 (0.60-2.83)	0.506		
Perineal flap	2.07 (1.21-3.52)	**0.008**	1.47 (0.83-2.62)	0.187	0.95 (0.44-2.03)	0.895		

Table 7.9: Surgical factors associated with major postoperative complications (Clavien Dindo grade 3+)

	LARC				**LRRC**	
	Univariate		Multivariate		Univariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Laparoscopic approach	0.24 (0.11-0.53)	**<0.001**	0.44 (0.19-1.05)	0.063	0.70 (0.13-3.77)	0.680
TPE	3.38 (1.91-5.99)	**<0.001**	2.10 (1.10-3.99)	**0.024**	4.01 (1.89-8.50)	**<0.001**
Pelvic sidewall	1.48 (0.85-2.56)	0.163			1.06 (0.50-2.24)	0.885
ELSiE	4.22 (2.25-7.92)	**<0.001**	2.76 (1.40-5.45)	**0.003**	1.69 (o.82-3.46)	0.154
Sacrectomy	2.79 (1.53-5.09)	**<0.001**	1.12 (0.50-2.53)	0.781	0.77 (0.37-1.59)	0.476
Perineal flap	2.19 (1.26-3.83)	**0.006**	1.18 (0.62-2.25)	0.608	0.72 (0.35-1.48)	0.377

Pathological factors and their associations with postoperative outcomes

No pathological factors were found to be associated with all 30-day postoperative complications in patients with LARC (Table 7.10). However, pathological factors were found to significantly influence major complications in patients with LARC (Table 7.11). Poorly differentiated tumours (HR 2.65, 95% CI 1.02-6.87, p = 0.045) and mucinous tumours (HR 2.40, 95% CI 1.16-4.95, p = 0.018) were associated with greater major complications on univariate analysis with mucinous tumours only retaining significance in the multivariate model (HR 3.03, 95% CI 1.34-6.90, p = 0.008). Poorly differentiated tumours were observed to be associated with increased 30-day (HR 7.92, 95%CI 1.24-50.70, p=0.029) and 90-day (HR 13.40, 95%CI 3.05- 58.98, p=<0.001) mortality for patients with LARC.

In patients with LRRC, none of the pathological factors evaluated demonstrated a significant association with major postoperative complications or short-term mortality on univariate analysis.

Table 7.10: Pathological factors associated with any postoperative complications (Clavien-Dindo grade 1-4)

	LARC		**LRRC**	
	Univariate		Univariate	
	HR (95%CI)	p value	HR (95%CI)	p value
T stage 0-2 vs 3-4	0.92 (0.50-1.680	0.781	N/A	
Involved lymph nodes	1.02 (0.58-1.79)	0.946	2.23 (0.71-7.04)	0.171
Lymphatic invasion present	0.68 (0.37-1.24)	0.206	1.08 (0.41-2.85)	0.867
Venous invasion present	0.79 (0.47-1.32)	0.374	1.77 (0.81-3.89)	0.155
EMVI	0.76 (0.45-1.27)	0.292	1.73 (0.68-4.29)	0.247
PNI	0.85 (0.50-1.44)	0.549	1.96 (0.87-4.41)	0.106
Differentiation well/mod vs poor	1.28 (0.47-3.50)	0.635	0.47 (0.12-1.79)	0.267
Mucinous features	2.16 (0.94-4.97)	0.069	0.61 (0.22-1.69)	0.338
R status (R0 vs R1/2)	1.21 (0.52-2.79)	0.658	1.50 (0.51-4.38)	0.462

Table 7.11: Pathological factors associated with major postoperative complications (Clavien-Dindo grade 3+)

	LARC				LRRC	
	Univariate		Multivariate		Univariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
T stage 0-2 vs 3-4	1.11 (0.57-2.17)	0.750			N/A	
Involved lymph nodes	1.42 (0.79-2.56)	0.247			1.74 (0.71-4.28)	0.227
Lymphatic invasion present	0.80 (0.41-1.58)	0.521			1.47 (0.61-3.53)	0.392
Venous invasion present	0.97 (0.56-1.69)	0.924			1.79 (0.87-3.69)	0.117
EMVI	0.99 (0.57-1.74)	0.979			1.41 (0.64-3.13)	0.394
PNI	1.28 (0.73-2.23)	0.397			1.46 (0.71-3.00)	0.306
Differentiation well/mod vs poor	2.65 (1.02-6.87)	**0.045**	2.47 (0.93-6.55)	0.070	0.74 (0.18-3.07)	0.682
Mucinous features	2.40 (1.16-4.95)	**0.018**	3.03 (1.34-6.90)	**0.008**	0.61 (0.21-1.82)	0.374
R status (R0 vs R1/2)	2.15 (0.96-4.81)	0.063			0.96 (0.37-2.46)	0.928

7.4 Discussion

These results emphasise that, although patients with primary disease and those with recurrent disease share broadly similar baseline characteristics, those with LRRC experience significantly poorer outcomes. This includes longer postoperative hospital stays, higher inpatient mortality, and a greater need for reoperation compared with patients with LARC. Several key factors likely contribute to these differences. One primary reason for the worse outcomes in LRRC patients is the complexity of the surgery required as extended bony resections are often necessary to achieve local control of the recurrent disease.

In analysing the impact of clinical factors on post-operative morbidity and mortality, it becomes evident that systemic inflammation and pre-existing comorbidities play a critical role in determining outcomes for LARC patients. Fewer predictive factors are evident for LRRC patients, which may reflect the overriding influence of the more aggressive nature of recurrent disease and the complexity of the surgery required to treat it.

For both LARC and LRRC patients, a higher ASA grade, which reflects greater baseline comorbidity, is a strong predictor of post-operative complications in this cohort. This finding aligns with established evidence, as patients who are less physically fit are inherently at greater risk for complications following major surgery[271]. Additionally, preoperative systemic inflammation, as measured by NLR and mGPS, was a significant predictor of postoperative morbidity in LARC patients. This is consistent with the existing literature, which associates systemic inflammation with worse outcomes in colorectal cancer patients[243,362]. The influence of systemic inflammation on postoperative outcomes is multifactorial. Chronic inflammation can lead to immune dysregulation and aberrations in body composition[235,363]. This complex interplay of factors can delay tissue healing, contribute to post-operative complications, and potentially exacerbate the risk of poor short-term outcomes. These mechanisms likely explain why inflammatory markers like NLR and mGPS have such a pronounced impact on morbidity in LARC patients. However, each of these factors such as ASA 3 and mGPS>1 affects less than 25% of patients undergoing pelvic exenteration. Therefore, these factors individually are not likely to preclude surgery but inform on the risk of surgery only.

Analysis of the surgical factors that influence post-operative outcomes revealed that TPE is consistently associated with higher complication rates in both LARC and LRRC patients compared with PPE. This aligns with the fact that TPE is a more extensive and challenging

surgical procedure and often requires complex reconstruction. Additionally, factors such as the use of the laparoscopic approach, en bloc sacrectomy, and extended pelvic side wall excisions showed variable impacts on outcomes, depending on the type of cancer and the method of analysis used. The potential increased operative times, blood loss, and the technically demanding nature of these procedures may contribute to higher rates of complications, including infection, wound dehiscence, and reoperation; however, due to the lack of data for this cohort, this could not be interrogated further.

Furthermore, patients undergoing sacrectomy are particularly prone to post-operative pain, which can delay mobilisation and recovery, further increasing the likelihood of complications[364,365]. These more aggressive surgical approaches are often necessary to achieve clear margins in patients with more extensive disease, but the increased surgical trauma and post-operative morbidity must be weighed against the potential benefits of achieving long-term local control.

In terms of pathological features, this chapter highlights that certain characteristics, particularly poor differentiation and mucinous histology, are associated with an increased risk of major complications following pelvic exenteration in LARC patients. While these factors are well-known to influence long-term survival and cancer-related outcomes, it is interesting to note their potential role in short-term surgical outcomes as well. Poorly differentiated tumours and mucinous tumours tend to be more aggressive, often invading adjacent structures, necessitating more extensive resections[366]. This, in turn, may increase the complexity of surgery and the associated risks of morbidity. In LRRC patients, however, the pathological factors evaluated appear to have a less pronounced effect on post-operative outcomes.

Limitations

Limitations of this chapter include the retrospective nature of data collection and that only patients from a single centre are included; therefore, this may not be representative of all patients with LARC and LRRC undergoing PE. The nature of PE surgery means that the cohort is heterogeneous in terms of the fine operative details, as the surgical approach to each patient is determined by the extent of their disease. The series of patients spans a thirteen-year time period, and as such, changes in surgical approach and oncological treatments will have varied, which may influence outcome.

7.5 Conclusions

This novel data presents the influence of clinical and pathological factors on outcomes in the modern era of pelvic exenteration surgery. Overall, this chapter highlights the importance of considering both clinical and pathological factors when evaluating post-operative outcomes in patients with LARC and LRRC. Patients with recurrent disease face higher complexity resections, greater complication rates, and poorer outcomes overall. Factors such as systemic inflammation, tumour pathology, and the need for extended resections play critical roles in influencing post-operative morbidity and mortality. Understanding these relationships can help guide preoperative risk stratification and inform surgical decision-making, ultimately improving outcomes for this challenging patient population.

Building on these findings, the next chapter will explore how the same surgical, clinical, and pathological factors not only influence immediate morbidity and mortality but also shape long-term survival outcomes, providing a more comprehensive view of prognosis following pelvic exenteration.

Chapter 8: The Clinical and Pathological Determinants of Outcome Following Resection of Locally Advanced or Locally Recurrent Rectal Cancer

8.1 Introduction

In the Chapter 7 the clinical and pathological factors that influence short-term outcomes after pelvic exenteration were explored. This chapter will focus on the influence of these factors on the long-term outcomes. This chapter has been reproduced in part with permission from Elsevier (appendix 3) from two of our published articles in the European Journal of Surgical Oncology (EJSO):

- Pathological Determinants of Outcome Following Resection of Locally Advanced or Locally Recurrent Rectal Cancer. LE Gould, ET Pring, M Moorghen, EM Burns, A Antoniou, CW Steele, CSD Roxburgh, JT Jenkins. EJSO, 2023, 49 (11)
- Clinical Determinants of Outcome Following Pelvic Exenteration for Locally Advanced Or Locally Recurrent Rectal Cancer. LE Gould, ET Pring, A Wallace, N Hodges, EM Burns, CW Steele, CSD Roxburgh, JT Jenkins.
  EJSO, 2025, 51 (10).

Clinical factors such as age, comorbidity and neoadjuvant oncological treatment influence survival following major abdominal surgery[222–224]. Numerous scoring systems and risk prediction models have been developed to help quantify the effect of comorbidities on outcome following surgery such as the American Society of Anesthesiologists performance status (ASA) and Charlson Combined Comorbidity Index[223,225]. Other clinical factors, such as preoperative systemic inflammation, have also been demonstrated to influence survival in patients with operable malignancy[367]. Inflammation has been linked to tumour development and progression and can be measured using a variety of metrics: Glasgow Prognostic Score (a scoring system utilising serum albumin concentration and C-Reactive Protein), neutrophil to lymphocyte ratio (NLR), and platelet to lymphocyte ratio (PLR)[242,243,245,368]. Unlike with primary rectal cancer, treated with standard total mesorectal excision, there is a paucity of evidence assessing the influence of these factors on the patient following pelvic exenteration

for advanced disease. Radiomics is another emerging area of research, with promising evidence supporting the use of MRI-based features to predict recurrence in patients with LARC[369,370].

Pathological factors that influence and predict survival following PE for rectal cancer, especially LRRC, remain poorly understood. A clear resection margin (R0) confers the greatest influence on survival[12,13]. The influence of other pathological features within resected tumours is infrequently reported in the literature[14]. With improving rates of complete resection in published cohorts, there is a need to look for other pathological features to quantify the risk of recurrence for these locally aggressive cancers and better predict patient outcomes. The ability to identify those tumours at greatest risk of local and distant recurrence may enable clinicians to tailor combined modality treatment strategies and surveillance programs on an individual patient basis with the aim of improving recurrence detection and survival.

Recent studies have highlighted the significant heterogeneity in outcome measurement and reporting in the pelvic exenteration literature, making comparison between studies challenging[371,372]. Additionally, national data from England has identified underreporting of pelvic exenteration procedures and outcomes, with a demonstrated improvement in survival rates after 2005 coinciding with increased use of MRI staging[373]. Despite these advances, quality of life outcomes following pelvic exenteration remain sparsely reported in the literature, with a recent systematic review highlighting the need for standardized reporting of both oncological and functional outcomes[371].

The purpose of this study was to perform a detailed analysis of the clinical and pathological determinants of oncological outcomes in a large series of patients with LARC and LRRC who have undergone PE at a tertiary referral centre.

8.2 Methods

Study Design and Patient Population

A retrospective review was performed of prospectively collected data for consecutive patients operated on from the Complex Cancer Clinic at St Marks Hospital, The National Bowel Hospital, London, UK between January 2008 and July 2021 as described in Chapter 4.

The same clinical and pathological factors were assessed as described in Chapter 5. A pre-planned analysis was performed to see how each clinical and pathological factor influenced

overall, disease-free and local recurrence-free survival. Overall survival (OS) was calculated from the month of resection to the month of death or the censor date of 05/05/2022. Disease-free survival (DFS) was calculated from the date of resection to the earliest recorded date of radiological or histopathological diagnosis of local recurrence or metastatic disease, death or censor date. Local recurrence-free survival (LRFS) was calculated from the date of resection to the month of death, local recurrence or censor. For LRRC, the date of the resection of the recurrent tumour was used to calculate these figures. LARC and LRRC were analysed separately, and comparisons were made between these two cohorts to ascertain if differences existed in prognostic clinical and pathological factors. Subgroup analysis was planned to assess the impact of key pathological factors in R0 resections, and a multivariate analysis was performed to combine both clinical and pathological factors.

8.3 Results

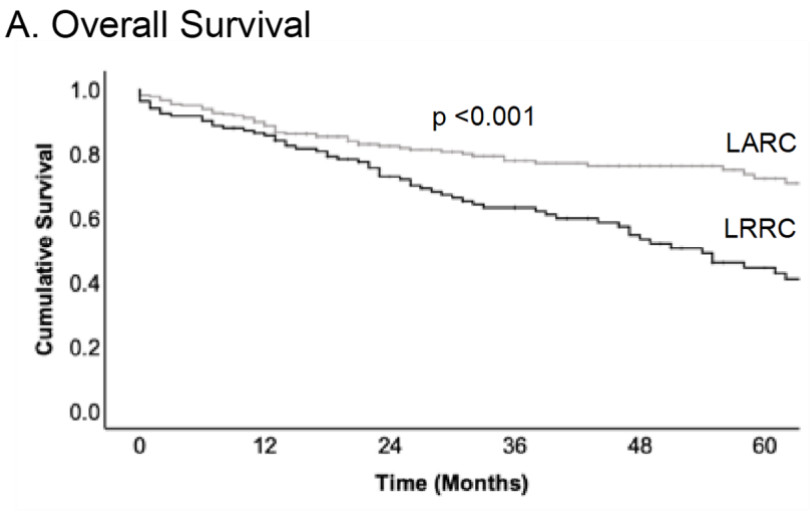
Between January 2008 – July 2021 a total of 388 patients met the inclusion criteria and were included in the final analysis with 66% (n=256) of resections for LARC and 33% (n=132) for LRRC. The baseline characteristics have previously been described in Chapter 4 and summarised in Tables 4.1 and 4.2.

The distribution of baseline clinical and pathological factors have been described in chapter 7 and summarised in tables 7.1 to 7.4.

Overall Survival

At a median follow up of 21 months (range 0-145) there were a total of 71 deaths amongst the patients with LARC; 36 (14.1%) cancer related, 29 (11.3%) non cancer related, and 6 (2.3%) unconfirmed causes of death. A total of 62 deaths were recorded for patients with LRRC; 31 (23.5%) cancer related, 17 (12.9%) non cancer related and 3 (2.3%) with an unconfirmed cause of death. The estimated five-year OS is 71% for LARC and 41% for LRRC (Figure 8.1A). Mean OS for patients with LARC was significantly longer than patients with LRRC, 105 months (95%CI 95-115) compared to 78 months (95%CI 64-91), $p<0.001$.

Figure 8.1. Survival analysis comparing LARC with LRRC - Overall Survival



Number. at risk

LARC	256	221	150	106	79	54
LRRC	132	110	80	61	41	27

Table 8.1: Cox regression analysis of the clinical and pathological factors associated with overall survival for LARC and LRRC

	LARC				**LRRC**	
	Univariate		Multivariate		Univariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Clinical factors						
Sex[+]	0.92 (0.55-1.53)	0.738			1.46(0.84-2.56)	0.181
Age >55y	1.40 (0.83-2.38)	0.209			1.37 (0.78-2.43)	0.278
BMI >30	1.04 (0.49-2.23)	0.922			0.84 (0.39-1.77)	0.641
Anaemia	1.71 (1.03-2.83)	0.039			0.88 (0.62-1.76)	0.591
NLR >3.0	2.37 (1.21-4.68)	0.012			1.56 (0.92-2.64)	0.881
PLR >150	2.65 (0.96-7.33)	0.059			1.13 (0.64-1.99)	0.676
Platelets >400	3.11 (1.68-5.75)	**<0.001**	1.65 (0.81-3.35)	0.165	0.78 (0.25-2.50)	0.679
Hypoalbuminaemia	3.18 (1.63-6.23)	**0.001**	**		0.96 (0.44-2.11)	0.921
mGPS ≥1	3.93 (2.23-6.91)	**<0.001**	3.82 (2.17-6.13)	**<0.001**	1.24 (0.68-2.25)	0.477
Hypertension	2.20 (1.25-3.85)	0.006			0.73 (0.37-1.44)	0.362
Cardiovascular disease	2.35 (1.01-5.48)	0.049			1.09 (0.34-3.47)	0.891
Diabetes	2.96 (0.96-3.99)	0.066			1.50 (0.5- 4.16)	0.433
Current smoker	2.47 (1.17-5.23)	0.018			1.75 (0.43-7.20)	0.436
ASA 3	2.87 (1.63-5.04)	**<0.001**	2.41 (1.31-4.44)	**0.005**	2.22 (1.27-3.89)	**0.005**
CCI 3+	1.20 (0.66-2.18)	0.554			0.89 (0.46-1.71)	0.727
Neoadjuvant therapy	0.75 (0.38-1.49)	0.410			0.96 (0.57-1.59)	0.859
Pathological factors						
Tumour stage 0-2 vs 3-4	3.97 (1.60-9.91)	**0.003**	3.20 (0.99-10.38)	0.053	N/A	
Involved lymph nodes	2.12 (1.28-3.53)	**0.004**	1.29 (0.71-2.34)	0.398	1.12 (0.58-2.15)	0.745
Lymphatic invasion present	1.10 (0.59-2.03)	0.773			1.38 (0.74-2.55)	0.309
Venous invasion present	1.81 (1.09-3.01)	**0.023**	0.95 (0.53-1.70)	0.864	1.34 (0.81-2.23)	0.254
EMVI	1.69 (1.01-2.82)	**0.045**	*		1.22 (0.75-2.37)	0.328
PNI	1.92 (1.15-3.22)	**0.013**	1.28 (0.71-2.33)	0.414	1.51 (0.92-2.50)	0.106
Differentiation well/mod vs poor	6.01 (3.22-11.49)	**<0.001**	5.38 (2.77-10.45)	**<0.001**	1.44 (0.65-3.19)	0.370
Mucinous features	0.95 (0.45-2.00)	0.884			1.24 (0.63-2.44)	0.541
R status (R0 vs R1/2)	3.19 (1.80-5.66)	**<0.001**	1.97 (1.08-3.60)	**0.027**	0.86 (0.44-1.70)	0.665

LARC: Locally advanced rectal cancer, LRRC: Locally recurrent rectal cancer, EMVI: Extramural venous invasion, PNI: Perineural invasion, R: Resection margin [+]Females used as reference population **Hypoalbuminaemia not included in multivariate model as GPS dependent on result, *Not included in the model as dependent on venous invasion status

Multiple clinical factors were significant on univariate analysis as negative prognostic markers for OS in patients with LARC (Table 1). A mGPS ≥1 and ASA III remained significant on multivariate analysis with hazard ratios of 3.82 (95% CI 2.17-6.13, p<0.001) and 2.41 (95% CI 1.31-4.44, p<0.005), respectively. For patients with LRRC the only negative prognostic marker for overall survival was ASA III with a HR 2.22 (95%CI 1.27-3.89, p=0.005).

Of the routinely reported pathological factors, several were associated with reduced OS for patients with LARC on univariate analysis (Table 8.1). Only poorly differentiated tumours and a positive resection margin retained significance on multivariate analysis with hazard ratios of 5.38 (95%CI 2.77-10.45, p<0.001) and 1.97 (95%CI 1.08-3.60, p=0.027), respectively. None of the reported pathological factors were found to have a significant impact on OS following resection of LRRC.

When these significant clinical and pathological factors were included in the multivariate analysis mGPS ≥ 1 (HR 3.08 95%CI 1.70-5.59, p <0.001), ASA III (HR 3.03, 95%CI 1.58-5.80, p<0.001) and poorly differentiated tumours (HR 4.81, 95%CI 2.40-9.75, p=<0.001) remained significant for LARC (Table 2). No factors reached the required significance to allow for multivariate analysis in patients with LRRC.

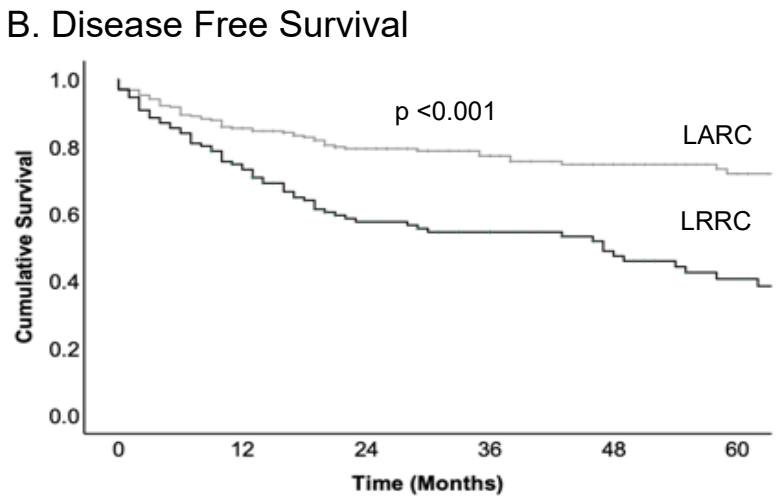
Table 8.2: Multivariate analysis of both clinical and pathological factors associated with overall survival for LARC

	Overall Survival	
	HR (95%CI)	p value
Platelets >400	0.92 (0.42-2.03)	0.844
mGPS ≥1	3.08 (1.70-5.59)	**<0.001**
ASA 3	3.03 (1.58-5.80)	**<0.001**
R status (R0 vs R1/2)	1.70 (0.86-3.37)	0.126
Differentiation well/mod vs poor	4.81 (2.40-9.75)	**<0.001**
Involved lymph nodes	1.30 (0.70-2.43)	0.412
Tumour stage 0-2 vs 3-4	3.80 (0.87-16.10)	0.070

Disease Free Survival

A total of 90 patients (23.2%) developed distant metastases; Forty-two patients (31.8%) with LRRC and 48 patients (18.8%) with LARC. The local recurrence rate was 12.6% (n=49); 21 patients (8.2%) following LARC and 28 patients (21.2%) developing re-recurrent disease after exenteration for LRRC. Patients with LARC had an increased mean DFS compared to LRRC, 90 months (95%CI 81-101) compared with 52 months (95% CI 41-64), p<0.001(Figure 8.2). The estimated five-year DFS was 58% for LARC and 25% for LRRC.

Figure 8.2. Survival analysis comparing LARC with LRRC – Disease Free Survival



Number at risk						
LARC	256	196	130	92	68	48
LRRC	132	87	51	38	28	19

Table 8.3: Cox regression analysis of the clinical and pathological factors associated with disease free survival for LARC and LRRC

	LARC				**LRRC**			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Clinical factors								
Sex[+]	0.88 (0.58-1.32)	0.526			1.10 (0.71-1.72)	0.644		
Age >55y	1.28 (0.84-1.95)	0.259			0.71 (0.46-1.10)	0.129		
BMI >30	1.04 (0.59-1.84)	0.890			1.10 (0.63-1.92)	0.734		
Anaemia	1.49 (0.99-2.24)	0.057			1.16 (0.75-1.79)	0.509		
NLR >3.0	1.60 (0.98-2.60)	0.059			1.10 (0.72-1.68)	0.666		
PLR >150	1.58 (0.81-3.05)	0.176			0.81 (0.52-1.28)	0.376		
Platelets >400	2.42 (1.39-4.22)	**0.002**	1.76 (0.94-3.30)	0.079	0.73 (0.27-2.00)	0.546		
Hypoalbuminaemia	2.47 (1.34-4.59)	**0.004**	**		1.05 (0.54-2.03)	0.888		
mGPS ≥1	2.24 (1.44-3.49)	**<0.001**	1.97 (1.16-3.19)	**0.005**	1.13 (0.68-1.89)	0.637		
Hypertension	1.90 (1.19-3.05)	0.008			0.68 (0.38-1.20)	0.184		
Cardiovascular disease	1.59 (0.75-3.44)	0.239			0.59 (0.19-1.86)	0.366		
Diabetes	1.79 (0.99-3.22)	0.054			2.21 (0.96-5.07)	0.063		
Current smoker	1.47 (0.74-2.93)	0.271			1.04 (0.26-4.24)	0.956		
ASA 3	2.12 (1.30-3.45)	**0.003**	1.95 (1.16-3.28)	**0.012**	1.42 (0.85-2.38)	0.185		
CCI 3+	1.09 (0.66-1.80)	0.968			0.90 (0.53-1.53)	0.705		
Neoadjuvant therapy	0.98 (0.52-1.85)	0.955			0.93 (0.61-1.42)	0.727		
Pathological factors								
Tumour stage 0-2 vs 3-4	3.92 (1.90-8.10)	**<0.001**	2.09 (0.89-4.88)	0.091	NA			
Involved lymph nodes	3.08 (2.04-4.63)	**<0.001**	2.06 (1.31-3.23)	**0.002**	1.71 (1.03-2.85)	**0.040**	1.33 (0.75-2.37)	0.327
Lymphatic invasion present	2.03 (1.31-3.14)	**0.002**	0.96 (0.58-1.58)	0.858	1.68 (1.02-2.78)	**0.043**	1.22 (0.67-2.19)	0.517
Venous invasion present	2.02 (1.34-3.06)	**0.001**	1.00 (0.63-1.60)	0.998	1.71 (1.12-2.61)	**0.013**	1.71 (1.12-2.61)	**0.013**
EMVI	2.04 (1.35-3.09)	**0.001**	*		1.37 (0.84-2.21)	0.205		
PNI	2.49 (1.65-3.76)	**<0.001**	1.52 (0.97-2.38)	0.068	1.49 (0.97-2.27)	0.063		
Differentiation well/mod vs poor	3.67 (2.05-6.54)	**<0.001**	2.41 (1.25-4.63)	**0.009**	1.44 (0.71-2.90)	0.311		
Mucinous features	0.78 (0.42-1.47)	0.449			0.85 (0.46-1.57)	0.602		
R status (R0 vs R1/2)	3.22 (1.98-5.25)	**<0.001**	1.73 (1.01-2.95)	**0.045**	1.29 (0.76-2.20)	0.339		

LARC: Locally advanced rectal cancer, LRRC: Locally recurrent rectal cancer, EMVI: Extramural venous invasion, PNI: Perineural invasion, R: Resection margin [+]Females used as reference population
**Hypoalbuminaemia not included in multivariate model as GPS dependent on result, *Not included in the model as dependent on venous invasion status

A platelet count of greater than 400x10^9/L, hypoalbuminaemia, mGPS score ≥1, hypertension, and an ASA score of III were associated with reduced DFS for patients with LARC on univariate analysis (Table 8.3). At multivariate Cox regression analysis mGPS ≥1 and ASA III remained independently associated with DFS with hazard ratios of 1.97 (95%CI 1.16-3.19, p=0.005) and 1.95 (95%CI 1.16-3.28, p=0.012), respectively. No clinical factors were significantly associated with DFS for LRRC in this analysis.

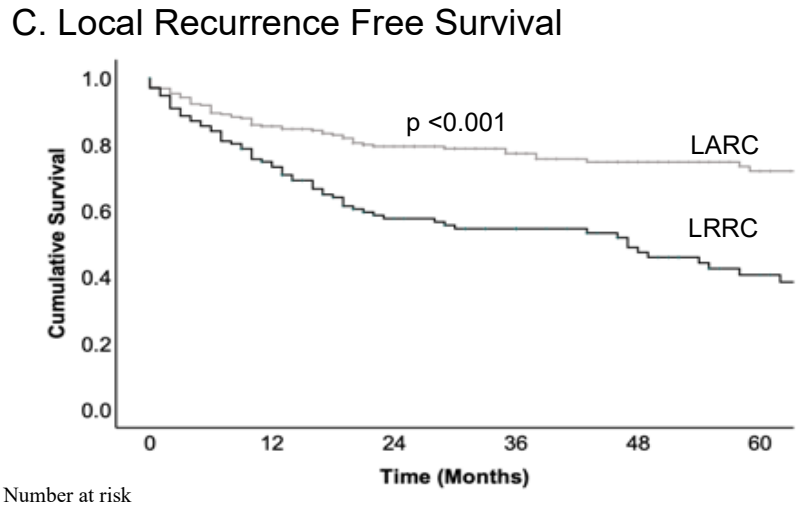
Of the routinely reported pathological factors, several were significantly associated with reduced DFS in LARC on univariate analysis (Table 8.3). Involved lymph nodes, HR 2.06 (95% CI 1.31-3.23, p=0.002), poorly differentiated lesions, HR 2.41 (95%CI 1.25-4.63, p=0.009) and positive resection margin, HR 3.22 (95%CI 1.98-5.25, p<0.001), remained significant on multivariate modelling. Lymph node involvement, lymphatic and venous invasion were significantly associated with a reduction in DFS in LRRC on univariate analysis with only venous invasion retaining significance on multivariate analysis, HR 1.71 (95%CI 1.12-2.61, p=0.013).

Combined analysis of the clinical and pathological factors associated with DFS was not possible due to too few events for the number of significant factors.

Local Recurrence Free Survival

Mean LRFS was significantly reduced when comparing LRRC with LARC; 59 months (95%CI 45 -75) vs 102 months (95%CI (93-112), p<0.001 (Figure 8.3). Multiple clinical factors were associated with reduced LRFS for LARC on univariate analysis (Table 8.4). On multivariate analysis a mGPS ≥1 and ASA III remained significant with hazard ratios of 2.84 (95%CI 1.57-5.13, p<0.001) and 1.94 (95% CI 1.06-3.56, p=0.032), respectively (Table 4). The only factor associated with reduced LRFS for LRRC was ASA III with a HR 1.81 (95% CI 1.03-3.17, p=0.039).

Figure 8.3. Survival analysis comparing LARC with LRRC – Local Recurrence Free Survival



Number at risk

LARC	256	207	140	102	75	51
LRRC	132	94	59	48	33	21

Table 8.4: Cox regression analysis of the clinical and pathological factors associated with local recurrence free survival for LARC and LRRC

	LARC				**LRRC**			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Clinical factors								
Sex[+]	0.78 (0.48-1.27)	0.323			1.49 (0.87-2.53)	0.143		
Age >55y	1.30 (0.79-2.15)	0.306			1.22 (0.72-2.08)	0.462		
BMI >30	1.18 (0.57-2.46)	0.650			1.00 (0.51-1.98)	0.998		
Anaemia	2.01 (1.22-3.28)	0.006			1.10 (0.67-1.81)	0.720		
NLR >3.0	2.54 (1.29-4.98)	0.007			1.17 (0.72-1.89)	0.537		
PLR >150	2.02 (0.81-5.06)	0.132			0.92 (0.54-1.54)	0.739		
Platelets >400	3.07 (1.67-5.67)	**<0.001**	1.89 (0.93-3.85)	0.080	0.57 (0.17-1.86)	0.350		
Hypoalbuminaemia	3.25 (1.70-6.22)	**0.004**	**		0.91 (0.41-1.99)	0.808		
mGPS ≥1	3.44 (2.00-5.93)	**<0.001**	2.84 (1.57-5.13)	**<0.001**	1.53 (0.87-2.69)	0.140		
Hypertension	2.07 (1.19-3.61)	0.010			0.86 (0.46-1.60)	0.623		
Cardiovascular disease	2.65 (1.20-5.85)	0.016			0.87 (0.27-2.76)	0.808		
Diabetes	1.89 (0.93-3.87)	0.079			1.45 (0.53-3.99)	0.476		
Current smoker	2.15 (1.02-4.55)	0.045			1.50 (0.37-6.15)	0.572		
ASA 3	2.38 (1.36-4.15)	**0.002**	1.94 (1.06-3.56)	**0.032**	1.81 (1.03-3.17)	**0.039**		
CCI 3+	0.99 (0.54-1.80)	0.968			0.74 (0.40-1.39)	0.352		
Neoadjuvant therapy	0.86 (0.43-1.70)	0.656			0.82 (0.51-1.33)	0.421		
Pathological factors								
Tumour stage 0-2 vs 3-4	3.41 (1.47-7.90)	**0.004**	2.41 (0.86-6.73)	0.091	N/A			
Involved lymph nodes	1.75 (1.07-2.86)	**0.027**	2.08 (0.61-1.90)	0.795	1.30 (0.73-2.30)	0.371		
Lymphatic invasion present	1.30 (0.75-2.27)	0.352			1.61 (0.92-2.82)	0.098		
Venous invasion present	1.69 (1.04-2.75)	**0.034**	0.99 (0.58-1.71)	0.994	1.79 (1.13-2.89)	**0.016**	1.38 (0.81-2.37)	0.235
EMVI	1.72 (1.05-2.81)	**0.031**	*		1.44 (0.84-2.50)	0.187		
PNI	1.47 (0.90-2.39)	0.122			1.71 (1.06-2.76)	**0.028**	1.10 (0.64-1.88)	0.736
Differentiation well/mod vs poor	3.72 (1.97-7.02)	**<0.001**	3.00 (1.54-5.85)	**<0.001**	2.10 (1.03-4.29)	**0.041**	2.10 (1.03-4.29)	**0.041**
Mucinous features	1.11 (0.57-2.19)	0.753			0.63 (0.30-1.32)	0.220		
R status (R0 vs R1/2)	3.41 (1.47-7.90)	**0.004**	2.41 (0.86-6.73)	0.091	N/A			

LARC: Locally advanced rectal cancer, LRRC: Locally recurrent rectal cancer, EMVI: Extramural venous invasion, PNI: Perineural invasion, R: Resection margin [+]Females used as reference population
**Hypoalbuminaemia not included in multivariate model as GPS dependent on result, *Not included in the model as dependent on venous invasion status

Tumour stage, lymph node involvement, venous and extramural venous invasion, poorly differentiated tumours, and a positive resection margin were all significant on univariate analysis for LRFS in patients with LARC (Table 8.4). Poor differentiation, HR 3.00 (95%CI 1.54-5.85, p<0.001) and positive resection margins, HR 2.10 (95%CI 1.16-3.80, p=0.014) were independently associated with reduced LRFS in the multivariate model. Venous invasion, perineural invasion and poorly differentiated tumours were significantly associated with LRFS in patients with LRRC on univariate analysis with poor differentiated tumours remaining significant on multivariate analysis, HR 2.10 (95% CI 1.03-4.29, P=0.041).

The clinical and pathological factors that retained significance on combined multivariate analysis were mGPS ≥ 1 (HR 2.32, 95%CI 1.27-4.25, p=0.006), ASA III (HR 2.52 95%CI 1.33-4.78, p=0.005), positive resection margin (HR 2.17, 95%CI 1.11-4.22, p=0.023) and poorly differentiated tumours (HR 3.93, 95%CI 1.94-7.97, p<0.001) for patients with LARC (Table 8.5). For LRRC only poorly differentiated tumours retain significance on multivariate analysis (HR 2.15, 95%CI 1.04-4.43, p=0.038).

Table 8.5: Multivariate analysis of both clinical and pathological factors associated with LRFS for LARC

	Local Recurrence Free Survival	
	HR (95%CI)	p value
Platelets >400	1.19 (0.55-2.57)	0.657
mGPS ≥1	2.32 (1.27-4.25)	**0.006**
ASA 3	2.52 (1.33-4.78)	**0.005**
R status (R0 vs R1/2)	2.17 (1.11-4.22)	**0.023**
Differentiation well/mod vs poor	3.93 (1.94-7.97)	**<0.001**
Tumour stage 0-2 vs 3-4	3.02 (0.89-10.26)	0.077

Subgroup analysis

In R0 resections the pathological factors associated with LRFS in patients with LARC were advancing T stage and poorly differentiated lesions on univariate analysis (Table 8.6). Poorly differentiated lesions retained significance on multivariate analysis, HR of 4.03 (95%CI 1.68-9.70), p=0.002. Venous invasion and perineural invasion were significantly associated with

reduced LRFS on univariate analysis for LRRC with perineural invasion retaining significant on multivariate analysis, HR 2.07 (95%CI 1.19-3.60), p=0.010.

Table 8.6: Subgroup analysis: Factors associated with Local Recurrence Free Survival following R0 resection

	LARC n=228				**LRRC n=109**			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value	HR (95%CI)	p value
Tumour stage 0-2 vs 3-4	3.09 (1.31- 7.28)	**0.010**	2.80 (1.00-7.89)	0.051	N/A			
Involved lymph nodes	1.77 (0.98-3.21)	0.059			1.37 (0.69-2.73)	0.373		
Lymphatic invasion present	0.74 (0.31-1.76)	0.497			1.80 (0.92-3.53)	0.086		
Venous invasion present	1.39 (0.79-2.45)	0.251			1.89 (1.10-3.25)	**0.021**	1.56 (0.87-2.80)	0.136
EMVI	1.39 (0.78-2.47)	0.260			1.29 (0.70-2.28)	0.413		
PNI	1.75 (0.96-3.19)	0.067			1.99 (1.15-3.45)	**0.014**	2.07 (1.19-3.60)	**0.010**
Differentiation well/mod vs poor	3.86 (1.61-9.26)	**0.002**	4.03 (1.68-9.70)	**0.002**	1.70 (0.72-4.04)	0.227		
Mucinous features	0.95 (0.40-2.25)	0.903			0.94 (0.43-2.08)	0.878		

LARC: Locally advanced rectal cancer, LRRC: Locally recurrent rectal cancer, EMVI: Extramural venous invasion, PNI: Perineural invasion

8.4 Discussion

This study demonstrates that despite broadly similar baseline clinical characteristics between locally advanced primary and recurrent advanced rectal cancer there are significant differences in the effect of these factors on long-term outcomes. Key clinical factors that influence survival are readily identifiable and easy to measure preoperatively. These factors could be used to help predict and quantify the risk of recurrence of these complex rectal cancers. The study results also demonstrate that long term survival is achievable for patients with LARC and LRRC following PE. The 5-year overall survival rates of 72% for LARC and 45% for LRRC are comparable to the literature[3,4,8–10].

Clinical factors

Non-modifiable clinical factors such as age and sex do not seem to influence survival in this cohort. These findings are in keeping with the reported literature where a significant difference in survival outcomes has only been demonstrated when comparing the extremes of age (80 years vs under 50 years[279,283,287,290]). Careful selection of patients fit enough to undergo pelvic exenteration is essential, but age alone should not be a discriminating factor. However, the impact on quality of life and postoperative functioning would be of interest in patients with advancing age. This is particularly relevant as recent studies have highlighted the paucity of quality of life data following pelvic exenteration, which may be an important consideration in patient selection and decision-making[371].

Comorbidities such as hypertension and cardiovascular disease were shown to negatively impact survival in patients with LARC on univariate analysis. Previous studies have demonstrated a potential increased risk of cancer development and cancer-related mortality associated with hypertension[374]. These findings have been reproduced in rectal cancer patients where hypertension was associated with reduced DFS and cancer-specific survival in a study of 328 patients with stage I-III rectal cancer with hazard ratios of 1.97 (95%CI 1.08-3.60) and 2.85 (95% CI 1.00-8.25, p=0.05), respectively[375]. There is also emerging evidence of the potential for a cancer-related survival benefit with adherence to antihypertensive treatment for patients with colorectal cancer[376]. The impact of comorbidity was not only seen to influence overall survival but also cancer-related survival, where ASA was a better prognostic marker than CCI in this cohort. For patients with LRRC, high ASA grade was the only clinical factor of significance, confirming that less medically fit patients have poorer outcomes following

resection. Patients with high ASA pose significant challenges for both surgical and anaesthetic teams, given the extent and length of surgery, blood loss and often prolonged recovery. Adequate preoperative optimisation is essential, and until recently, there was no clear guidance for this patient group, with resultant wide variations in practice internationally, something that an attempt to address has been made by the PelvEx Collaborative[377].

The use of neoadjuvant therapy did not appear to influence outcome and confer any survival benefit in this study. Only a small subset (10%) of LARC cases did not have any oncological treatment; therefore, the sample size may not have been adequate to see its effects. However, these findings support those reported by the large multicentre PelvEx Collaborative study on patients with LARC[142]. Comparable findings have been reported for LRRC with no improvement in survival with neoadjuvant therapy, as seen in our cohort, but increased rates of postoperative morbidity[141]. Given the large time span of both this study and the PelvEx Collaborative papers, the influence of the more modern oncological therapy may not be truly reflected. This finding contrasts with recent national data from England, which showed improved 5-year overall survival rates after 2005 (61.7% vs 37%, $p<0.001$), coinciding with increased use of MRI staging and changes in perioperative treatment approaches[373].

Disease-related clinical factors such as inflammation and anaemia have been demonstrated to influence survival in patients with colorectal cancer[378]. Elevated preoperative inflammatory status, quantified by NLR, PLR and mGPS has been associated with worse outcomes for primary rectal cancer and this relationship is also demonstrated in our cohort[242,244,357]. Interestingly, this influence was only demonstrated in patients with LARC, not LRRC, in this study. The timing of measuring these values for prognostic purposes is still unclear, as they may be altered following neoadjuvant therapy [357,379]. Modification of inflammatory status could be a target for treatment rather than just markers of disease activity and prognosis. Advanced histopathological tissue analysis may afford a better understanding of local and systemic inflammation and the effect of local tumour invasion.

Pathological factors

Pathological factors that influence survival in LARC differ from those influencing outcomes for LRRC. Although the resection margin status was shown to be important in LARC it was not demonstrated to be a key determinant of survival for LRRC in this cohort, underlining the

need to consider other pathological characteristics for prognostication in this cohort. The R0 resection rate of 89.1% for LARC in this study is comparable to the literature with reported rates of 75-91%[14]. However, the R0 rate of 86.6% for LRRC in this study is significantly higher than most reported series, with a range of 55.4- 59% reported from two large multicentre studies[10,13]. Due to the high R0 rate, the importance of a clear resection margin may not be as apparent in this study compared with other case series and thus incur Type II error. This exceptionally high rate of complete resection may be accounted for by the radicality of the procedures performed. 42% of patients with LRRC had a sacral resection in this series, and 63.6% underwent pelvic side wall resection compared with 31.8% and 24%, respectively, in a large multicentre study of similar patients[134]. Increasingly radical resections may be associated with greater patient morbidity and mortality, but we noted no significant increase in either major complications or mortality in this group when compared with patients undergoing less extensive resections for LARC. Patient quality of life data were not available, and it would be of interest to assess the impact of such increasingly aggressive resections. The 3- and 5-year OS for LRRC of 63% and 45% in this study are significantly higher than those reported by the PelvEx Collaborative study (3yr OS 48.1%) and another large multicentre study by Harris *et al.* (5yr OS 28%)[134,141]. How much of this difference is related to obtaining a higher rate of complete pathological clearance is unclear but can be inferred.

Poor tumour differentiation is an indicator of poor prognosis with reduced OS, DFS and LRFS in LARC and associated with reduced LRFS in LRRC. This factor retained significance in the context of R0 resections for LARC. Similar findings of a reduced 3yr OS in LARC following PE have previously been demonstrated[281]. Although these patients may only represent a small subset of the overall cohort, they appear to have a significantly worse outcome and therefore may benefit from targeted surveillance and oncological therapies.

Tumour stage influenced DFS in LARC in this study when comparing stages T0-2 with T3-4 tumours. This finding was not replicated by Koda *et al.* when comparing outcomes for T3 and T4 tumours in LARC[280]. Due to the efficacy of different downstaging neoadjuvant oncological regimes and the different stages used for comparison in studies; it is difficult to draw meaningful conclusions regarding the impact of tumour stage. There is no internationally agreed classification for tumour stage for LRRC making comparisons between studies challenging.

Nodal involvement was demonstrated to influence DFS for LARC in this study. Similar hazard ratios of 2.29-2.32 have been reported in comparable cohort studies[280,281]. DFS was not reported in the PelvEx Collaborative study, however, a more modest impact on OS was shown, HR 1.27[142]. Involved lymph nodes did not appear to affect survival for patients with LRRC. This result is consistent with the reported literature[141,282,289]. Venous invasion was the only significant negative prognostic marker for DFS in patients with LRRC, with no effect seen for patients with LARC. Venous invasion is known to increase the risk of metastasis, primarily through haematogenous spread[380].

There have been significant advances in the molecular understanding of rectal cancers in the last decade. Numerous factors have been identified as important prognostic markers in primary cancer that may also have prognostic value in LRRC; these include tumour stromal volume and immune cell infiltration[212,216]. Gene expression profiling has enabled the identification of prognostic gene signatures in colorectal cancer, allowing for subdivision of tumours into consensus molecular subtypes (CMSs)[381]. Gene expression has also identified that mucinous tumours relate to BRAF mutations, microsatellite instability and CpG island methylator phenotype pathway[382]. These more modern techniques could be applied to this cohort to further elucidate prognostic markers.

Interestingly, when the pathological and clinical factors are combined, the significance of a negative resection margin for patients with LARC is lost. This may be in part due to the high R0 rates in this cohort. Poorly differentiated tumours appear to confer the worst outcomes for patients with LARC, although this affects a relatively small proportion of patients (7.5%). The importance of patient selection is highlighted by the fact that ASA III and systemic inflammation appear to play a greater role in this cohort than resection margin in those with LARC for overall and disease-free survival.

Study Limitations

Limitations of this study include its retrospective nature and the potential heterogeneity of the included patients in terms of their disease, surgical resection, and the differences in neoadjuvant therapy. The cohorts included span thirteen years with advances in pathology reporting, surgical techniques, and refinement of surgical practice during this time. There will also have been an evolution in oncological therapies throughout this time, which may influence

results. This study period encapsulates patients undergoing resections during the COVID-19 pandemic, where changes to neoadjuvant therapy delivery and delays in surgery, due to the availability of resources, may have impacted survival outcomes. Quality of life data were not available for the patients in this study, and we recognise that this is an important endpoint to consider for patients following pelvic exenteration, as highlighted in recent systematic reviews.

8.5 Conclusions

This study highlights that preoperatively assessable clinical factors can help identify patients with LARC at the highest risk of reduced survival and recurrence following pelvic exenteration. In contrast, fewer clinical determinants were identified for LRRC, underlining the need to discover reliable biomarkers to predict recurrence and metastasis in this group. Resection margin status and tumour differentiation remain important prognostic markers in LARC; however, margin status was not significant in our cohort, likely reflecting the high overall R0 rate achieved. These findings emphasise the importance of seeking novel prognostic indicators, particularly in LRRC, beyond those captured in existing standard reporting datasets. A greater understanding of the relationship between systemic inflammation, tumour biology, and the microenvironment may help identify new pathological or molecular markers to guide treatment selection and surveillance strategies in this complex patient population

Building on this, the next chapter examines the role of CT-derived body composition analysis in predicting outcomes. These readily measurable imaging biomarkers, once primarily confined to research, have gained increasing clinical relevance over the past decade and have been a particular area of interest at St Mark's in the primary colorectal cancer population, as evidenced by the work from Malietzis and Pring *et al.*[363,383–386]. A detailed analysis was therefore undertaken to explore their potential utility in guiding prognosis and perioperative optimisation.

Chapter 9: The influence of body composition on outcomes following pelvic exenteration for locally advanced and locally recurrent rectal cancer

9.1 Introduction

As previously discussed and demonstrated in chapters 5 through 8, a number of factors, including those related to the resection, tumour and patient factors, have been shown to influence outcome in exenteration surgery. Host factors such as body composition have been of increasing interest over the past decade and have been shown to influence prognosis in patients with different malignancies [229,233,235,253,387]. Sarcopenia and myosteatosis (fatty infiltration of muscle) influence both short and long-term outcomes in patients with primary colorectal cancer and have been demonstrated in a large cohort of patients with colorectal cancer treated at St Mark's Hospital [234,235,253]. However, there is limited data available regarding its influence on outcomes following exenteration surgery for LARC or LRRC.

Assessment of body composition can be achieved using a number of different methods including the use of computerised tomography (CT), magnetic resonance imaging, dual-energy X ray or bioimpedance analysis. Patients undergoing assessment for colorectal cancer routinely undergo CT imaging to assess tumour stage during the preoperative period and for disease surveillance thereafter. Therefore, the use of CT imaging to study body composition in patients with primary colorectal cancer is most frequently reported. The assessment of area (cm2) of visceral adipose tissue and skeletal muscle at the level of the third lumbar vertebrate (L3) in the axial plane on CT has demonstrated good correlation with whole body adipose tissue and skeletal muscle in both cancer and non-cancer populations[229,388].

This study aimed to assess the influence of body composition profiles derived from CT imaging on short term outcomes following surgery (postoperative complications, readmission, re-operation and early mortality) and survival (overall, disease-free and local-recurrence free survival) following pelvic exenteration for LARC and LRRC.

9.2 Methods

The St Mark's CCC cohort, as previously outlined in chapter 4 was used to analyse the impact of CTBC. CTBC was performed utilising preoperative CT images, including the abdomen and pelvis that were retrieved for each patient from the local Picture Archiving and Communication System (PACS), (*Sectra IDS7, Linköping, Sweden)*. Images were then segmented by the Data Analysis Facility Suite (DAFS), an automated deep learning software (*Voronoi Health Analytics, BC, Canada*). The author (LEG) checked segmentations, following training from a consultant radiologist, and any discrepancies were discussed and resolved with a Consultant Radiologist experienced in automated segmentation. Total skeletal muscle (SM) and visceral adipose tissue (VAT) were quantified as surface areas at the L3 level. The total skeletal cross-sectional muscle area was normalised for stature and reported as the lumbar skeletal muscle index (LSMI). Reduced LSMI indicating sarcopenia was recorded using predefined sex and BMI-specific cut-off values[389] (Table 9.1). The radiodensity (Hounsfield Units (HU)) of all skeletal muscle at the L3 level was used to calculate mean muscle attenuation (MA). Myosteatosis was identified as MA below predefined sex and BMI-specific thresholds for each patient[389]. Sarcopenic obesity was defined as the combination of sarcopenia with a BMI greater than 30kg/m^2 [229]. Visceral obesity was defined as increased VAT using clinically relevant sex-specific thresholds[390].

Table 9.1. Computerised Tomography Body Composition cut off values

	CTBC Measure	Males	Females
Sarcopenia[389]	LSMI (cm^2/m^2)	<43 in BMI <25kg/m^2 <53 in BMI ≧25 kg/m^2	<41 at any BMI
Myosteatosis[389]	MA (mean HU)	<41 in BMI <25 kg/m^2 <33 in BMI ≧25 kg/m^2	<41 in BMI <25 kg/m^2 <33 in BMI ≧25 kg/m^2
Sarcopenic Obesity[229]	LSMI (cm^2/m^2)	<52.4 and BMI ≧30 kg/m^2	<38.5 and BMI ≧30 kg/m^2
Visceral Obesity[390]	VAT (cm^2)	163.8	80.1

Overall survival (OS) was calculated from the month of surgery to the month of death or censor date (5th May 2022). Disease free survival (DFS) was calculated from the date of surgery to the date of radiological, clinical or histopathological diagnosis of distant metastasis or local recurrence (LR), death or censor date. Local recurrence free survival (LRFS) was calculated from the date of surgery to the month of death, LR or censor date. For LRRC the date of the resection of the recurrent tumour was used to calculate these figures.

Statistics

Continuous variables are presented with median and interquartile range [IQR], and categorical data with frequency and percentage. To detect differences between the groups the Mann–Whitney U-test was used for continuous data and Fisher's Exact test or Pearson's Chi-square test for categorical data. Binary logistic regression analysis was performed to assess for association between CTBC profiles and postoperative outcomes, with factors with a p value <0.05 entered into the multivariate model. Cox regression analysis was performed to assess for association between factors and survival. A p-value of less than 0.05 was considered significant. Data were analysed using SPSS software (version 24) (*IBM, Armonk, New York, USA*).

9.3 Results

A total of 388 patients underwent pelvic exenteration for LARC or LRRC during the study period as described in Chapter 4. CTBC was not possible for 147 patients due to scans not being retrievable or unable to be used for analysis, and a further 60 patients had missing data regarding height or weight measurements. Therefore, 181 patients were included in the final analysis, of whom 118 were male (65.2%) with a median age of 58 years (Table 9.2). The majority of patients underwent pelvic exenteration for LARC (130, 72%), with 51 (28.2%) resections performed to treat locally recurrent disease. Most patients received neo-adjuvant oncological therapy prior to exenteration (159, 71.8%). High levels of systemic inflammation, as demonstrated by a raised NLR, were seen in 120 patients (66.3%).

A partial pelvic exenteration was the more commonly performed procedure compared with total pelvic exenteration, with just over a fifth of cases performed by a laparoscopic approach. En bloc pelvic side wall resection was required in 101 (55.8%) cases, and an extended posterior resection was required in 75 (41.4%) of patients. A clear resection margin (R0) was achieved in 161 (89%) of resections. Tumour histopathology demonstrated the presence of venous invasion in 81 patients (44.8%), lymphovascular invasion in 42 patients (23.2%), and node-positive disease in 47 patients (26%).

Table 9.2: Baseline demographics, neoadjuvant therapy, and operative details

	Total		
	181	**Surgical approach**	
Male	118 (65.2)	Laparoscopic	39 (21.5)
Age (median years, IQR)	58 (47.5-66)	Open	139 (76.8)
ASA		Lap converted to open	3 (1.7)
2	151 (83.4)	**Urological resection**	
3	30 (16.6)	Ileal conduit	72 (39.8)
BMI		Boari/ureteric reimplantation	8 (4.4)
Median BMI (kg/m^2,IQR)	25.3 (22.5-29.9)	**Vascular resection**	11 (6.1)
Cancer type		**Lateral pelvic resection**	
LARC	130 (71.8)	Side wall resection (any)	101 (55.8)
LRRC	51 (28.2)	ELSiE[156]	55 (30.4)
Neoadjuvant therapy		**Posterior resection**	
Any	159 (87.8)	Extended posterior resection (any)	75 (41.4)
Chemotherapy only	24 (12.5)	High sacrectomy	18 (9.9)
Chemoradiotherapy	57 (31.5)	Distal sacrectomy	20 (11)
Short course Radiotherapy	7 (3.9)	HiSS[153]	18 (9.9)
Total neoadjuvant therapy	68 (37.6)	Subperiosteal resection	19 (10.5)
No therapy	22 (12.2)	**Tumour characteristics**	
Systemic inflammation		Well/moderately differentiated	166 (91.7)
NLR >3.0 (n=180)	120 (66.3)	Poorly differentiated	15 (8.3)
mGPS >0 (n=146)	45 (24.9)	Positive lymph nodes	47 (26.0)
Resection magnitude		Lymphovascular invasion	42 (23.2)
Partial pelvic exenteration	116 (64.1)	Venous invasion	81 (44.8)
Total pelvic exenteration	65 (35.9)		

Body composition parameters

In females the median intra-abdominal VAT area was 76.5cm^2 (IQR 33.5, 120.0), median LSMI was 39.2 cm^2 (IQR 33.6, 42.8) and median MA 37.8HU (IQR 31.8, 47.0). In males median VAT area was 163.2 cm^2 (IQR 91.5, 248.6), median LSMI 44.4 cm^2 (IQR 39.2, 51.7) and median MA 41.4HU (IQR 33.5-47.2). The body composition profiles using sex-specific cut offs are shown in Table 9.3.

Table 9.3: CT Body Composition profiles for all patients with LARC and LRRC undergoing pelvic exenteration

Body composition	Definition and patient number (%)
Sarcopenia	Lumbar skeletal muscle index <43cm^2/m^2 in BMI <25kg/m^2, and <53cm^2/m^2 in BMI ≧25 kg/m^2 in males, <41cm^2/m^2 in females at any BMI
Yes	114 (63.0)
No	67 (37.0)
Myosteatosis	Mean muscle attenuation <41 mean HU in BMI <25 kg/m^2 and <33 mean HU in BMI ≧25 kg/m^2
Yes	66 (36.5)
No	115 (63.5)
Sarcopenic obesity	Lumbar skeletal muscle index <52.4cm^2/m^2 and BMI ≧30 kg/m^2 in males and <38.5cm^2/m^2 and BMI ≧30 kg/m^2 in females
Yes	12 (6.6)
No	169 (93.4)
Visceral Obesity	Visceral adipose tissue of 163.8cm^2 in males or 80.1cm^2 in females
Yes	89 (49.2)
No	92 (50.8)
BMI obesity	Body mass index of >30kg/m^2
Yes	44 (24.3)
No	137 (75.7)

Sarcopenia was present in 114 patients (63.0%) and was associated with increasing age (53.2% <55 years vs 70.2% >55 years p0.029) (Table 9.4). Myosteatosis was present in 66 patients (36.5%) and was also associated with increasing age (24.7% <55 years vs 45.2% >55years, p=0.005). The incidence of myosteatosis was significantly greater in ASA 3 patients compared with ASA 2 (60% vs 31.8%, p0.006). Both sarcopenia and myosteatosis were present in 42 patients (23%) (Table 9.5). Sarcopenic obesity was present in only 12 patients (6.6%) and had a higher incidence in ASA 3 patients (20% vs 4 %, p=0.006). However, 48 patients (26.5%) had both sarcopenia and visceral obesity. Visceral obesity was seen in 89 patients (49.2%) and was also more frequently observed in ASA 3 patients compared with ASA 2 (66.7% vs 45.7%, p=0.045). No association was found between CT body composition profiles and sex, systemic inflammation (NLR/mGPS), primary or recurrent disease or tumour characteristics.

Table 9.4: Association between CT-derived body composition profiles and patient factors, systemic inflammation and neoadjuvant therapy using Fisher's Exact test, p values presented.

	Sarcopenia	Myosteatosis	Visceral Adiposity	Sarcopenic obesity
Age >55	**0.020**	**0.005**	0.293	0.241
Sex	0.519	0.521	0.876	0.547
ASA 3	0.685	**0.006**	**0.045**	**0.006**
NLR>3	0.143	0.623	0.875	1.000
mGPS>=1	0.580	0.468	1.000	0.275
Neoadjuvant therapy	0.645	0.096	1.000	1.000

Table 9.5: The inter-relation of different CT-derived body composition profiles for all patients with LARC and LRRC

	Sarcopenia	Myosteatosis	Visceral Adiposity	Sarcopenic obesity
Total	**114 (63%)**	**66 (36.5%)**	**89 (49.2%)**	**12 (6.6%)**
Sarcopenia		42 (23%)	48 (26.5%)	
Myosteatosis	42 (23%)		37 (20.4%)	6 (3.3%)
Visceral Adiposity	48 (26.5%)	37 (20.4%)		11 (6.1%)
Sarcopenia obesity		6 (3.3%)	11 (6.1%)	

Short term outcomes

Overall, the median length of stay was 19 days (IQR 11,29) with 112 patients (61.9%) experiencing a postoperative complication, of which 49 patients (27.1%) had a major complication defined as Clavien Dindo grade III or above (Table 9.6). Three patients (1.7%) died within 30 days of surgery. Twenty-two patients (12.2%) returned to theatre within 30 days and 23 patients (12.7%) were readmitted within 30 days of discharge.

Patients with myosteatosis (p=0.002) and visceral obesity (p=0.041) experienced significantly longer postoperative hospital stays. Myosteatosis, visceral obesity and BMI obesity were all

significantly associated with any 30-day postoperative complication on univariate analysis. Myosteatosis and BMI obesity retained significance on multivariate analysis with hazard ratios of 1.97 (95%CI 1.01-3.83, p0.047) and 2.19 (95%CI 1.17-4.10, p0.014), respectively. However, only myosteatosis was associated with increased 30-day major complications (Clavien Dindo grade III or above) with a HR 2.31 (95%CI 1.12-4.52, p=0.014). No CTBC profiles were associated with 30-day mortality, but myosteatosis was associated with increased 90-day mortality, HR 9.34 (95%CI 1.07-81.79, p0.043). BMI Obesity was associated with increased 30-day readmissions, HR 3.44 (95%CI 1.40-8.50, p=0.007). Sarcopenia and sarcopenic obesity were not associated with worse postoperative outcomes in this cohort.

Table 9.6 : Body composition profiles and short-term outcomes

	Length of stay (days)		30-day complication (any, C-D I-V) (%)				30-day major complication (C-D III+) (%)		30-day mortality (%)		90-day mortality (%)		Return to theatre (%)		Readmission within 30 days (%)	
Total (%)			112 (61.9)				49 (27.1)		3 (1.7)		6 (3.3)		22 (12.2)		23 (12.7)	
			Univariate		Multivariate		Univariate		Univariate		Univariate		Univariate		Univariate	
	Median (IQR) 19 (11,29.5)	p-value+	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value	HR (95%CI)	p-value
Sarcopenia	19 (11,30)	0.660	1.05 (0.56-1.95)	0.88			1.02 (0.52-2.00)	0.962		0.997		0.997	1.30 (0.50-3.37	0.591	0.90 (0.37-2.21)	0.822
Myosteatosis	22.5 (14,42)	**0.002**	2.13 (1.1-4.09)	**0.024**	1.97 (1.01-3.83)	**0.047**	2.31 (1.12-4.52)	**0.014**	3.56 (0.32-40.06)	0.303	9.34 (1.07-81.79)	**0.043**	1.53 (0.62-3.77)	0.352	2.10 (0.87-5.07)	0.099
Sarcopenic obesity	20 (16,28)	0.576	0.85 (0.26-2.80)	0.79			0.52 (0.11-2.46)	0.409	0.51 (0.05-5.74)	0.587	0.20 (0.02-1.72)	0.143	1.58 (0.64-3.90)	0.324	2.13 (0.85-5.30)	0.105
Visceral obesity	20 (13,35)	**0.041**	2.37 (1.27-4.35)	**0.007**	2.19 (1.17-4.10)	**0.014**	1.24 (0.64-2.39)	0.524		0.999		0.999	1.49 (0.30-7.29)	0.623	2.48 (0.62-9.95)	0.199
BMI obesity	20 (14,34)	0.252	2.17 (2.02-4.64)	**0.047**	1.33 (0.53-3.34)	0.538	1.17 (0.55-2.47)	0.691		0.998		0.998	1.53 (0.58-4.03)	0.393	3.44 (1.40-8.50)	**0.007**

+ Mann Whitney U test

In Chapter 7, the clinical factors associated with postoperative morbidity were analysed. In patients with LARC, on univariate analysis, NLR>3.0, hypertension and ASA3 were significantly associated with a postoperative complication of any grade. When this is combined with visceral obesity and myosteatosis, visceral obesity only retains significance on combined multivariate analysis (Table 9.7). A multivariate analysis for major complications in LARC was not possible due to too few events for the number of significant factors on univariate analysis.

Table 9.7: Multivariate analysis of significant clinical and CT body composition profile factors associated with postoperative complications in LARC of any grade (Clavien-Dindo grade 1-4)

	LARC	
	Multivariate	
	HR (95%CI)	p value
Myosteatosis	1.16 (0.51-2.67)	0.726
Visceral obesity	2.41 (1.12-5.16)	**0.023**
NLR >3.0	1.40 (0.61-3.21)	0.434
Hypertension	2.81 (0.85-9.34)	0.092
ASA 3	3.36 (0.89-12.73)	0.075

For patients with LRRC the significant clinical factors in chapter 7 associated with postoperative complications of any grade in LRRC were anaemia and male sex. On combined analysis with CT body composition profiles only anaemia retained significance (Table 9.8). A multivariate analysis for major complications in LRRC was also not possible due to too few events for the number of significant factors.

Table 9.8: Multivariate analysis of significant clinical and CT body composition profile factors associated with postoperative complications in LRRC of any grade (Clavien-Dindo grade 1-4)

	LRRC	
	Multivariate	
	HR (95%CI)	p value
Myosteatosis	3.68 (0.76-14.75)	0.105
Visceral obesity	1.90 (0.42-8.61)	0.450
Anaemia	9.85 (1.12-87.84)	**0.040**
Sex (male)	3.83 (0.90-16.23)	0.068

Long term outcomes

Fifty-six patients (30.9%) developed disease recurrence, with 13 patients (7.2%) having local recurrence only at a median of 8 months (IQR 5, 17 months). 36 patients (19.9%) developed distant metastases, and 7 patients (3.9%) had both local and distant disease (Table 9.9). The median 5-year OS, DFS and LRFS were 121 months (95% CI 52 to 190), 81 months (95%CI 68-93), 102 months (95% CI 41-163), respectively. No CTBC profiles influenced survival. However, there was a trend toward reduced LRFS in patients with myosteatosis (p=0.070).

Table 9.9: Cox regression analysis of body composition profiles and long-term outcomes

	OS		**DFS**		**LRFS**	
		p-value		p-value		p-value
Sarcopenia	1.54 (0.76-3.13)	0.225	1.04 (0.64-1.68)	0.885	1.23 (0.67-2.34)	0.528
Myosteatosis	1.69 (0.88-3.26)	0.119	1.36 (0.85-2.18)	0.205	1.74 (0.96-3.17)	0.070
Sarcopenic obesity	0.92 (0.22-3.83)	0.902	1.00 (0.40-2.48)	0.999	0.64 (0.16-2.66)	0.542
Visceral obesity	0.91 (0.46-1.77)	0.769	1.28 (0.80-2.05)	0.298	1.11 (0.61-2.04)	0.715
BMI obesity	0.76 (0.34-1.67)	0.492	1.30 (0.78-2.16)	0.321	0.98 (0.49-1.96)	0.961

OS: Overall Survival, DFS: Disease Free Survival, LRFS: Local Recurrence Free Survival

9.4 Discussion

The associations between sarcopenia, myosteatosis, visceral obesity and outcomes in primary colorectal cancer are well established[229,234,235,389,391,392]. This study aimed to assess whether these relationships exist in the more unique group of patients with locally advanced and recurrent rectal cancer undergoing exenteration surgery. This group of patients have a greater burden of disease, involving more organ systems and crossing multiple tissue fascial planes. The short- and long-term outcomes of 181 patients undergoing pelvic exenteration for LARC or LRRC were assessed. As anticipated these data demonstrate that a high proportion of patients have aberrant body composition profiles as measured by CT. These data suggest that

proportionally this patient population has a similar incidence of sarcopenia, visceral obesity and high BMI when compared with published series of primary colorectal cancers from St Mark's Hospital, but a lower incidence of myosteatosis (36.5% vs 77%)[235] .

In primary colorectal cancers, myosteatosis presages worse short and long-term outcomes[235]. There is evidence to support that these patients have a more inflammatory tumour type, which may exert a greater systemic effect on the host, leading to immune dysfunction in this group [363,383]. Interestingly, the effect of myosteatosis on outcome appears to be restricted to short-term outcomes in the LARC/LRRC cohort and doesn't exert an effect on long-term outcome in this cohort. This may support the concept of a temporary state of immunomodulation and suppression, which resolves over time once the instigating factors are removed, for example, when the tumour is resected from the host. Despite more anatomically advanced tumours, a more profound response of the host in terms of body composition was not observed. It could therefore be asserted that these tumours are no more inflammatory than the primary disease, or alternatively, only a set proportion of tumours behave in an inflammatory fashion irrespective of size of recurrence. It may be that only tumours which invoke myosteatosis from their outset are responsible for myosteatosis once the tumour leaves the bounds of the mesorectum. Further cellular and molecular work on the tumours in patients with myosteatosis is required to ascertain what it is within these tumours that drive myosteatosis and poor prognosis.

Sarcopenia appeared to exert a lesser effect on outcome in this population compared with primary rectal cancer[234,235]. Sarcopenia is associated with numerous factors and perhaps is less determined by the disease than myosteatosis. It may be considered a premorbid state and has been shown to be associated with factors such as deprivation in both cancer and non-cancer populations[385,393]. Sarcopenia also increases with age, and importantly, the exenteration population is usually younger and, by nature of the surgery, deemed fit enough to cope with the insult of major pelvic surgery. There is, therefore, an element of selection bias in this group, which may be less apparent than in the primary cancer population.

Obesity was also influential in terms of short-term outcome; there could be a number of reasons to explain this. Firstly, the technical aspects of surgery are more challenging in the obese patient. This increased technical difficulty may be related to increased intraoperative blood loss, longer operation times, increased transfusion requirement, poorer specimens with mesenteric breeches and cancer cell shedding[394]. These factors need to be looked at in more

detail in future as they may confound the results in relation to BC. Secondly, obesity also affects metabolic status; obese patients have a chronic low-grade inflammatory state. This inappropriate activation of the immune system may hinder host immune responses in the postoperative period[395]. Immunosuppression by obesity, particularly in relation to metabolic disease states such as diabetes or the metabolic syndrome, may also have an important impact on the host's ability to effectively cope with the effects of tumour shedding and subsequent implantation, although this is not represented in the long-term outcome data in this study population[396]. Interestingly, visceral obesity exerted a stronger influence on short-term postoperative complications in patients with locally advanced rectal cancer than other clinical factors, such as ASA grade 3, NLR > 3, or hypertension. This finding underscores the important role of body composition, particularly visceral adiposity, in determining postoperative morbidity among cancer patients.

Sarcopenic obesity, the presence of sarcopenia and a BMI greater than 30kg/m^2, which has previously been shown to have a deleterious effect in terms of cancer outcomes, appears to play a far less important role in short- and long-term outcomes in LARC and LRRC[235]. Once again, this may in part be due to selection bias in this patient population. There are relatively few patients in this population with sarcopenic obesity, and therefore, the results may be subject to Type 2 error.

Limitations of this study include its retrospective data collection. Only patients who are suitable to undergo pelvic exenteration are included; therefore, the body composition profiles may not be fully representative of all patients with LARC/LRRC. Not all patients who underwent PE during the study period were included due to missing data from imaging or anthropometry. Data regarding perioperative nutritional status and functional assessments were not included, and we believe that these measures would be important to assess in future studies. Future research directed to improving postoperative outcomes for patients undergoing pelvic exenteration is required, and the influence of prehabilitation and targeted nutritional support in those patients with aberrant body composition profiles may help to achieve this.

9.5 Conclusion**s**

This study demonstrates that abnormal body composition profiles, particularly myosteatosis and visceral obesity, are common among patients undergoing pelvic exenteration for LARC and LRRC. Myosteatosis was associated with increased postoperative morbidity, while visceral obesity independently predicted postoperative complications in patients with LARC. In contrast, sarcopenia and sarcopenic obesity exerted little influence on either short- or long-term outcomes in this cohort, suggesting that their effects may be attenuated in a highly selected surgical population deemed fit for exenteration. No body composition parameter significantly impacted overall, disease-free, or local recurrence-free survival, although a trend toward reduced local recurrence-free survival was observed in patients with myosteatosis. These findings highlight the importance of considering host-related factors such as visceral adiposity and muscle quality, in addition to traditional clinical and pathological variables, when assessing surgical risk and recovery potential. Future studies incorporating longitudinal and molecular analyses may help clarify the mechanisms linking altered body composition with adverse outcomes. Optimising preoperative fitness through targeted prehabilitation and nutritional interventions offers a promising strategy to mitigate risk and improve outcomes in this complex patient group.

Chapter 10: Histological evaluation of tumour characteristics of locally recurrent rectal cancer specimens

10.1 Introduction

As discussed in previous chapters 5-10% of patients will present with LRRC [397,398]. There is no standard reporting of resected recurrent tumour specimens, and when the usual reported pathological factors for primary rectal cancer are applied, there is limited evidence that these factors influence survival, as demonstrated in the review of the literature in Chapter 3. In contrast to primary rectal cancer, locally recurrent tumours are relatively rare, exist in difficult to access areas within the pelvis and often require exenteration surgery by a specialised team to permit complete resection. This means that large cohorts of these tumours do not exist and therefore, historically, are a difficult group to study. In the CCC cohort, limited pathological factors appear to influence outcomes for patients with LRRC, as demonstrated in Chapters 7 and 8.

Currently, all methods employed to stratify tumours at risk of local recurrence relate to clinical and pathological staging criteria, including, for example, tumour stage, nodal stage, and margin status. There are no additional known molecular biomarkers of local recurrence, despite a widely held view among clinicians that these tumours behave differently from the majority of rectal cancers and represent a specific phenotype. Within the current literature, the predominant determinant of survival has been shown to be achieving a negative resection margin following pelvic exenteration for either LARC or LRRC[134,141]. However, locally recurrent rectal cancer that progresses to salvage surgery appears to constitute a biologically distinct subset with a marked propensity for further local failure, even after technically complete resection. This suggests that LRRC may possess inherent biological features predisposing it to local recurrence, yet the underlying "local recurrence phenotype" remains poorly defined. Research to date has largely focused on surgical outcomes such as the resection margin, rather than on elucidating the molecular or pathological mechanisms that underpin this behaviour. A more detailed understanding of tumour morphology, genomic and transcriptomic expression

profiles, and their interaction with the host and pelvic microenvironment may help clarify why these tumours recur and identify new strategies to mitigate the risk of further local failure.

There is a growing understanding of the interaction between the immune system and tumour activity. The host immune response is thought to influence tumour behaviour and growth[399]. There is evidence of the impact of both local tumoural inflammatory signalling and systemic inflammation, as measured by modified Glasgow Prognostic Score (mGPS) and Neutrophil:lymphocyte ratio (NLR), on survival and recurrence in patients with colorectal cancer (CRC)[243]. Features readily assessed using H&E images, such as tumour stromal percentage, tumour necrosis and peritumoural inflammatory cell infiltrates, have been shown to be negative predictors of survival in patients with primary CRC[215,400,401]. These characteristics have not been evaluated in LRRC, but due to the poorer prognosis of these tumours, it was hypothesised that local recurrent tumours would exhibit a more aggressive or poorer prognostic phenotype, namely lower levels of lymphocytic or inflammatory infiltrate, higher levels of tumour necrosis and higher stromal volume.

This study aims to characterise the tumour characteristics and tumour microenvironment on haematoxylin and eosin (H&E) based assessments of a unique cohort of patients who have undergone curative resection of LRRC by pelvic exenteration at a tertiary referral centre. There is currently no published literature looking at these factors in LRRC. By investigating these features further in tumour specimens and comparing them with long-term outcomes, the aim is to identify specific risk factors for recurrence. Comparisons are made with a separate cohort of primary rectal cancers. Defining poor prognostic subtypes in this population may aid improved risk stratification and the development of novel targeted strategies. This study will also enable the development of a tissue cohort for this unique group, which will be used for this study and future work.

10. 2 Materials and methods

Patients were identified from the prospectively maintained database of all complex cancer resections performed at St Mark's Hospital, as described in Chapter 4. All patients who had undergone pelvic exenteration for LRRC between January 2008 and April 2017 were identified to allow for a 5-year follow-up period. Patients were excluded if they had undergone a palliative or abandoned resection or if tumour blocks of the resected specimen were unavailable.

Baseline demographics and reported histopathological details of the tumour specimens were collated. History of neoadjuvant oncological treatment was recorded. Data were validated with Cancer Registry data (Office for Data Release, Public Health England). Preoperative levels of haemoglobin, platelet count, neutrophils, lymphocytes, albumin and C-Reactive Protein were recorded from blood taken within two weeks of resection. Standard thresholds for anaemia were used (Hb: 130g/L in males, 120g/L in females)[312]. Cut-off values of 3.0 for neutrophil-lymphocyte ratio (NLR) and 400 for platelet count were used as these have been demonstrated to be clinically significant thresholds in the literature in patients with colorectal cancer[302,314,402]. For patients with available CRP and albumin results the modified Glasgow Prognostic score was calculated[242].

Overall survival (OS) was calculated from the month of resection of the recurrence to the month of death or the censor date of 5th May 2022. Disease-free survival (DFS) was calculated from the date of resection of the recurrent tumour to the date of radiological or histopathological diagnosis of subsequent local re-recurrence or metastatic disease, death or censor date. Local recurrence-free survival (LRFS) was calculated from the date of resection of the recurrence to the month of death, local re-recurrence or censor.

Formalin fixed paraffin embedded blocks were selected for each patient, sectioned and stained with H&E and scanned. Scans were then reviewed by colorectal specialist consultant histopathologists, and cases with unusable slides due to poor staining, no viable tumour or severe distortion were excluded prior to analysis. H&E-stained sections were assessed for tumour stroma percentage (TSP), tumour necrosis, mucin percentage, and peritumoral cellular infiltrates using Klintrup–Mäkinen grading[240].

TSP was semi quantitatively assessed by two investigators (LEG, KP) who were blinded to the clinical outcomes as previously described in the literature[215]. Representative sections of the invasive margin were used to make this assessment. Tumour sections were scanned using the Hamamatsu NanoZoomer (Welwyn Garden City, Hertfordshire, UK). Using x5 magnification a representative area of the tumour front was selected. Using x10 magnification, ensuring tumour cells were within all four sides of the image, the field was assessed. A percentage score of stroma within the tumour area was estimated to the nearest 5% for each image field. Samples were then classified as either low (<50%) or high (>50%) TSP. All samples were scored by a

single investigator (LEG) with corroboration of scores by a second assessor (KP) to ensure consistency. The interobserver intraclass correlation coefficient was 0.725 for TSP grouping. Discrepancies for the assessment of TSP group were resolved by discussion between the two investigators to reach a consensus opinion.

Inflammatory infiltrates at the invasive margin of the tumour were semi-quantitatively assessed using the Klintrup–Mäkinen grade as previously described[240]. Again, the invasive margin of the tumour was used to assess the inflammatory cell reaction on H&E-stained sections. The four-point scale used to grade the inflammatory cell density (0- no increase in inflammatory cells, 1-mild patchy increase in inflammatory cells, 2-band-like infiltrate of inflammatory cells, 3-very prominent cup-like reaction with destruction of tumour islets) was subsequently classified into low (0-1) and high grade (2-3) for each tumour specimen. All samples were scored by a single investigator (LEG) with corroboration of scores by a second independent assessor (KP) to ensure consistency and discrepancies resolved by discussion. The interobserver intraclass correlation coefficient was for KM grade was 0.80.

Tumour necrosis was examined on each section as previously described by Richards *et al.* Sections were initially examined at x40 magnification to look for evidence of tumour necrosis and graded as absent, focal (<10% of tumour area), moderate (10-30% of tumour area) and extensive (>30% of tumour area)[401] . This was scored by a single investigator (LEG), and once again, a second independent investigator (KP) co-scored the cohort with an interobserver intraclass correlation coefficient of 0.87.

The percentage of mucin present was semi-quantitatively assessed for each specimen as described by Li et al[403]. Tumour sections were examined, and the percentage of mucin was assessed. All specimens with 5% or greater of mucin were classified as having mucinous features, and cases with no mucin or less than 5% were considered to be standard rectal cancers, a classification previously described in patients with primary rectal cancer[403].

A comparative cohort of patients with primary rectal cancer from a dataset of patients treated in Scotland (Glasgow Royal Infirmary, Western Infirmary, Gartnavel General and Stobhill Hospitals) were used to compare the key tumour microenvironment factors between recurrent and primary rectal cancers. These patients had undergone elective rectal cancer resection with curative intent between 1997 – 2013. A total of 393 patients with stage I-III primary rectal

cancer were included in this dataset. H&E assessment of the tumour microenvironment factors was carried out using the same methodology described for this study by Ross McMahon, (University of Glasgow PhD research fellow) who consents to its use in this thesis.

Ethical approval

Use of the prospective database for research was given approval by the NHS Health Research Authority (HRA), UK with ethical approval from the South East London NHS Research Ethics Committee (reference number: 12/LO/1556). Use of tumour specimens for research was given approval by HRA with ethical approval from Health and Care Research Wales Ethics Committee (reference number: 21/EE/0058). The West of Scotland Research Ethics Committee provided ethical approval for the research of the primary rectal cancer cohort.

Statistical analysis

Continuous variables are presented with median and interquartile range (IQR), and categorical data with frequency and percentage. Differences between groups were detected using Fisher's Exact test or Pearson's Chi square test for categorical data and the Mann–Whitney U-test for continuous data. Kaplan-Meier survival plots were performed and differences between groups assessed using a log rank test. A p-value of less than 0.05 was considered significant. Data were analysed using SPSS software (version 24) (IBM, Armonk, New York, USA).

10. 3 Results

During the study period there were 39 LRRC patients who met the inclusion criteria. One patient was excluded as the tumour blocks were unavailable. A further 11 patients were excluded following sectioning and staining due to either tissue fragmentation or no viable tumour visible on the block leaving 27 patients included in the final analysis.

The majority of patients were male (n=20, 74%) with a median age of 63 years (Table 10.1). Prior to resection of the recurrent tumour 16 patients (59.3%) received oncological treatment with most patients receiving long course chemoradiation (n=9, 33.3%). Tumour regression was reported for 8 of these patients, 4 patients had minimal or no tumour regression and 4 had moderate tumour regression. The median time to recurrence from primary cancer resection was 20 months (IQR 14-47 months). A raised NLR (>3.0) and mGPS ≧1 were present in 59% and 56% respectively demonstrating a systemic inflammatory response in the majority of these

patients. Data was available to calculate both NLR and mGPS for 20 patients, of which 8 (40%) had both NLR >3.0 and mGPS ≧1.

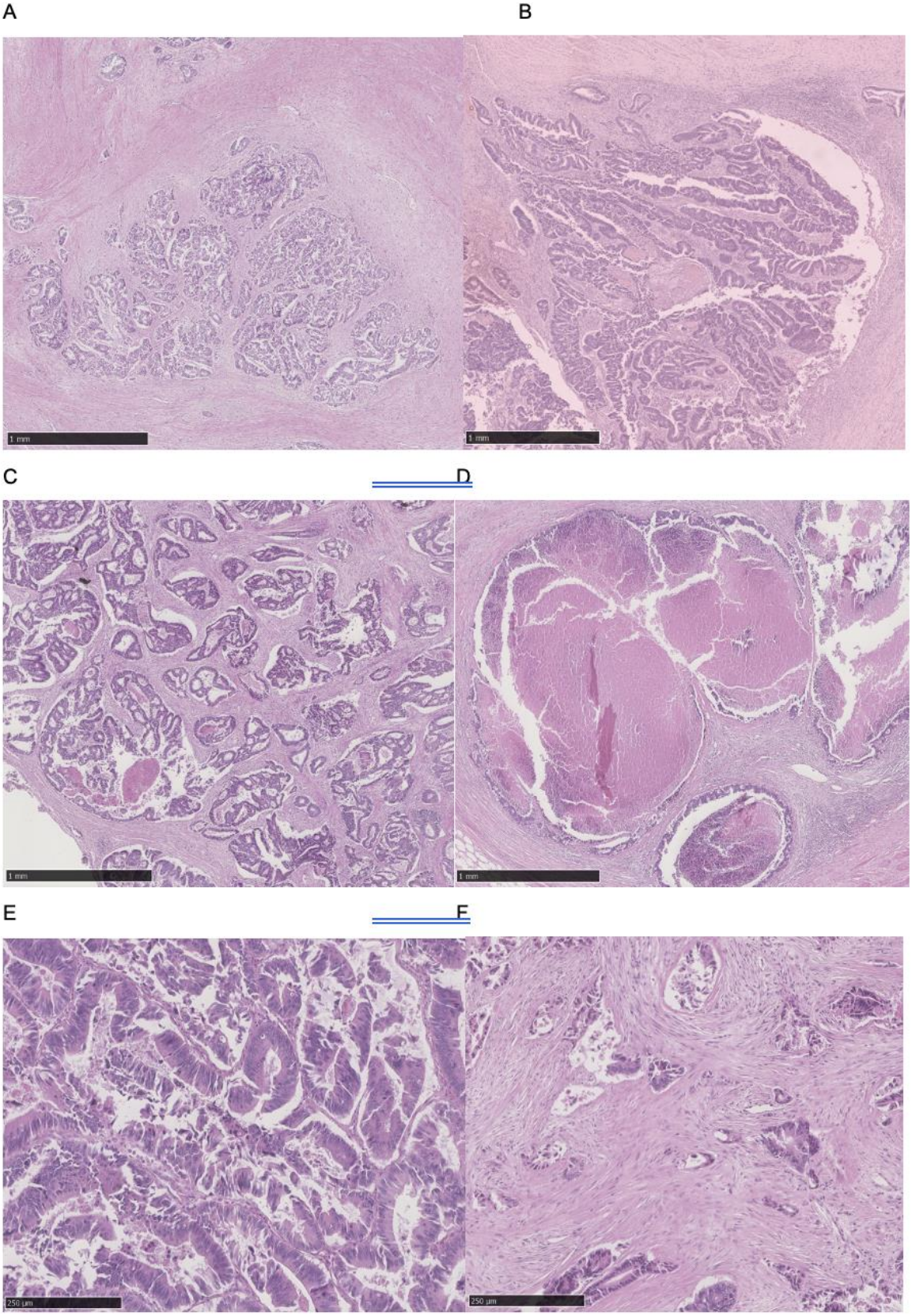
Table 10.1: Baseline characteristics and histology of resected tumour

Demographics	Total (n=27)		Histology	Total (n=27)
	N (%)			N (%)
Male	20 (74.1)		Positive lymph nodes	6 (22.2)
Age, median years (IQR)	63 (59,67)		Lymphatic invasion	5 (18.5)
<55years	5 (18.5)		Venous invasion	16 (59.3)
55-75 years	19 (70.4)		Perineural invasion	14 (51.9)
>75 years	3 (11.1)		Resection margin	
ASA			R0	20 (74.1)
1	1 (3.7)		R1	5 (18.5)
2	18 (66.7)		R2	2 (7.4)
3	8 (29.6)			
Neoadjuvant therapy (within 6 months of surgery for recurrence)			Histological characteristics (n=25)	
Chemotherapy only	3 (11.1)		Differentiation	
Chemoradiotherapy	9 (33.3)		Poor	5 (18.5)
Short course Radiotherapy	3 (11.1)		Moderate/well	20 (74.1)
Total neoadjuvant therapy	1 (3.7)			
No therapy	11 (40.7)		Tumour diameter (median, mm)	50 (40, 70)
Preoperative blood results			Recurrence	
Anaemia	9 (33.3)		Distant metastasis only	2 (7.4)
Plts >400	2 (7.4)		Local recurrence only	7 (25.9)
NLR >3.0	16 (59.3)		Both local and distant	4 (14.8)
mGPS (n=16)			None	14 (51.9)
0	7 (43.8)			
1	6 (37.5)		Overall Survival	
2	3 (18.8)		5-year survival	18.5%

A complete resection (R0) was achieved in 20 patients (74%), with 5 (18.5%) R1 resections and 2 (7.4%) R2 resections. Involved lymph nodes were identified in 6 patients (22%), venous invasion in 16 patients (59%) and perineural invasion in 14 patients (52%). During the follow up period 13 patients developed recurrence (48%): 2 (7%) with distant metastasis only, 7 (26%) with local recurrence only and 4 patients (15%) with both local and distant disease. The overall survival rate at 5 years was 18.5% with 12 (55%) cancer related deaths, 8 (36%) non cancer related and 2 (9%) unknown causes of death.

Following assessment of the H&E-stained tumour blocks, the TSP was shown to be high in 19 (70%) patients. The Klintrup–Mäkinen grade was weak in almost all patients (n=25, 93%). A tumour mucin percentage was greater than 5% in 9 (33%) cases, and there was a high tumour necrosis percentage (>30%) in 8 patients (30%). Examples of the histological appearances of these tumours are demonstrated in Figure 10.1.

Figure 10.1: Spectrum of peritumoral inflammation: A. Low grade inflammatory cell infiltration B High Klintrup–Mäkinen grade. Examples of tumour necrosis: C Focal necrosis D Extensive necrosis. Spectrum of tumour stroma: E Low tumour stroma ratio F High tumour stroma ratio



There was no significant association of any of these factors with the incidence of re-recurrent disease (Table 10.2). When comparing these four tumour factors against age and sex, there were no significant differences between groups (Table 10.3). Oncological therapy prior to resection of recurrent disease was the same across groups. Preoperative inflammation-based scores including mGPS and NLR did not significantly differ across these tumour characteristics. When comparing histological characteristics of the resected tumours, a high TSP was significantly associated with venous invasion (74% vs 25%, p=0.033) and perineural invasion (74% vs 0%, p<0.001). Low tumour necrosis percentage was also associated with venous invasion (74% vs 25%, p=0.033). No significant associations were identified between Klintrup–Mäkinen grade or tumour necrosis percentage and other routinely reported histological characteristics. Lymphatic invasion, cellular differentiation and resection margin status were not significantly associated with the tumour characteristics assessed. A shorter time to recurrence from resection of the primary tumour was seen in patients with low TSP compared with high (75% v 22%, p=0.026).

Table 10.2: Tumour microenvironment and morphology characteristics

	Tumour stroma percentage			Klintrup–Mäkinen grade			Tumour mucin percentage			Tumour necrosis percentage		
	Low	High	p value	Weak (0-1)	Strong (2-3)	p value	<5%	>5%	p value	<30%	>30%	p value
Totals	8 (29.6)	19 (70.4)		25 (92.6)	2 (7.4)		18 (66.7)	9 (33.3)		19 (70.4)	8 (29.6)	
Recurrence												
None	5 (62.5)	9 (47.4)	0.678	12 (48.0)	2 (100.0)	0.270	9 (50.0)	5 (55.6)	1.00	9 47.4)	5 (62.5)	0.678
Any	3 (37.5)	10 (52.6)		13 (52.0)	0		9 (50.0)	4 (44.4)		10 (52.6)	3 (37.5)	

Table 10.3: Demographics, neoadjuvant therapy and tumour histopathology

	Tumour stroma percentage			Klintrup–Mäkinen grade			Tumour mucin percentage			Tumour necrosis percentage		
	Low	High	p value	Weak	Strong	p value	<5%	>5%	p value	<30%	>30%	p value
Totals	8 (29.6)	19 (70.4)		25 (92.6)	2 (7.4)		18 (66.7)	9 (33.3)		19 (70.4)	8 (29.6)	
Demographics												
Age >55 years	6 (75.0)	16 (84.2)	0.616	21 (84.0)	1 (50.0)	0.342	15 (83.5)	7 (77.8)	1.000	14 (73.7)	8 (100.0)	0.144
Male	7 (87.5)	13 (68.4)	0.633	19 (76.0)	1 (50.0)	0.459	14 (77.8)	6 (66.7)	0.653	13 (68.4)	7 (87.5)	0.301
Preoperative bloods												
mGPS >1	2 (50.0)	7 (58.3)	0.608	8 (53.3)	1 (100.0)	0.563	6 (54.5)	3 (60.0)	1.000	7 (58.3)	2 (50.0)	1.000
Anaemia	3 (37.5)	6 (31.6)	1.000	8 (32.0)	1 (50.0)	1.00	8 (44.4)	1 (11.1.0	0.193	6 (31.6)	3(37.5)	1.000
NLR >3	5 (62.5)	11 (57.9)	1.000	14 (56.0)	2 (100.0)	0.499	11 (61.1)	5 (55.6)	1.000	11 (57.9)	5 (62.5)	1.000
Time to recurrence												
<18months	6 (75.0)	4 (22.2)	**0.026**	8 (33.3)	2 (100.0)	0.138	7 (41.2)	3 (33.3)	1.000	7 (38.9)	3 (37.5)	1.000
>18 months	2 (25.0)	14 (77.8)		16 (66.7)	0		10 (58.8)	6 (66.7)		11 (61.1)	5 (62.5)	
Neoadjuvant												
No	4 (50.0)	7 (36.8)	0.675	9 (36.0)	2 (100.0)	0.157	9 (50.0)	2 (2.2)	0.231	7 (36.8)	4 (50.0)	0.675
Yes	4 (50.0)	12 (63.2)		16 (64.0)	0		9 (50.0)	7 (77.8)		12 (63.2)	4 (50.0)	
Histology												
Positive lymph nodes	1 (12.5)	5 (26.3)	0.633	6 (24.0)	0	0.651	2 (11.1)	4 (44.4)	0.136	6 (31.6)	0	0.092
Lymphatic invasion	1 (12.5)	4 (21.1)	1.000	5 (20.0)	0	1.000	2 911.1)	3 (33.3)	0.295	4 (21.1)	1(12.5)	1.000
Venous invasion	2 (25.0)	14 (73.7)	**0.033**	16 (64.0)	0	0.157	11 (61.1)	5 (55.6)	1.000	14 (73.7)	2 (25.0)	**0.033**
Perineural invasion	0	14 (73.7)	**<0.001**	14 (56.0)	0	0.222	9 (50.0)	5 (55.6)	1.000	11 (57.9)	3 (37.5)	0.420
Differentiation												
Poor	1 (12.5)	4 (22.2)	1.000	5 (20.8)	0		2 (11.8)	3 (33.3)	0.302	3 (16.7)	2 (25.0)	0.628
Moderate/well	7 (87.5)	14(77.8)		19 (79.2)	2 (100.0)	1.000	15 (88.2)	6 (66.7)		15 (83.3)	6 (75.0)	
Resection margin												
R0	8 (100.0)	13 (68.4)	0.136	19 (76.0)	2 (100.0)	1.000	15 (83.3)	6 (66.7)	0.367	14 (73.7)	7 (87.5)	0.633
R1/R2	0	6 (31.6)		6 (24.0)	0		3 (16.7)	3 (33.3)		5 (26.3)	1 (12.5)	

Survival analysis demonstrated a significant reduction in OS with tumours that had a mucin percentage >5%, p=0.008 (Figure 10.2) and a trend towards reduced DFS, p=0.062 (Figure 10.3). There were no significant differences in OS or DFS based on TSP, Klintrup–Mäkinen grade and tumour necrosis percentage. mGPS was seen to influence recurrence with a reduced DFS associated with a mGPS score of 1 or greater, p=0.037. Increased systemic inflammation was associated with reduced OS with NLR >3.0, p=0.043. Time to recurrence, neoadjuvant therapy and resection margin status did not significantly affect overall or disease-free survival.

Differences exist between primary and LRRC biology as demonstrated in table 10.4. LRRC patients were more likely to have received neoadjuvant therapy (59.3% vs 19.6%) and have a resection resulting in a positive resection margin (26.9% vs 10.2%). Tumours from LRRC had higher-risk histological characteristics when compared with primary rectal cancers with increased rates of venous invasion (59.3 % vs 44.3%), perineural invasion (51.9% vs 27.5%) and poor differentiation (18.5% vs 8.7%). A higher proportion of weak KM grade tumours were seen in LRRCs (92.6% vs 71.8%), indicating lower peritumoural lymphocytic infiltrates. LRRCs exhibited much higher TSP scores compared with primary tumours (TSP>50% was prevalent in 70.4% LRRCs vs 31.3% primary tumours). The use of neoadjuvant therapy in primary rectal cancers did not significantly seem to alter the percentage of high stromal tumours (31.3% vs 29.1%). Similar numbers of tumour mucin and tumour necrosis were seen between groups. LRRC were more likely to have local re-recurrence compared with primary tumours (25.9% vs 5.9%).

Figure 10.2: Kaplan Meir plots for Overall Survival comparing (A) Mucin percentage, (B) Tumour necrosis (C) Tumour Stroma Percentage (D) Neoadjuvant therapy (E) Resection margin status (F) Time to recurrence (G) Modified Glasgow Prognostic Score (H) Neutrophil to Lymphocyte Ratio

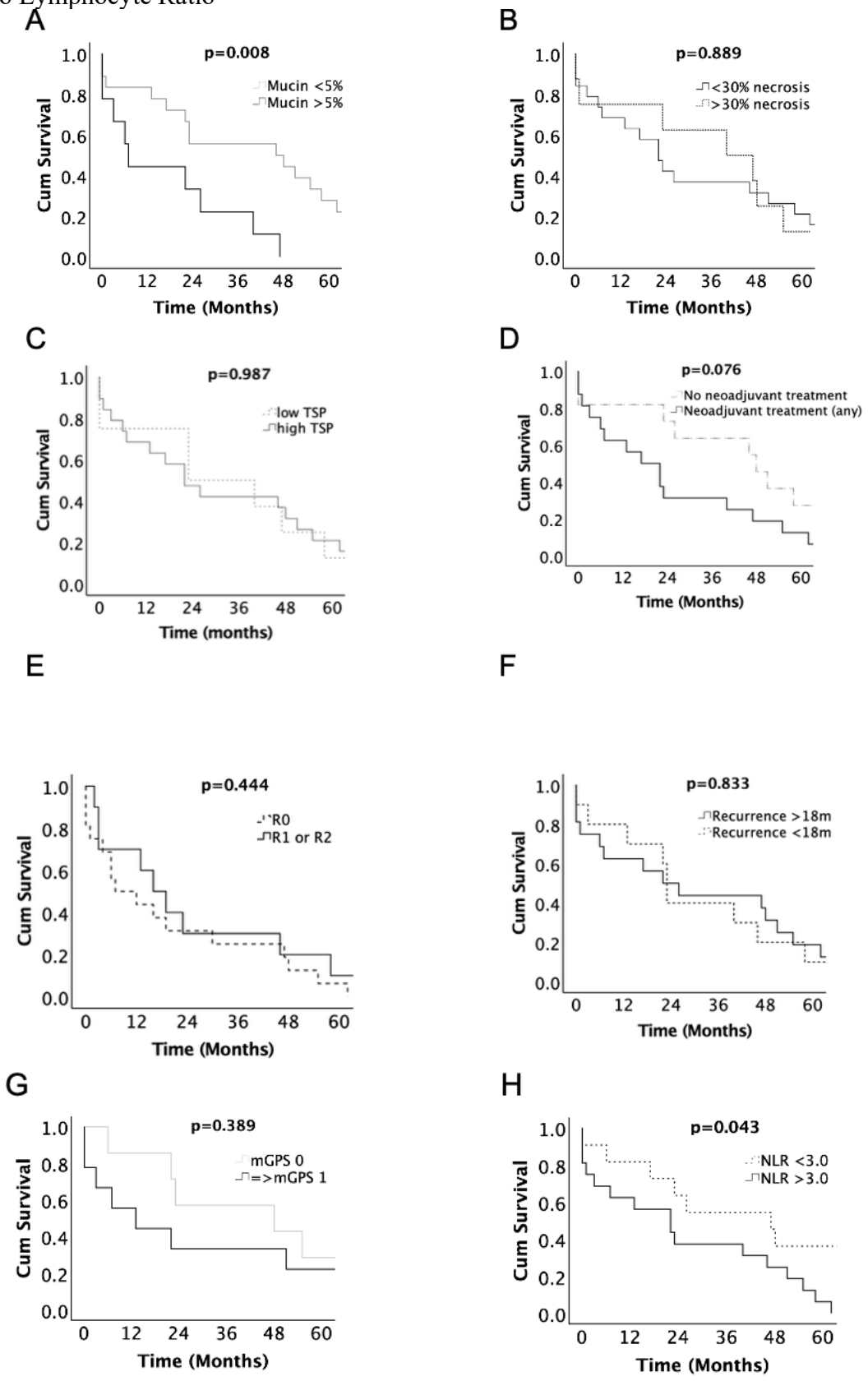


Figure 10.3: Kaplan Meir plots for Disease Free Survival comparing (A) Mucin percentage, (B) Tumour necrosis (C) Tumour Stroma Percentage (D) Neoadjuvant therapy (E) Resection margin status (F) Time to recurrence (G) Modified Glasgow Prognostic Score (H) Neutrophil to Lymphocyte Ratio

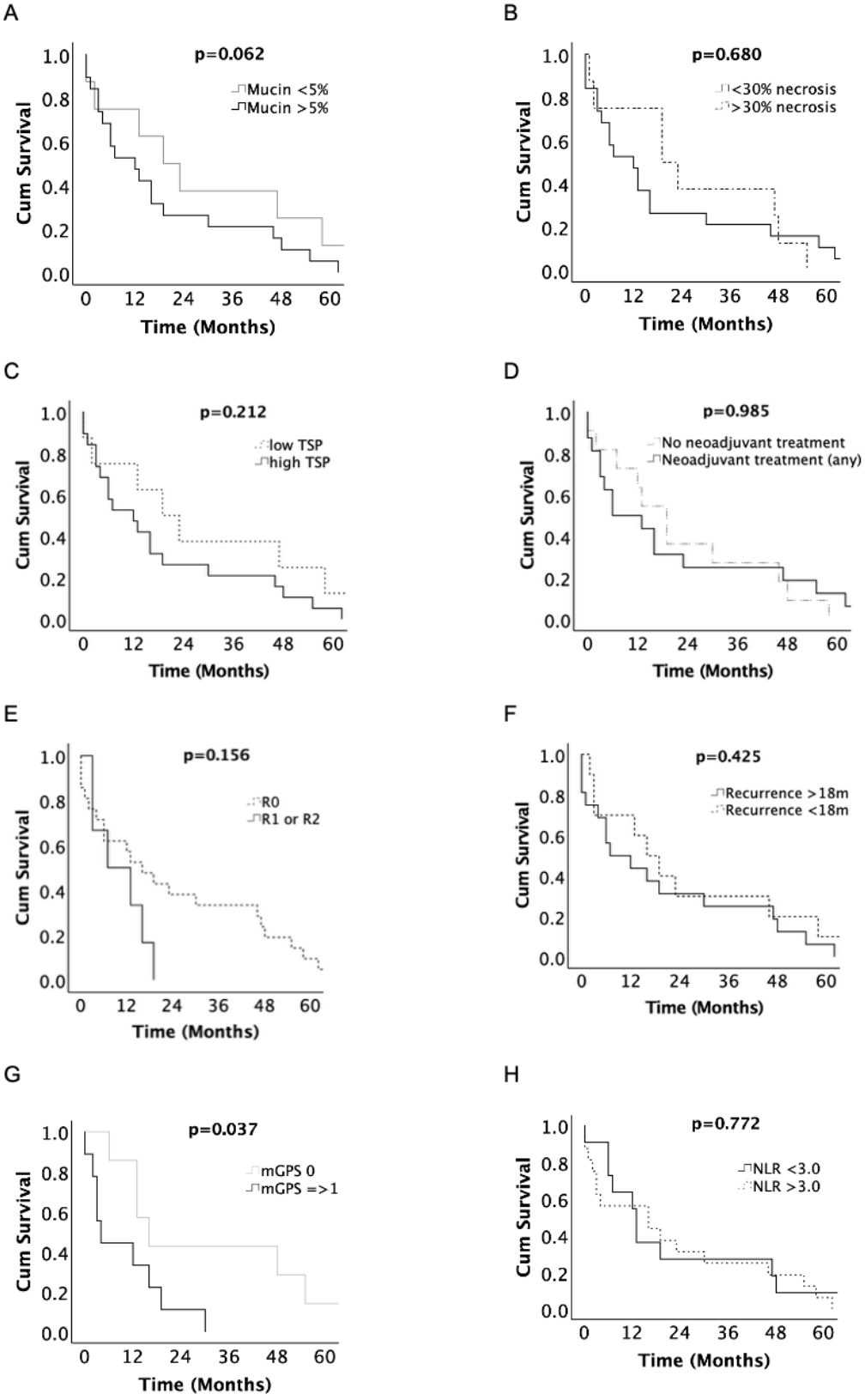


Table 10.4: Selected clinical and pathological characteristics of primary rectal cancers and recurrent rectal cancers

	Primary Rectal Cancers (GRI 1997-2013)	**Recurrent Rectal Cancers (St Marks 2008-2017)**
Totals	393	27
Neoadjuvant therapy (any)	77 (19.6)	16 (59.3)
Histology		
Venous invasion	174 (44.3)	16 (59.3)
Perineural invasion	28 (27.5) n=102	14 (51.9)
Differentiation		
Poor	34 (8.7)	5 (18.5)
Moderate/well	359 (91.3)	20 (74.1)
Resection margin		
R0	353 (89.8)	20 (74.1)
R1	40 (10.2)	5 (18.5)
R2	0	2 (7.4)
Tumour microenvironment and morphology characteristics		
Klintrup–Mäkinen grade weak	282 (71.8)	25 (92.6)
Tumour Stromal volume high (>50%)	123 (31.3)	19 (70.4)
Tumour Stomal volume high (>50%) (no neoadjuvant therapy)	92 (29.1) n=316	
Tumour mucin percentage (>5%)	11 (21.6) n=51	9 (33.3)
Tumour necrosis percentage (>30%)	64 (34.0) n=188	8 (29.6)
Recurrence		
Distant metastasis only	9 (17.6)	2 (7.4)
Local recurrence only	3 (5.9)	7 (25.9)
Both local and distant	6 (11.8)	4 (14.8)
None	33 (64.7)	14 (51.9)

10.4 Discussion

This study describes a unique cohort of patients with recurrent rectal cancer with novel assessment of the tumour microenvironment in this patient group. The results have demonstrated that the majority of tumours are immune deplete with a high TSP. Furthermore, these LRRC patients exhibit higher levels of systemic inflammation (defined by mGPS and NLR) compared with reported figures for primary colorectal tumours[302,314]. These novel results are important steps towards defining the biological phenotype of LRRCs.

Over the last decade there has been an increasing recognition of the influence that the tumour microenvironment has on tumour progression and metastasis. The fact that LRRCs are so stromally dense suggests stromal features play a major role in development of the disease phenotype and outcome. The tumour stroma includes fibroblasts, leukocytes, endothelial cells and extra-cellular matrix with feedback between tumour and stroma via paracrine communication[404]. The role of the tumour stroma, its interplay with cancer cells and influence on tumour progression has been described in solid organ cancers[215,405–407]. A recent meta-analysis demonstrated reduced DFS and OS with high tumour stroma percentage in over 4000 patients with primary colorectal cancer with a pooled hazard ratios of 1.54 (95%CI: 1.32–1.79, $p<0.001$) and 1.52 (95% CI: 1.34–1.73, $P < 0.001$), respectively[214]. They also demonstrated an association with high TSP and venous invasion as we have demonstrated in our study population[214].

High circulating levels of systemic inflammation and upregulation of innate non-specific immune cell responses in peripheral blood have been demonstrated to be a negative prognostic marker in colorectal cancer as evidenced by the Glasgow Prognostic Score[243]. In this study we observed increased prevalence of high inflammation-based scores in the LRRC cohort. Despite the relatively small cohort size these systemic immunological changes were associated with disease progression and reduced survival.

The results of this study also demonstrate LRRCs have lower KM grades indicative of low levels of lymphocytic infiltrate within the tumour microenvironment. The Klintrup–Mäkinen score, is a validated H&E based assessment of immune/ inflammatory cell infiltrate that is strongly related to other measures of intratumoural T-cell density, including CD3+ and CD8+ T cells, and correlates with disease outcome[240,408]. We demonstrated that 93% of these

aggressive recurrent tumours had low levels of immune cells at the invasive margin indicative of an immune deplete tumour microenvironment[25,26]. Given that 92.6% of tumours in this cohort were classified as KM-weak, it is unsurprising that no survival disadvantage was observed, as the marked imbalance in group sizes limits the discriminatory ability of this analysis.

Mucinous rectal adenocarcinoma is defined by the World Health Organisation as a tumour that has extracellular mucin in more than 50% of the tumour volume[409]. Mucinous colorectal cancers are more frequently diagnosed at an advanced stage and associated with poor prognosis[410,411]. There is a growing interest in the association of colorectal adenocarcinomas with mucinous features (>50% of tumour area) and outcomes. Several studies have reported reduced survival in patients with tumours with a mucinous component using a range of cut off values[412,413]. Here we demonstrated that tumours with over 5% of mucin were associated with reduced OS. Tumours containing >5% mucin were found to be associated with B-raf and K-ras mutations in a study of 166 colorectal cancers[412].

Tumour necrosis has been demonstrated to be associated with poor prognosis in solid organ cancers such as breast, pancreatic, lung and renal[414–417]. This has also been demonstrated in colorectal cancer, independent of tumour stage[401,418]. The mechanism for this association is unclear. One hypothesis is that tumour necrosis is a result of hypoxia and nutrient depletion and that this may stimulate tumour proliferation and angiogenesis[419]. Another hypothesis is that necrosis may be related to the systematic inflammatory response[420]. In a study of patients with colorectal cancer higher levels of tumour necrosis were associated with an increased inflammatory response, as measured by the modified Glasgow Score[401]. Although we found low levels of tumour necrosis were associated with venous invasion in our study population other larger studies of patients with primary colorectal cancer have demonstrated tumour necrosis to be associated with other hallmarks of aggressive tumours such as vascular invasion[401,421].

Although differences in baseline characteristics between primary and recurrent rectal cancers make drawing comparisons challenging, there do appear to be major phenotypic differences between cohorts. LRRC specimens tend to be immune deplete and stromally dense with systemic immune/ inflammatory alterations. The patient groups compared in this study are from different centres but the results reported in primary rectal cancers are comparable with

other series[215,422]. It is unclear to what extent the use of neoadjuvant therapy would significantly alter the tumour microenvironment and may therefore contribute to some of the differences observed, particularly expansion of the stromal compartment. Further studies controlling for confounders would help to assess these differences. Future work could include more in-depth characterisation of the tumour immune microenvironment using immunohistochemistry, multiplex immunofluorescence, and gene expression analyses. In addition, more comprehensive biological profiling, such as genomic and transcriptomic analyses, would represent a logical next step to further elucidate the underlying mechanisms driving tumour behaviour.

This study is limited by the small sample size, and therefore meaningful statistical analysis to allow detection of associations between subgroups was not possible. The analysis may also be limited by using semi-quantitative methods in the assessment of the tumour microenvironment and characteristics. However, excellent agreement between observers was demonstrated.

10.5 Conclusions

In conclusion, this study presents a novel assessment of LRRC following resection by pelvic exenteration using H&E based methods to quantify tumour stromal percentage, inflammatory infiltrates, mucin and necrosis. Most tumours were found to have a high tumour stroma percentage and low level of inflammatory infiltration. Further analysis is planned using RNA sequencing and immunohistochemistry to identify adverse prognostic features in this group of aggressive recurrent rectal cancers. These features, if identified on primary rectal cancers, may help to tailor patient's oncological surveillance and treatment following primary resection to identify those at greatest risk of recurrence. Further prospective trials are needed to help validate the importance of these adverse tumour features.

Chapter 11: Discussion

The aim of this thesis was to evaluate the clinical and pathological factors influencing outcomes following treatment for LARC and LRRC by pelvic exenteration, with a focus on the interplay between host-related factors, tumour biology, and surgical technique. Analyses of a unique high-volume tertiary referral cohort, the St Mark's Complex Cancer Clinic, were integrated with a systematic review, surgical outcome studies, and novel biological investigations of the tumour microenvironment and host physiology. Collectively, these findings, described in the earlier chapters, contribute to an enhanced understanding of prognostic determinants in this challenging patient population, informing strategies for patient selection, perioperative optimisation, and follow-up.

11.1 Surgical Outcomes and Technical Challenges

A consistent theme throughout this thesis is that surgical technique and resection margins are the key determinants of oncological outcome. The systematic review (Chapter 3) demonstrated that across 23 studies involving over 4000 patients, R0 resection was the single most consistent predictor of survival for patients with locally advanced and locally recurrent rectal cancer. This aligns with broader colorectal cancer literature, underscoring the principle that margin-negative surgery is paramount, regardless of the extent of resection required [423].

R0 resection is not always achievable, particularly in the context of recurrent disease where anatomy is distorted, fibrosis is extensive, and vital structures are involved. Therefore, the key to success of pelvic exenteration lies in balancing the possibility of achieving cure against the risks of extensive and morbid surgery.

Historically, cases involving high sacral or pelvic sidewall invasion were considered unresectable. Patients were managed palliatively, with surgery reserved for symptom control rather than cure[424]. Chapter 5 explored how this paradigm has shifted. Advances in imaging, surgical technique, and multidisciplinary working have enabled resections for disease extents once considered impossible for salvage; notably, en bloc sacrectomy at or above S2/3 with en bloc extended lateral pelvic sidewall excisions are now feasible in specialist centres. These procedures are associated with greater morbidity, but, when R0 resection is achieved, survival outcomes approach those of less extensive cases[141,143]. This evolution reflects a broader trend

in oncological surgery: As technical capability improves, the boundaries of resectability are continually redefined[425].

Radical surgery is achieved with a shift in the equilibrium between risk and benefit and thus carries significant "trade-offs". Patients undergoing high sacrectomy may experience long-term or lifelong functional limitations, including reduced mobility, altered gait, and chronic pain[150]. Similarly, resections involving the pelvic sidewall often necessitate sacrifice of major neurovascular structures, with consequences for continence, sexual function, and quality of life[156,359]. Thus, surgical decision-making extends beyond technical feasibility to encompass functional outcomes and survivorship. Shared decision-making, with frank discussions about risks, benefits, and alternatives, is essential.

With extensive surgical resection techniques, including those described in Chapter 5, successful reconstruction of the surgical defects is paramount in reducing morbidity and maintaining an acceptable quality of life. There is no current consensus approach to reconstruction of the perineal defect in this patient population. Chapter 6 demonstrated that our institution's approach of gluteal fasciocutaneous perforator flaps provides durable perineal coverage, even in high-complexity resections. Importantly, flap reconstruction did not independently increase morbidity, countering concerns that extensive resections would be compromised by wound complications. Instead, risk factors for perineal morbidity were patient characteristics such as obesity, advanced age, and ileal conduit complications. This highlights the importance of preoperative optimisation and careful multidisciplinary planning. Early involvement of plastic surgeons, tailored flap selection, and meticulous postoperative care all contribute to optimising outcomes.

From a broader perspective, this thesis illustrates how a specialist centre can deliver outcomes that challenge historical dogma. In doing so, we demonstrate that concentrating expertise, standardising surgical approach and fostering multidisciplinary collaboration allows a high-volume centre to safely expand the anatomical and technical boundaries of complex resections. Based on the findings and conclusions of Chapters 3, 4, 5 and 6, exploration the implications of such extensive surgery on patient outcomes was prompted in this cohort with identification of modifiable targets to improve these outcomes.

11.2 Short-Term Outcomes

Chapter 7 provided a large single-centre analysis of short-term outcomes following pelvic exenteration. Overall morbidity was high, with two-thirds of patients experiencing complications and nearly one-third experiencing major morbidity (Clavien–Dindo ≥III). This aligns with the published international literature, where morbidity rates between 40–70% are consistently reported [141,142,426]. Importantly, the study demonstrated that patients with recurrent disease fared worse in the short term than those with primary LARC, with higher rates of reoperation, longer hospital stay, and greater inpatient mortality.

These findings underscore the need for careful patient selection and perioperative optimisation. While a degree of morbidity is inevitable given the magnitude of exenteration, certain risk factors are modifiable. Elevated systemic inflammation, anaemia, malnutrition, and comorbidities such as diabetes were all associated with poorer outcomes. Interventions addressing these factors with nutritional supplementation, iron therapy, and optimised medical management may represent tangible opportunities to reduce perioperative risk.

Surgical factors also played a significant role. Total pelvic exenteration was independently associated with higher complication rates, reflecting the greater physiological insult of removing both anterior and posterior compartments. Additional procedures such as sacrectomy and extended sidewall excision further increased risk. These findings suggest that while radical surgery is sometimes necessary for cure (Chapters 3 and 5), the threshold for undertaking such procedures must remain high. Careful case selection, guided by MDT consensus and patient preference, is crucial.

Pathological factors were less predictive of short-term morbidity, though mucinous histology and poor differentiation in LARC were associated with adverse outcomes. This finding likely reflects the technical challenges posed by mucinous tumours, which are often bulky, gelatinous, and infiltrative, complicating surgical dissection and more frequently leading to a positive resection margin compared with non-mucinous tumours[427,428].

11.3 Long-Term Outcomes

Chapters 8 provided a comprehensive analysis of long-term survival after exenteration. Overall, survival was superior for LARC compared to LRRC, with five-year OS of 71% versus

41% respectively. These figures reflect the inherent biological aggressiveness of recurrent disease and the challenges of achieving complete resection in a distorted pelvis.

For LARC, long-term outcomes were influenced by both host and tumour factors. Elevated systemic inflammation (mGPS ≥1, NLR >3) and ASA III status were consistent independent predictors of reduced OS, DFS, and LRFS. Poor tumour differentiation and positive resection margins also conferred an adverse prognosis. These findings suggest that survival is shaped by a combination of technical, biological, and host-related factors. Encouragingly, many of these factors are measurable preoperatively, allowing for refined risk stratification and patient counselling.

In LRRC, prognostic determinants were less clear. ASA III status and venous invasion predicted poorer outcomes, while systemic inflammatory indices were not independently prognostic. This divergence reinforces the concept that recurrent tumours are biologically distinct. Standard host inflammatory markers, useful in primary disease, may lose prognostic power in local recurrence.

These findings also highlight the heterogeneity of outcomes. While some patients achieve durable cure following exenteration, others relapse quickly despite technically complete resections. This variability suggests that unmeasured biological factors such as genetic alterations, clonal selection, stromal dynamics, and immune competence may drive recurrence[429–431]. Identifying such factors is a priority for future research.

11.4 Host Physiology: Body Composition and Systemic Inflammation

Host physiology emerged as a major determinant of both short- and long-term outcomes in the findings within Chapters 7 and 8. Systemic inflammation, reflected by elevated NLR and mGPS, consistently predicted poor survival in LARC. This proinflammatory milieu at the systemic level may contribute to a systemic catabolic state which may compromise resilience to surgery and ability to control micrometastatic disease[250].

Chapter 9 expanded upon this concept through analysis of CT-derived body composition metrics. Sarcopenia and myosteatosis were common phenomena in the cohort and strongly associated with adverse oncological outcomes. Myosteatosis was particularly indicative of a worse prognosis. This finding is important because muscle quality, rather than quantity, may

better reflect a more favourable physiological reserve. Sarcopenia appears multifactorial and may not capture the metabolic dysfunction and chronic local and systemic inflammation characterised by myosteatosis[385].

BMI was not predictive of outcome, underlining the limitations of such crude anthropometric measures for example, obese patients may be sarcopenic whilst normal BMI patients may have poor muscle quality. CT body composition provides a more nuanced, objective assessment and could be incorporated into preoperative assessment. CT imaging is already routine in rectal cancer staging, making this approach feasible without additional cost or burden.

These findings have direct clinical implications. Firstly, they provide a rationale for integrating CT body composition into risk stratification algorithms. Secondly, they support targeted prehabilitation strategies: Resistance exercise, protein supplementation, and metabolic optimisation. Thirdly, they highlight the need for tailored counselling, as patients with sarcopenia or myosteatosis face higher risks of complications and mortality.

Aberrant body composition phenotypes brought about from the host response to the tumour and the tumour microenvironment may be target for future therapeutic interventions and further work should explore this concept. Randomised trials of exercise and nutritional interventions, stratified by CT body composition, would provide valuable evidence. Additionally, mechanistic studies exploring the links between myosteatosis, inflammation, and tumour biology could uncover novel therapeutic targets. Such a target could be the peritumoural tissue and the tumour microenvironment itself. A proinflammatory tumour may be driving this systemic response and be a causal factor in the host deconditioning seen secondary to cancer. This implication of the behaviour and biology of the tumour microenvironment is unknown in the complex cancer cohort, in order to elucidate the potential effect the tumour may have on the host is was necessary to explore this in more detail. Chapter 10 provided novel insights into the biological underpinnings of LRRC which may in turn explain some of the findings seen in Chapter 9.

11.5 Tumour Biology and the Microenvironment

Histological assessment of LRRC tumour blocks revealed that recurrent tumours are characterised by a stromally dense, immune-deplete microenvironment. High stromal proportion and weak immune infiltrates were common, and both correlated with adverse

outcomes. Compared with primary cancers, LRRCs had higher stromal content and fewer peritumoral immune cells, suggesting a shift in tumour–host interactions.

These findings may explain why conventional pathological and inflammatory markers are less prognostic in LRRC; the biology of recurrence is fundamentally different. They could also elucidate the role of the tumour microenvironment in driving recurrence; dense stroma may act as a physical and biochemical barrier, preventing immune cell infiltration and promoting tumour progression[216]. Importantly, these findings direct us to potential therapeutic strategies such as novel agents targeting stroma, its formation and proliferation or enhancing immune infiltration. Such adjuncts to surgery could be explored in relation to recurrent disease in this population and should make up part of the body of future work in our group. The immune-deplete phenotype of LRRC aligns with observations in other treatment-resistant cancers, where immune evasion is a hallmark of recurrence.[432,433] This raises the possibility that LRRC patients may not benefit from conventional immunotherapies, such as checkpoint inhibitors, unless combined with strategies to remodel the stroma or enhance antigen presentation[433]. Translational studies integrating histological, genomic, and transcriptomic data are needed to define these mechanisms more precisely.

11.6 Limitations

Several limitations should be acknowledged. The single-centre design ensures consistency of surgical technique and data collection but may limit generalisability. Retrospective analyses are prone to selection bias, although prospective databases mitigate this. Some biological investigations were constrained by small sample sizes and missing data. Quality of life outcomes were not captured, leaving an incomplete picture of survivorship. Molecular and genetic data were not available, limiting biological insights to histology and systemic markers. Despite these limitations, the thesis provides a comprehensive single-centre analysis of exenteration outcomes, integrated with novel biological investigations. The CCC cohort represents a unique resource, with detailed clinical, surgical, and pathological data spanning more than a decade. This work supports the creation of high-volume units, benchmarking of outcomes and standardisation of terminology and inclusion/ exclusion criteria for those undergoing pelvic exenteration.

11.7 Future Directions

Future research should aim to extend and validate the findings presented in this thesis across several important domains. Firstly, the prognostic value of biomarkers such as CT-derived body composition and systemic inflammatory indices requires multicentre validation in larger and more diverse populations. Incorporating these measures into predictive nomograms could allow for more accurate risk stratification and improve clinical decision-making for complex cancer patients. Secondly, further biological characterisation of LRRC using genomic, transcriptomic, and immunological profiling is required to help define the unique biology of recurrent disease and to identify novel therapeutic targets. Thirdly, prehabilitation also represents a promising avenue. Randomised studies are required to determine whether targeted interventions to address sarcopenia and myosteatosis can meaningfully improve physiological reserve and, in turn, enhance oncological outcomes. Alongside this, greater emphasis should be placed on quality of life and survivorship. The routine collection of patient-reported outcome measures in exenteration cohorts would provide valuable insight into the functional and psychosocial consequences of surgery and could inform the development of structured rehabilitation and survivorship programmes. Finally, the pursuit of novel biology driven therapeutics remains critical. Clinical trials investigating stromal-targeted and immune-modulatory approaches in LRRC could open new avenues for treatment in a disease that remains notoriously resistant to conventional therapies. This thesis also strongly supports that the interventions and outcomes for patients with LARC and LRRC should be investigated and reported separately. Throughout this thesis, it has been demonstrated that LARC and LRRC appear to represent two distinct diseases with differing prognostic factors and outcomes and therefore should be treated as such.

11.8 Patient-Centred Perspectives

Earlier chapters have focused on multiple factors which directly impact the host's quality of life and function. We have detailed in achieving the vital R0 resection margin, it is necessary to undertake an extensive surgical resection defined by the anatomical and radiological bounds of the disease (Chapters 3 and 5). Chapters 9 and 10 have demonstrated that the systemic inflammatory response, in part potentially driven by the tumour microenvironment has a deleterious effect on body composition, which in turn is related to outcomes. These oncological outcomes remain the primary endpoint of most studies; however, patient-centred outcomes are of equal importance, and the study and reporting of these outcomes are often neglected. The CCC cohort highlights the trade-offs faced by patients. While survival can be extended, the

cost is often permanent stomas, urinary conduits, or major functional impairment. High sacrectomy may compromise mobility, while sidewall resections may necessitate the sacrifice of pelvic nerves, resulting in incontinence or sexual dysfunction. Perineal reconstruction, while effective in reducing wound morbidity, may alter body image, limit physical activity and have long-term benign sequelae such as fistulae and perineal hernias. Pelvic exenteration is one of the most morbid procedures in colorectal surgery, with profound impacts on physical function, body image, sexuality, continence, and quality of life. Findings in this thesis have established a basic science and clinical background from which these patient-centred studies can be established.

Tools such as patient-reported outcome measures (PROMs) should be integrated into clinical practice and research to capture the full impact of exenteration. Additionally, survivorship programmes addressing psychological well-being, rehabilitation, and social support are critical.

The outcomes from this thesis support the development of more sophisticated decision-support tools that integrate both patient factors (age, comorbidity, frailty, fitness) and tumour factors (stage, MRI risk features, biology). These tools should be embedded in patient-facing information, presenting personalised absolute risks and benefits (postoperative morbidity, organ preservation, recurrence-free/overall survival) and recovery/quality-of-life trajectories in plain language with clear visuals. They should be calibrated to local outcomes and validated in exenteration populations to ensure accuracy, then updated as new data accrue. Used in the clinic, they can strengthen shared decision-making by aligning treatment intensity with patient priorities and tolerance of risk.

11.9 Conclusions

This thesis demonstrates that while R0 resection remains the cornerstone of curative intent surgery for LARC and LRRC, long-term outcomes are profoundly influenced by host physiology and tumour biology. Systemic inflammation, sarcopenia, and myosteatosis represent quantifiable host determinants of outcome, while recurrent tumours exhibit unique stromal and immune profiles that may underpin their poor prognosis. By integrating these biomarkers with surgical and pathological determinants, clinicians can refine patient selection, optimise perioperative care, and move towards precision medicine in pelvic exenteration.

In doing so, the work presented here redefines pelvic exenteration not simply as a technical challenge but as a multidisciplinary endeavour at the intersection of surgery, oncology, biology, and survivorship. The findings set the stage for future studies that aim to personalise treatment, enhance survivorship, and ultimately improve outcomes for patients facing one of the most formidable challenges in colorectal cancer care.

References

1. GLOBOCAN 2022 Available from: https://gco.iarc.who.int/media/globocan/factsheets/cancers/41-colorectum-fact-sheet.pdf. Accessed May 6, 2025.
2. Morgan E, Arnold M, Gini A, et al. Global burden of colorectal cancer in 2020 and 2040: incidence and mortality estimates from GLOBOCAN. *Gut*. 2023;72:338–344.
3. Cancer Today, International Agency for Research on Cancer Available from: https://gco.iarc.who.int/today/en/dataviz/bars?mode=population&cancers=41. Accessed March 12, 2025.
4. Bowel cancer statistics | Cancer Research UK Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer#heading-One. Accessed March 12, 2025.
5. Bowel cancer statistics | Cancer Research UK. *Cancer research UK*. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer. 2018. Accessed November 19, 2020.
6. Logan RFA, Patnick J, Nickerson C, et al. Outcomes of the Bowel Cancer Screening Programme (BCSP) in England after the first 1 million tests. *Gut*. 2012;61:1439–1446.
7. Vuik FE, Nieuwenburg SA, Bardou M, et al. Increasing incidence of colorectal cancer in young adults in Europe over the last 25 years. *Gut*. 2019;68:1820–1826.
8. Siegel RL, Torre LA, Soerjomataram I, et al. Global patterns and trends in colorectal cancer incidence in young adults. *Gut*. 2019;68:2179–2185.
9. Fearon EF, Vogelstein B. A Genetic Model for Colorectal Tumorigenesis Available from: https://www.cell.com/cell/pdf/0092-8674(90)90186-I.pdf?_returnURL=https%3A%2F%2Flinkinghub.elsevier.com%2Fretrieve%2Fpii%2F0092867490901861%3Fshowall%3Dtrue. 1990. Accessed April 11, 2025.
10. Vogelstein B, Fearon ER, Hamilton SR, et al. Genetic Alterations during Colorectal-Tumor Development. *New England Journal of Medicine*. 1988;319:525–532.
11. Lengauer C, Kinzler KW, Vogelstein B. Genetic instabilities in human cancers. *Nature 1998 396:6712*. 1998;396:643–649.
12. Fearnhead NS, Britton MP, Bodmer WF. The ABC of APC. *Hum Mol Genet*. 2001;10:721–733.
13. Fearon ER. Molecular genetics of colorectal cancer. *Annual Review of Pathology: Mechanisms of Disease*. 2011;6:479–507.
14. Smith KJ, Johnson KA, Bryan TM, et al. The APC gene product in normal and tumor cells. *Proc Natl Acad Sci U S A*. 1993;90:2846–50.

15. Muzny DM, Bainbridge MN, Chang K, et al. Comprehensive molecular characterization of human colon and rectal cancer. *Nature*. 2012;487:330–337.
16. Tomlinson IPM, Novelli MR, Bodmer WF. The mutation rate and cancer. *Proc Natl Acad Sci U S A*. 1996;93:14800–14803.
17. De La Chapelle A, Hampel H. Clinical Relevance of Microsatellite Instability in Colorectal Cancer. *Journal of Clinical Oncology*. 2010;28:3380.
18. Li GM. Mechanisms and functions of DNA mismatch repair. *Cell Research 2008 18:1*. 2007;18:85–98.
19. Vilar E, Gruber SB. Microsatellite instability in colorectal cancer—the stable evidence. *Nature Reviews Clinical Oncology 2010 7:3*. 2010;7:153–162.
20. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for Cancer Detection and Familial Predisposition: Development of International Criteria for the Determination of Microsatellite Instability in Colorectal Cancer. *Cancer Res*. 1998;58:5248–5257.
21. Mundade R, Imperiale TF, Prabhu L, et al. Genetic pathways, prevention, and treatment of sporadic colorectal cancer. *Oncoscience*. 2014;1:400–6.
22. Weisenberger DJ, Siegmund KD, Campan M, et al. CpG island methylator phenotype underlies sporadic microsatellite instability and is tightly associated with BRAF mutation in colorectal cancer. *Nature Genetics 2006 38:7*. 2006;38:787–793.
23. Lynch HT, de la Chapelle A. Hereditary Colorectal Cancer. *New England Journal of Medicine*. 2003;348:919–932.
24. Lynch HT, de la Chapelle A. Hereditary Colorectal Cancer. *New England Journal of Medicine*. 2003;348:919–932.
25. Kuiper RP, Vissers LELM, Venkatachalam R, et al. Recurrence and variability of germline EPCAM deletions in Lynch syndrome. *Hum Mutat*. 2011;32:407–14.
26. Bonadona V, Bonaïti B, Olschwang S, et al. Cancer Risks Associated With Germline Mutations in MLH1, MSH2, and MSH6 Genes in Lynch Syndrome. *JAMA*. 2011;305:2304–2310.
27. Molecular testing strategies for Lynch syndrome in people with colorectal cancer Diagnostics guidance Available from: www.nice.org.uk/guidance/dg27. 2017. Accessed April 14, 2025.
28. Monahan KJ, Bradshaw N, Dolwani S, et al. Guidelines for the management of hereditary colorectal cancer from the British Society of Gastroenterology (BSG)/Association of Coloproctology of Great Britain and Ireland (ACPGBI)/United Kingdom Cancer Genetics Group (UKCGG). *Gut*. 2020;69:411–444.
29. Nishisho I, Nakamura Y, Miyoshi Y, et al. Mutations of chromosome 5q21 genes in FAP and colorectal cancer patients. *Science*. 1991;253:665–669.
30. Mori Y, Nagse H, Ando H, et al. Somatic mutations of the APC gene in colorectal tumors: mutation cluster region in the APC gene. *Hum Mol Genet*. 1992;1:229–233.

31. Half E, Bercovich D, Rozen P. Familial adenomatous polyposis. *Orphanet J Rare Dis*. 2009;4:22.
32. Groen EJ, Roos A, Muntinghe FL, et al. Extra-Intestinal Manifestations of Familial Adenomatous Polyposis. *Ann Surg Oncol*. 2008;15:2439.
33. Sieber OM, Lipton L, Crabtree M, et al. Multiple colorectal adenomas, classic adenomatous polyposis, and germ-line mutations in MYH. *N Engl J Med*. 2003;348:791–799.
34. Win AK, Reece JC, Dowty JG, et al. Risk of extracolonic cancers for people with biallelic and monoallelic mutations in MUTYH. *Int J Cancer*. 2016;139:1557–63.
35. Nagtegaal ID, Odze RD, Klimstra D, et al. The 2019 WHO classification of tumours of the digestive system. *Histopathology*. 2020;76:182–188.
36. IJspeert JEG, Rana SAQ, Atkinson NSS, et al. Clinical risk factors of colorectal cancer in patients with serrated polyposis syndrome: a multicentre cohort analysis. *Gut*. 2017;66:278–284.
37. Carballal S, Rodríguez-Alcalde D, Moreira L, et al. Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study. *Gut*. 2016;65:1829–1837.
38. McGarrity TJ, Amos CI, Baker MJ. Peutz-Jeghers Syndrome. University of Washington, Seattle Available from: http://www.ncbi.nlm.nih.gov/pubmed/18391202. 1993. Accessed May 8, 2025.
39. Blatter R, Tschupp B, Aretz S, et al. Disease expression in juvenile polyposis syndrome: a retrospective survey on a cohort of 221 European patients and comparison with a literature-derived cohort of 473 SMAD4/BMPR1A pathogenic variant carriers. *Genetics in Medicine*. 2020;22:1524–1532.
40. Yehia L, Eng C. PTEN Hamartoma Tumor Syndrome. University of Washington, Seattle Available from: http://www.ncbi.nlm.nih.gov/pubmed/10360391. 1993. Accessed May 8, 2025.
41. Bowel cancer incidence statistics | Cancer Research UK Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer/incidence#heading-One. Accessed May 2, 2025.
42. Sell NM, Qwaider YZ, Goldstone RN, et al. Octogenarians present with a less aggressive phenotype of colon adenocarcinoma. *Surgery*. 2020;168:1138–1143.
43. Pretzsch E, Nieß H, Bösch F, et al. Age and metastasis – How age influences metastatic spread in cancer. Colorectal cancer as a model. *Cancer Epidemiol*. 2022;77:102112.
44. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results From the Women's Health Initiative randomized controlled trial. *JAMA*. 2002;288:321–33.
45. Kennelly R, Kavanagh DO, Hogan AM, et al. Oestrogen and the colon: potential mechanisms for cancer prevention. *Lancet Oncol*. 2008;9:385–391.
46. Slattery ML, Potter JD, Curtin K, et al. Estrogens reduce and withdrawal of estrogens increase risk of microsatellite instability-positive colon cancer. *Cancer Res*. 2001;61:126–30.

47. Bhaskaran K, Douglas I, Forbes H, et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5·24 million UK adults. *Lancet*. 2014;384:755–65.
48. Gunter MJ, Leitzmann MF. Obesity and colorectal cancer: epidemiology, mechanisms and candidate genes. *J Nutr Biochem*. 2006;17:145–156.
49. Parida S, Siddharth S, Sharma D. Adiponectin, Obesity, and Cancer: Clash of the Bigwigs in Health and Disease. *International Journal of Molecular Sciences 2019, Vol 20, Page 2519*. 2019;20:2519.
50. Otake S, Takeda H, Fujishima S, et al. Decreased levels of plasma adiponectin associated with increased risk of colorectal cancer. *World J Gastroenterol*. 2010;16:1252–7.
51. Ratke J, Entschladen F, Niggemann B, et al. Leptin stimulates the migration of colon carcinoma cells by multiple signaling pathways. *Endocr Relat Cancer*. 2010;17:179–189.
52. Giovannucci E. Insulin, Insulin-Like Growth Factors and Colon Cancer: A Review of the Evidence. *J Nutr*. 2001;131:3109S-3120S.
53. Nadeem MS, Kumar V, Al-Abbasi FA, et al. Risk of colorectal cancer in inflammatory bowel diseases. *Semin Cancer Biol*. 2020;64:51–60.
54. Munkholm P. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther*. 2003;18:1–5.
55. Eaden JA. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. *Gut*. 2001;48:526–535.
56. Edward East J, Gordon M, Bhaskar Nigam G, et al. British Society of Gastroenterology guidelines on colorectal surveillance in inflammatory bowel disease. *Gut*. 2025;0:1–34.
57. Baker A-M, Cross W, Curtius K, et al. Evolutionary history of human colitis-associated colorectal cancer. *Gut*. 2019;68:985–995.
58. Brentnall TA, Crispin DA, Rabinovitch PS, et al. Mutations in the p53 gene: an early marker of neoplastic progression in ulcerative colitis. *Gastroenterology*. 1994;107:369–78.
59. Robles AI, Traverso G, Zhang M, et al. Whole-Exome Sequencing Analyses of Inflammatory Bowel Disease-Associated Colorectal Cancers. *Gastroenterology*. 2016;150:931–43.
60. Grivennikov SI, Greten FR, Karin M. Immunity, Inflammation, and Cancer. *Cell*. 2010;140:883.
61. Kakourou A, Koutsioumpa C, Lopez DS, et al. Interleukin-6 and risk of colorectal cancer: results from the CLUE II cohort and a meta-analysis of prospective studies. *Cancer Causes & Control*. 2015;26:1449–1460.
62. Chan AT, Ogino S, Fuchs CS. Aspirin Use and Survival After Diagnosis of Colorectal Cancer. *JAMA*. 2009;302:649.
63. Bosetti C, Santucci C, Gallus S, et al. Aspirin and the risk of colorectal and other digestive tract cancers: an updated meta-analysis through 2019. *Ann Oncol*. 2020;31:558–568.

64. Burn J, Sheth H, Elliott F, et al. Cancer prevention with aspirin in hereditary colorectal cancer (Lynch syndrome), 10-year follow-up and registry-based 20-year data in the CAPP2 study: a double-blind, randomised, placebo-controlled trial. *Lancet*. 2020;395:1855–1863.
65. Clinical Trials Register Available from: https://www.clinicaltrialsregister.eu/ctr-search/trial/2014-000411-14/GB. Accessed October 23, 2025.
66. Liao X, Lochhead P, Nishihara R, et al. Aspirin use, tumor PIK3CA mutation, and colorectal-cancer survival. *N Engl J Med*. 2012;367:1596–606.
67. Kostic AD, Chun E, Robertson L, et al. Fusobacterium nucleatum Potentiates Intestinal Tumorigenesis and Modulates the Tumor-Immune Microenvironment. *Cell Host Microbe*. 2013;14:207–215.
68. Sears CL. Enterotoxigenic *Bacteroides fragilis* : a Rogue among Symbiotes. *Clin Microbiol Rev*. 2009;22:349–369.
69. Louis P, Hold GL, Flint HJ. The gut microbiota, bacterial metabolites and colorectal cancer. *Nature Reviews Microbiology 2014 12:10*. 2014;12:661–672.
70. Flint HJ, Duncan SH, Scott KP, et al. Links between diet, gut microbiota composition and gut metabolism. *Proceedings of the Nutrition Society*. 2015;74:13–22.
71. Wu N, Yang X, Zhang R, et al. Dysbiosis signature of fecal microbiota in colorectal cancer patients. *Microb Ecol*. 2013;66:462–70.
72. Liu G, Tang J, Zhou J, et al. Short-chain fatty acids play a positive role in colorectal cancer. *Discover Oncology*. 2024;15:425.
73. Wolin KY, Yan Y, Colditz GA, et al. Physical activity and colon cancer prevention: a meta-analysis. *Br J Cancer*. 2009;100:611.
74. Morris JS, Bradbury KE, Cross AJ, et al. Physical activity, sedentary behaviour and colorectal cancer risk in the UK Biobank. *British Journal of Cancer 2018 118:6*. 2018;118:920–929.
75. Courneya KS, Vardy JL, O'Callaghan CJ, et al. Structured Exercise after Adjuvant Chemotherapy for Colon Cancer. *New England Journal of Medicine*. 2025;393:13–25.
76. Aykan NF. Red Meat and Colorectal Cancer. *Oncol Rev*. 2015;9:288.
77. Bouvard V, Loomis D, Guyton KZ, et al. Carcinogenicity of consumption of red and processed meat. *Lancet Oncol*. 2015;16:1599–1600.
78. Veettil SK, Wong TY, Loo YS, et al. Role of Diet in Colorectal Cancer Incidence. *JAMA Netw Open*. 2021;4:e2037341.
79. Aune D, Chan DSM, Lau R, et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. *BMJ*. 2011;343:d6617.
80. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, phosphate, and calcium: a hypothesis. *J Natl Cancer Inst*. 1984;72:1323–5.

81. Norat T, Riboli E. Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur J Clin Nutr*. 2003;57:1–17.
82. Bagnardi V, Rota M, Botteri E, et al. Alcohol consumption and site-specific cancer risk: a comprehensive dose-response meta-analysis. *Br J Cancer*. 2015;112:580–593.
83. Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol*. 2006;7:149–56.
84. Botteri E, Iodice S, Bagnardi V, et al. Smoking and Colorectal Cancer. *JAMA*. 2008;300:2765.
85. Dukes CE. The classification of cancer of the rectum. *J Pathol Bacteriol*. 1932;35:323–332.
86. UICC and the TNM Classification of Malignant Tumours | UICC Available from: https://www.uicc.org/who-we-are/about-uicc/uicc-and-tnm#:~:text=The%20TNM%20(%E2%80%9CTumour%E2%80%9D%2C,language%20to%20facilitate%20cancer%20staging. Accessed May 7, 2025.
87. Brierley J, Gospodarowicz MD, Wittekind CT. TNM Classification of Malignant Tumors International Union Against Cancer. 8th. Oxford, England: Wiley; 2017. *Wiley*. 2017;pp57-62.
88. Early Diagnosis Hub Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. Accessed May 7, 2025.
89. Zhang C, Yin S, Tan Y, et al. Patient Selection for Adjuvant Chemotherapy in High-Risk Stage II Colon Cancer: A Systematic Review and Meta-Analysis. *Am J Clin Oncol*. 2020;43:279–287.
90. Pricolo VE, Steingrimsson J, McDuffie TJ, et al. Tumor Deposits in Stage III Colon Cancer: Correlation With Other Histopathologic Variables, Prognostic Value, and Risk Stratification-Time to Consider "N2c". *Am J Clin Oncol*. 2020;43:133–138.
91. Chen K, Collins G, Wang H, et al. Pathological Features and Prognostication in Colorectal Cancer. *Curr Oncol*. 2021;28:5356–5383.
92. Early Diagnosis Hub Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/. Accessed May 7, 2025.
93. Bowel cancer screening: programme overview - GOV.UK Available from: https://www.gov.uk/guidance/bowel-cancer-screening-programme-overview. Accessed October 28, 2025.
94. 1 Recommendations | Quantitative faecal immunochemical testing to guide colorectal cancer pathway referral in primary care | Guidance | NICE.
95. Monahan KJ, Davies MM, Abulafi M, et al. Faecal immunochemical testing (FIT) in patients with signs or symptoms of suspected colorectal cancer (CRC): a joint guideline from the Association of Coloproctology of Great Britain and Ireland (ACPGBI) and the British Society of Gastroenterology (BSG). *Gut*. 2022;0:1–24.
96. D'Souza N, de Neree tot Babberich MPM, d'Hoore A, et al. Definition of the Rectum. *Ann Surg*. 2019;270:955–959.
97. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28:iv22–iv40.

98. Moran BJ, Holm T, Brannagan G, et al. The English National Low Rectal Cancer Development Programme: key messages and future perspectives. *Colorectal Disease*. 2014;16:173–178.
99. Cunningham C, Leong K, Clark S, et al. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) – Diagnosis, Investigations and Screening. *Colorectal Disease*. 2017;19:9–17.
100. MERCURY Study Group. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. *BMJ*. 2006;333:779.
101. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Annals of Oncology*. 2017;28:iv22–iv40.
102. Rectal Cancer - Guidelines Detail Available from: https://www.nccn.org/guidelines/guidelines-detail?id=1461. Accessed October 28, 2025.
103. Morton D, Seymour M, Magill L, et al. Preoperative Chemotherapy for Operable Colon Cancer: Mature Results of an International Randomized Controlled Trial. *Journal of Clinical Oncology*. 2023;41:1541–1552.
104. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:29–42.
105. Conroy T, Bosset JF, Etienne PL, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22:702–715.
106. Gollins S, Moran B, Adams R, et al. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) – Multidisciplinary Management. *Colorectal Disease*. 2017;19:37–66.
107. Ciseł B, Pietrzak L, Michalski W, et al. Long-course preoperative chemoradiation versus 5 × 5 Gy and consolidation chemotherapy for clinical T4 and fixed clinical T3 rectal cancer: long-term results of the randomized Polish II study. *Ann Oncol*. 2019;30:1298–1303.
108. Dijkstra EA, Nilsson PJ, Hospers GAP, et al. Locoregional Failure During and After Short-course Radiotherapy Followed by Chemotherapy and Surgery Compared With Long-course Chemoradiotherapy and Surgery: A 5-Year Follow-up of the RAPIDO Trial. *Ann Surg*. 2023;278:E766–E772.
109. Sebag-Montefiore D, Stephens RJ, Steele R, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet*. 2009;373:811.

110. Van Gijn W, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12:575–582.
111. Schrag D, Shi Q, Weiser MR, et al. Preoperative Treatment of Locally Advanced Rectal Cancer. *New England Journal of Medicine*. 2023;389:322–334.
112. Hofheinz R, Fokas E, Benhaim L, et al. Localised rectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up 5 on behalf of the ESMO Guidelines Committee. *Annals of Oncology*. 2025;36:1007–1024.
113. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair–Deficient, Locally Advanced Rectal Cancer. *New England Journal of Medicine*. 2022;386:2363–2376.
114. Cercek A, Sinopoli JC, Shia J, et al. Durable complete responses to PD-1 blockade alone in mismatch repair deficient locally advanced rectal cancer. *Journal of Clinical Oncology*. 2024;42:LBA3512–LBA3512.
115. R G, J B, C M, et al. Adjuvant chemotherapy versus observation in patients with colorectal cancer: a randomised study. *Lancet*. 2007;370:2020–2029.
116. Moran B, Cunningham C, Singh T, et al. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) – Surgical Management. *Colorectal Disease*. 2017;19:18–36.
117. Colorectal cancer NICE guideline Available from: www.nice.org.uk/guidance/ng151. 2020. Accessed May 8, 2025.
118. Heald RJ, Moran BJ, Ryall RD, et al. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. *Arch Surg*. 1998;133:894–9.
119. Hanna GB, Mackenzie H, Miskovic D, et al. Laparoscopic Colorectal Surgery Outcomes Improved After National Training Program (LAPCO) for Specialists in England. *Ann Surg*. 2022;275:1149–1155.
120. Rullier E, Vendrely V, Asselineau J, et al. Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. *Lancet Gastroenterol Hepatol*. 2020;5:465–474.
121. Stijns RCH, De Graaf EJR, Punt CJA, et al. Long-term Oncological and Functional Outcomes of Chemoradiotherapy Followed by Organ-Sparing Transanal Endoscopic Microsurgery for Distal Rectal Cancer: The CARTS Study. *JAMA Surg*. 2019;154:47–54.
122. Garcia-Aguilar J, Shi Q, ThomasJr. CR, et al. Pathologic complete response (pCR) to neoadjuvant chemoradiation (CRT) of uT2uN0 rectal cancer (RC) treated by local excision (LE): Results of the ACOSOG Z6041 trial. *Journal of Clinical Oncology*. 2010;28:3510–3510.
123. ESTRO-European Society for Radiotherapy-Avenue Available from: www.estro.org. Accessed October 28, 2025.

124. Miller AS, Boyce K, Box B, et al. The Association of Coloproctology of Great Britain and Ireland consensus guidelines in emergency colorectal surgery. *Colorectal Disease*. 2021;23:476.
125. Sineshaw HM, Jemal A, Thomas CR, et al. Changes in treatment patterns for patients with locally advanced rectal cancer in the United States over the past decade: An analysis from the National Cancer Data Base. *Cancer*. 2016;122:1996–2003.
126. Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg*. 2013;100:1009–14.
127. Bosset J-F, Collette L, Calais G, et al. Chemotherapy with Preoperative Radiotherapy in Rectal Cancer. *New England Journal of Medicine*. 2006;355:1114–1123.
128. Valentini V, Van Stiphout RGPM, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of european randomized clinical trials. *Journal of Clinical Oncology*. 2011;29:3163–3172.
129. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *Journal of Clinical Oncology*. 2006;24:4620–4625.
130. de Wilt JHW, Vermaas M, Ferenschild FTJ, et al. Management of locally advanced primary and recurrent rectal cancer. *Clin Colon Rectal Surg*. 2007;20:255–63.
131. Hansen MH, Balteskard L, Dørum LM, et al. Locally recurrent rectal cancer in Norway. *British Journal of Surgery*. 2009;96:1176–1182.
132. Hahnloser D, Nelson H, Gunderson LL, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. *Ann Surg*. 2003;237:502–8.
133. Palmer G, Martling A, Cedermark B, et al. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. *Ann Surg Oncol*. 2007;14:447–54.
134. Harris CA, Solomon MJ, Heriot AG, et al. The Outcomes and Patterns of Treatment Failure After Surgery for Locally Recurrent Rectal Cancer. *Ann Surg*. 2016;264:323–329.
135. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up†. *Annals of Oncology*. 2017;28:iv22–iv40.
136. Glimelius BLG. The Role of Preoperative and Postoperative Radiotherapy in Rectal Cancer. *Clin Colorectal Cancer*. 2002;2:82–92.
137. Gambacorta MA, Romano A, Caravatta L, et al. Radiotherapy & total neoadjuvant therapy for recurrent rectal cancer in previously irradiated patients, (RETRY): a multicenter prospective observational study. *Radiat Oncol*.;19 . Epub ahead of print December 1, 2024. DOI: 10.1186/S13014-024-02555-X.
138. Voogt ELK, Nordkamp S, Aalbers AGJ, et al. Induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally

recurrent rectal cancer: study protocol of a multicentre, open-label, parallel-arms, randomized controlled study (PelvEx II). *BJS Open*.;5 . Epub ahead of print May 1, 2021. DOI: 10.1093/BJSOPEN/ZRAB029.

139. Denost Q, Frison E, Salut C, et al. A phase III randomized trial evaluating chemotherapy followed by pelvic reirradiation versus chemotherapy alone as preoperative treatment for locally recurrent rectal cancer - GRECCAR 15 trial protocol. *Colorectal Dis*. 2021;23:1909–1918.
140. BRUNSCHWIG A. Complete excision of pelvic viscera for advanced carcinoma; a one-stage abdominoperineal operation with end colostomy and bilateral ureteral implantation into the colon above the colostomy. *Cancer*. 1948;1:177–83.
141. PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *British Journal of Surgery*. 2018;105:650–657.
142. PelvEx Collaborative. Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer: Results From an International Collaboration. *Ann Surg*. 2019;269:315–321.
143. Steffens D, Solomon MJ, Young JM, et al. Cohort study of long-term survival and quality of life following pelvic exenteration. *BJS Open*. 2018;2:328–335.
144. Harji DP, Williams A, McKigney N, et al. Utilising quality of life outcome trajectories to aid patient decision making in pelvic exenteration. *European Journal of Surgical Oncology*. 2022;48:2238–2249.
145. Majithia J, Baheti AD, Haria PD, et al. Pelvic Compartments and Imaging Considerations Beyond TME Surgery for Rectal Cancer Patients. *J Gastrointestinal Abdominal Radiol ISGAR*. 2025;8:130–139.
146. Pring ET, Burling DN, Glover TE, et al. Rectal cancer surgery: radiology roadmaps. *BJS*. 2025;112:270.
147. Inoue A, Sheedy SP, Wells ML, et al. Rectal cancer pelvic recurrence: imaging patterns and key concepts to guide treatment planning. *Abdom Radiol (NY)*. 2023;48:1867–1879.
148. Burns EM, Quyn A, Al Kadhi O, et al. The 'Pelvic exenteration lexicon': Creating a common language for complex pelvic cancer surgery. *Colorectal Disease*. . Epub ahead of print February 15, 2023. DOI: 10.1111/codi.16476.
149. Solomon MJ, Austin KKS, Masya L, et al. Pubic Bone Excision and Perineal Urethrectomy for Radical Anterior Compartment Excision During Pelvic Exenteration. *Dis Colon Rectum*. 2015;58:1114–1119.
150. McCarthy ASE, Solomon MJ, Koh CE, et al. Quality of life and functional outcomes following pelvic exenteration and sacrectomy. *Colorectal Disease*. 2020;22:521–528.
151. Milne T, Solomon MJ, Lee P, et al. Sacral resection with pelvic exenteration for advanced primary and recurrent pelvic cancer: a single-institution experience of 100 sacrectomies. *Dis Colon Rectum*. 2014;57:1153–61.

152. Wanebo HJ, Antoniuk P, Koness RJ, et al. Pelvic resection of recurrent rectal cancer: Technical considerations and outcomes. *Dis Colon Rectum*. 1999;42:1438–1448.
153. Shaikh I, Holloway I, Aston W, et al. High subcortical sacrectomy: a novel approach to facilitate complete resection of locally advanced and recurrent rectal cancer with high (S1-S2) sacral extension. *Colorectal Dis*.;18 . Epub ahead of print 2016. DOI: 10.1111/CODI.13226.
154. Kokelaar RF, Evans MD, Davies M, et al. Locally advanced rectal cancer: management challenges. *Onco Targets Ther*. 2016;9:6265–6272.
155. Brown KGM, Solomon MJ, Koh CE. Pelvic Exenteration Surgery: The Evolution of Radical Surgical Techniques for Advanced and Recurrent Pelvic Malignancy. *Dis Colon Rectum*. 2017;60:745–754.
156. Shaikh I, Aston W, Hellawell G, et al. Extended lateral pelvic sidewall excision (ELSiE): an approach to optimize complete resection rates in locally advanced or recurrent anorectal cancer involving the pelvic sidewall. *Tech Coloproctol*. 2014;18:1161–1168.
157. Otero de Pablos J, Mayol J. Controversies in the Management of Lateral Pelvic Lymph Nodes in Patients With Advanced Rectal Cancer: East or West? *Front Surg*. 2020;6:497475.
158. Syk E, Torkzad MR, Blomqvist L, et al. Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer. *Br J Surg*. 2006;93:113–119.
159. Fujita S, Mizusawa J, Kanemitsu Y, et al. Mesorectal Excision with or Without Lateral Lymph Node Dissection for Clinical Stage II/III Lower Rectal Cancer (JCOG0212). *Ann Surg*. 2017;266:201–207.
160. Ogura A, Konishi T, Beets GL, et al. Lateral Nodal Features on Restaging Magnetic Resonance Imaging Associated With Lateral Local Recurrence in Low Rectal Cancer After Neoadjuvant Chemoradiotherapy or Radiotherapy. *JAMA Surg*.;154 . Epub ahead of print September 1, 2019. DOI: 10.1001/JAMASURG.2019.2172.
161. Kawai K, Shiratori H, Hata K, et al. Optimal Size Criteria for Lateral Lymph Node Dissection After Neoadjuvant Chemoradiotherapy for Rectal Cancer. *Dis Colon Rectum*. 2021;64:274–283.
162. Austin KKS, Solomon MJ. Pelvic exenteration with en bloc iliac vessel resection for lateral pelvic wall involvement. *Dis Colon Rectum*. 2009;52:1223–1233.
163. Brown KGM, Koh CE, Solomon MJ, et al. Outcomes After En Bloc Iliac Vessel Excision and Reconstruction During Pelvic Exenteration. *Dis Colon Rectum*. 2015;58:850–856.
164. Apte SS, Cohen LC, Larach JT, et al. Major vascular reconstruction in colorectal adenocarcinoma and retroperitoneal sarcoma: A retrospective study of safety and margins in a tertiary referral centre. *Surg Oncol*. 2022;45:101871.
165. Khan O, Patsouras D, Ravindraanandan M, et al. Total Pelvic Exenteration for Locally Advanced and Recurrent Rectal Cancer: Urological Outcomes and Adverse Events. *Eur Urol Focus*. . Epub ahead of print July 2, 2020. DOI: 10.1016/J.EUF.2020.06.008.

166. Kerdegari N, Singh CT, MacAskill F, et al. Urological Outcomes and Adverse Events Following Total Pelvic Exenteration for Locally Advanced and Recurrent Rectal Cancer: A Single-center Retrospective Study. *Urology*. 2025;198:160–166.
167. Johnson YL, West MA, Gould LE, et al. Empty pelvis syndrome: a systematic review of reconstruction techniques and their associated complications. *Colorectal Disease*. 2022;24:16–26.
168. West CT, Tiwari A, Smith J, et al. Empty pelvis syndrome as a cause of major morbidity after pelvic exenteration: validation of a core data set. *BJS*. 2025;112:70.
169. Devulapalli C, Jia Wei AT, DiBiagio JR, et al. Primary versus Flap Closure of Perineal Defects following Oncologic Resection. *Plast Reconstr Surg*. 2016;137:1602–1613.
170. Chessin DB, Hartley J, Cohen AM, et al. Rectus Flap Reconstruction Decreases Perineal Wound Complications After Pelvic Chemoradiation and Surgery: A Cohort Study. *Ann Surg Oncol*. 2005;12:104–110.
171. Nelson RA, Butler CE. Surgical Outcomes of VRAM versus Thigh Flaps for Immediate Reconstruction of Pelvic and Perineal Cancer Resection Defects. *Plast Reconstr Surg*. 2009;123:175–183.
172. van Ramshorst GH, Young JM, Solomon MJ. Complications and Impact on Quality of Life of Vertical Rectus Abdominis Myocutaneous Flaps for Reconstruction in Pelvic Exenteration Surgery. *Dis Colon Rectum*. 2020;63:1225–1233.
173. Kontovounisios C, Tekkis P. Locally Advanced Disease and Pelvic Exenterations. *Clin Colon Rectal Surg*. 2017;30:404.
174. Kroon HM, Dudi-Venkata NN, Bedrikovetski S, et al. Palliative pelvic exenteration: A systematic review of patient-centered outcomes. *Eur J Surg Oncol*. 2019;45:1787–1795.
175. Kelly ME, O'Sullivan NJ, Fahy MR, et al. Contemporary Management of Locally Advanced and Recurrent Rectal Cancer: Views from the PelvEx Collaborative. *Cancers (Basel)*. 2022;14:1161.
176. Loughrey M, Quirke P, Shepherd Neil. Standards and datasets for reporting cancers Dataset for histopathological reporting of colorectal cancer Available from: www.nice.org.uk/accreditation. 2023. Accessed June 3, 2025.
177. Däster S, Shin J-S, Loizides S, et al. Pathology reporting of pelvic exenteration specimens for locally recurrent rectal cancer. *European Journal of Surgical Oncology*. 2021;47:2100–2107.
178. Bosman FT, Carneiro F, Hruban RH, et al. WHO Classification of Tumours of the Digestive System. IARC Press; 2010.
179. Luo C, Cen S, Ding G, et al. Mucinous colorectal adenocarcinoma: clinical pathology and treatment options. *Cancer Commun (Lond)*. 2019;39:13.

180. Hyngstrom JR, Hu C-Y, Xing Y, et al. Clinicopathology and outcomes for mucinous and signet ring colorectal adenocarcinoma: analysis from the National Cancer Data Base. *Ann Surg Oncol*. 2012;19:2814–21.
181. Derwinger K, Kodeda K, Bexe-Lindskog E, et al. Tumour differentiation grade is associated with TNM staging and the risk of node metastasis in colorectal cancer. *Acta Oncol*. 2010;49:57–62.
182. Chapuis PH, Dentt F, Fisher R, et al. A multivariate analysis of clinical and pathological variables in prognosis after resection of large bowel cancer Available from: https://academic.oup.com/bjs/article/72/9/698/6193358. 1985. Accessed June 3, 2025.
183. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. *Lancet*. 1994;344:707–11.
184. Liu Q, Luo D, Cai S, et al. Circumferential resection margin as a prognostic factor after rectal cancer surgery: A large population-based retrospective study. *Cancer Med*. 2018;7:3673–3681.
185. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *Lancet*. 2009;373:821–8.
186. About NBOCA - National Cancer Audit Collaborating Centre Available from: https://www.natcan.org.uk/audits/bowel/about/. Accessed October 30, 2025.
187. Colorectal cancer quality performance indicators (QPIs) patients diagnosed from April 2019 to March 2022 - Colorectal cancer quality performance indicators (QPIs) - Publications - Public Health Scotland Available from: https://publichealthscotland.scot/publications/colorectal-cancer-quality-performance-indicators-qpis/colorectal-cancer-quality-performance-indicators-qpis-patients-diagnosed-from-april-2019-to-march-2022/. Accessed October 30, 2025.
188. Detering R, Saraste D, de Neree tot Babberich MPM, et al. International evaluation of circumferential resection margins after rectal cancer resection: insights from the Swedish and Dutch audits. *Colorectal Disease*. 2020;22:416–429.
189. Petersson J, Matthiessen P, Jadid KD, et al. Short-term results in a population based study indicate advantage for minimally invasive rectal cancer surgery versus open. *BMC Surg*. 2024;24:1–13.
190. Borstlap WAA, Deijen CL, den Dulk M, et al. Benchmarking recent national practice in rectal cancer treatment with landmark randomized controlled trials. *Colorectal Disease*. 2017;19:O219–O231.
191. Brown KGM, Solomon MJ, Koh CE, et al. Defining Benchmarks for Pelvic Exenteration Surgery: A Multicentre Analysis of Patients with Locally Advanced and Recurrent Rectal Cancer. *Ann Surg*. . Epub ahead of print May 15, 2024. DOI: 10.1097/SLA.0000000000006348.

192. Koh CE, Brown KGM, Steffens D, et al. What Constitutes a Clear Margin in Patients With Locally Recurrent Rectal Cancer Undergoing Pelvic Exenteration? *Ann Surg*.;Publish Ah . Epub ahead of print February 14, 2020. DOI: 10.1097/sla.0000000000003834.
193. Lord AC, Graham Martínez C, D'Souza N, et al. The significance of tumour deposits in rectal cancer after neoadjuvant therapy: a systematic review and meta-analysis. *Eur J Cancer*. 2019;122:1–8.
194. Betge J, Pollheimer MJ, Lindtner RA, et al. Intramural and extramural vascular invasion in colorectal cancer: prognostic significance and quality of pathology reporting. *Cancer*. 2012;118:628–38.
195. Kirsch R, Messenger DE, Riddell RH, et al. Venous invasion in colorectal cancer: impact of an elastin stain on detection and interobserver agreement among gastrointestinal and nongastrointestinal pathologists. *Am J Surg Pathol*. 2013;37:200–10.
196. Yuan H, Dong Q, Zheng B, et al. Lymphovascular invasion is a high risk factor for stage I/II colorectal cancer: a systematic review and meta-analysis. *Oncotarget*. 2017;8:46565–46579.
197. Al-Sukhni E, Attwood K, Gabriel EM, et al. Lymphovascular and perineural invasion are associated with poor prognostic features and outcomes in colorectal cancer: A retrospective cohort study. *International Journal of Surgery*. 2017;37:42–49.
198. Barresi V, Reggiani Bonetti L, Vitarelli E, et al. Immunohistochemical assessment of lymphovascular invasion in stage I colorectal carcinoma: prognostic relevance and correlation with nodal micrometastases. *Am J Surg Pathol*. 2012;36:66–72.
199. Law WL, Chu KW. Anterior Resection for Rectal Cancer With Mesorectal Excision. *Ann Surg*. 2004;240:260–268.
200. Wilkins B. Standards and datasets for reporting cancers Dataset for histopathological reporting of colorectal cancer Available from: https://www.rcpath.org/static/c8b61ba0-ae3f-43f1-85ffd3ab9f17cfe6/G049-Dataset-for-histopathological-reporting-of-colorectal-cancer.pdf. 2018. Accessed June 3, 2025.
201. Royal College of Pathologists. G049 Dataset for histopathological reporting of colorectal cancer Available from: https://www.rcpath.org/profession/guidelines/cancer-datasets-and-tissue-pathways.html. 2018. Accessed February 8, 2022.
202. Kitz J, Fokas E, Beissbarth T, et al. Association of Plane of Total Mesorectal Excision With Prognosis of Rectal Cancer: Secondary Analysis of the CAO/ARO/AIO-04 Phase 3 Randomized Clinical Trial. *JAMA Surg*. 2018;153:e181607.
203. Quirke P, Steele R, Monson J, et al. Effect of the plane of surgery achieved on local recurrence in patients with operable rectal cancer: a prospective study using data from the MRC CR07 and NCIC-CTG CO16 randomised clinical trial. *The Lancet*. 2009;373:821–828.
204. Kanazawa H, Mitomi H, Nishiyama Y, et al. Tumour budding at invasive margins and outcome in colorectal cancer. *Colorectal Dis*. 2008;10:41–7.

205. Rogers AC, Winter DC, Heeney A, et al. Systematic review and meta-analysis of the impact of tumour budding in colorectal cancer. *Br J Cancer*. 2016;115:831–40.
206. Klintrup K, Mäkinen JM, Kauppila S, et al. Inflammation and prognosis in colorectal cancer. *Eur J Cancer*. 2005;41:2645–2654.
207. Roxburgh CSD, Salmond JM, Horgan PG, et al. Tumour inflammatory infiltrate predicts survival following curative resection for node-negative colorectal cancer. *Eur J Cancer*. 2009;45:2138–2145.
208. Guo L, Wang C, Qiu X, et al. Colorectal Cancer Immune Infiltrates: Significance in Patient Prognosis and Immunotherapeutic Efficacy. *Front Immunol*. 2020;11:528129.
209. Galon J, Mlecnik B, Bindea G, et al. Towards the introduction of the 'Immunoscore' in the classification of malignant tumours. *J Pathol*. 2013;232:199.
210. Zhang X, Yang J, Du L, et al. The prognostic value of Immunoscore in patients with cancer: A pooled analysis of 10,328 patients. *Int J Biol Markers*. 2020;35:3–13.
211. Anitei MG, Zeitoun G, Mlecnik B, et al. Prognostic and predictive values of the immunoscore in patients with rectal cancer. *Clin Cancer Res*. 2014;20:1891–1899.
212. Pagès F, Mlecnik B, Marliot F, et al. International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. *The Lancet*. 2018;391:2128–2139.
213. Mlecnik B, Bindea G, Angell HK, et al. Integrative Analyses of Colorectal Cancer Show Immunoscore Is a Stronger Predictor of Patient Survival Than Microsatellite Instability. *Immunity*. 2016;44:698–711.
214. Zhu Y, Jin Z, Qian Y, et al. Prognostic Value of Tumor-Stroma Ratio in Rectal Cancer: A Systematic Review and Meta-analysis. *Front Oncol*. 2021;11:685570.
215. Park JH, Richards CH, McMillan DC, et al. The relationship between tumour stroma percentage, the tumour microenvironment and survival in patients with primary operable colorectal cancer. *Ann Oncol*. 2014;25:644–651.
216. Park JH, Richards CH, McMillan DC, et al. The relationship between tumour stroma percentage, the tumour microenvironment and survival in patients with primary operable colorectal cancer. *Annals of Oncology*. 2014;25:644–651.
217. Mesker WE, Junggeburt JMC, Szuhai K, et al. The carcinoma-stromal ratio of colon carcinoma is an independent factor for survival compared to lymph node status and tumor stage. *Cell Oncol*. 2007;29:387–98.
218. Peddareddigari VG, Wang D, Dubois RN. The tumor microenvironment in colorectal carcinogenesis. *Cancer Microenviron*. 2010;3:149–66.
219. Yancik R, Wesley MN, Ries LAG, et al. Comorbidity and Age as Predictors of Risk for Early Mortality of Male and Female Colon Carcinoma Patients A Population-Based Study . Epub ahead of print 1998. DOI: 10.1002/(SICI)1097-0142(19980601)82:11.

220. Gross CP, McAvay GJ, Guo Z, et al. The impact of chronic illnesses on the use and effectiveness of adjuvant chemotherapy for colon cancer. *Cancer*. 2007;109:2410–2419.
221. Sarfati D, Hill S, Blakely T, et al. The effect of comorbidity on the use of adjuvant chemotherapy and survival from colon cancer: a retrospective cohort study. *BMC Cancer*. 2009;9:116.
222. Massarweh NN, Legner VJ, Symons RG, et al. Impact of Advancing Age on Abdominal Surgical Outcomes. *Archives of Surgery*. 2009;144:1108.
223. Charlson,' M, Szatrowski,' TP, Peterson' J, et al. VALIDATION OF A COMBINED COMORBIDITY INDEX Available from: http://www.publichealth.it/wp-content/uploads/2020/05/3.-Validation-of-a-combined-comorbidity-index.pdf. 1994. Accessed August 8, 2022.
224. Pule ML, Buckley E, Niyonsenga T, et al. The effects of comorbidity on colorectal cancer mortality in an Australian cancer population. *Sci Rep*. 2019;9:8580.
225. Saklad M. GRADING OF PATIENTS FOR SURGICAL PROCEDURES. *Anesthesiology*. 1941;2:281–284.
226. Van Cutsem E, Arends J. The causes and consequences of cancer-associated malnutrition. *Eur J Oncol Nurs*.;9 Suppl 2 . Epub ahead of print 2005. DOI: 10.1016/J.EJON.2005.09.007.
227. Garth AK, Newsome CM, Simmance N, et al. Nutritional status, nutrition practices and post-operative complications in patients with gastrointestinal cancer. *Journal of Human Nutrition and Dietetics*. 2010;23:393–401.
228. Schwegler I, Von Holzen A, Gutzwiller JP, et al. Nutritional risk is a clinical predictor of postoperative mortality and morbidity in surgery for colorectal cancer. *British Journal of Surgery*. 2009;97:92–97.
229. Prado CM, Lieffers JR, McCargar LJ, et al. Prevalence and clinical implications of sarcopenic obesity in patients with solid tumours of the respiratory and gastrointestinal tracts: a population-based study. *Lancet Oncol*. 2008;9:629–635.
230. Prado CMM, Baracos VE, Mccargar LJ, et al. Cancer Therapy : Clinical Body Composition as an Independent Determinant of 5-Fluorouracil ^ Based Chemotherapy Toxicity. *Clinical Cancer Research*. 2007;13:3264–3269.
231. Malietzis G, Aziz O, Bagnall NM, et al. The role of body composition evaluation by computerized tomography in determining colorectal cancer treatment outcomes: a systematic review. *Eur J Surg Oncol*. 2015;41:186–196.
232. Caan BJ, Meyerhardt JA, Kroenke CH, et al. Explaining the Obesity Paradox: The Association between Body Composition and Colorectal Cancer Survival (C-SCANS Study). *Cancer Epidemiology Biomarkers & Prevention*. 2017;26:1008–1015.
233. Mourtzakis M, Prado CMM, Lieffers JR, et al. A practical and precise approach to quantification of body composition in cancer patients using computed tomography images acquired during routine care. *Applied Physiology, Nutrition and Metabolism*. 2008;33:997–1006.

234. Kotti A, Holmqvist A, Woisetschläger M, et al. Computed tomography-measured body composition and survival in rectal cancer patients: a Swedish cohort study. *Cancer Metab*. 2022;10:19.
235. Malietzis G, Currie AC, Athanasiou T, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. *British Journal of Surgery*. 2016;103:572–580.
236. Park JW, Chang SY, Lim JS, et al. Impact of Visceral Fat on Survival and Metastasis of Stage III Colorectal Cancer. *Gut Liver*. 2022;16:53–61.
237. Falz R, Bischoff C, Thieme R, et al. Effects and duration of exercise-based prehabilitation in surgical therapy of colon and rectal cancer: a systematic review and meta-analysis. *J Cancer Res Clin Oncol*. 2022;148:2187–2213.
238. Molenaar CJL, van Rooijen SJ, Fokkenrood HJP, et al. Prehabilitation versus no prehabilitation to improve functional capacity, reduce postoperative complications and improve quality of life in colorectal cancer surgery. *Cochrane Database of Systematic Reviews*.;2022 . Epub ahead of print May 19, 2022. DOI: 10.1002/14651858.CD013259.PUB2/MEDIA/CDSR/CD013259/REL0002/CD013259/IMAGE_N/NCD013259-FIG-03.SVG.
239. Colotta F, Allavena P, Sica A, et al. Cancer-related inflammation, the seventh hallmark of cancer: links to genetic instability. *Carcinogenesis*. 2009;30:1073–1081.
240. Klintrup K, Mäkinen JM, Kauppila S, et al. Inflammation and prognosis in colorectal cancer. *Eur J Cancer*. 2005;41:2645–54.
241. Roxburgh CSD, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncol*. 2010;6:149–63.
242. Proctor MJ, Morrison DS, Talwar D, et al. An inflammation-based prognostic score (mGPS) predicts cancer survival independent of tumour site: a Glasgow Inflammation Outcome Study. *Br J Cancer*. 2011;104:726–34.
243. McMillan DC. The systemic inflammation-based Glasgow Prognostic Score: A decade of experience in patients with cancer. *Cancer Treat Rev*. 2013;39:534–540.
244. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2014;23:1204–12.
245. Templeton AJ, McNamara MG, Šeruga B, et al. Prognostic Role of Neutrophil-to-Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. *JNCI: Journal of the National Cancer Institute*.;106 . Epub ahead of print June 1, 2014. DOI: 10.1093/jnci/dju124.
246. Roxburgh CSD, Salmond JM, Horgan PG, et al. Comparison of the prognostic value of inflammation-based pathologic and biochemical criteria in patients undergoing potentially curative resection for colorectal cancer. *Ann Surg*. 2009;249:788–93.

247. Roxburgh CSD, Salmond JM, Horgan PG, et al. The Relationship Between the Local and Systemic Inflammatory Responses and Survival in Patients Undergoing Curative Surgery for Colon and Rectal Cancers. *Journal of Gastrointestinal Surgery*. 2009;13:2011–2019.
248. Dolan RD, Lim J, McSorley ST, et al. The role of the systemic inflammatory response in predicting outcomes in patients with operable cancer: Systematic review and meta-analysis. *Sci Rep*. 2017;7:16717.
249. Dolan RD, McSorley ST, Horgan PG, et al. The role of the systemic inflammatory response in predicting outcomes in patients with advanced inoperable cancer: Systematic review and meta-analysis. *Crit Rev Oncol Hematol*. 2017;116:134–146.
250. McMillan DC. Systemic inflammation, nutritional status and survival in patients with cancer. *Curr Opin Clin Nutr Metab Care*. 2009;12:223–226.
251. Abbass T, Dolan RD, Horgan PG, et al. The relationship between systemic inflammation, body composition and clinical outcomes in patients with operable colorectal cancer at low and medium to high nutritional risk. *JCSM Clin Rep*. 2020;5:99–107.
252. Skipworth RJE, Stewart GD, Dejong CHC, et al. Pathophysiology of cancer cachexia: Much more than host–tumour interaction? *Clinical Nutrition*. 2007;26:667–676.
253. Pring ETET, Malietzis G, Kennedy RHRH, et al. Cancer cachexia and myopenia – Update on management strategies and the direction of future research for optimizing body composition in cancer – A narrative review. *Cancer Treat Rev*.;70:245–254.
254. Morris EJA, Taylor EF, Thomas JD, et al. Thirty-day postoperative mortality after colorectal cancer surgery in England. *Gut*. 2011;60:806–813.
255. Addae JK, Gani F, Fang SY, et al. A comparison of trends in operative approach and postoperative outcomes for colorectal cancer surgery. *Journal of Surgical Research*. 2017;208:111–120.
256. Maudsley J, Clifford RE, Aziz O, et al. A systematic review of oncosurgical and quality of life outcomes following pelvic exenteration for locally advanced and recurrent rectal cancer. *Ann R Coll Surg Engl*.;106 . Epub ahead of print February 1, 2024. DOI: 10.1308/RCSANN.2023.0031/ASSET/IMAGES/RCSANN.2023.0031.05.JPG.
257. Fahy M, Kelly ME, Abecasis N, et al. Contemporary results from the PelvEx collaborative: improvements in surgical outcomes for locally advanced and recurrent rectal cancer. *Colorectal Disease*. 2024;26:926–931.
258. Fearon KCH, Ljungqvist O, Von Meyenfeldt M, et al. Enhanced recovery after surgery: a consensus review of clinical care for patients undergoing colonic resection. *Clin Nutr*. 2005;24:466–477.
259. Arnold M, Sierra MS, Laversanne M, et al. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66:683–691.

260. Caravati-Jouvenceaux A, Launoy G, Klein D, et al. Health-Related Quality of Life Among Long-Term Survivors of Colorectal Cancer: A Population-Based Study. *Oncologist*. 2011;16:1626.
261. Jansen L, Herrmann A, Stegmaier C, et al. Health-related quality of life during the 10 years after diagnosis of colorectal cancer: a population-based study. *J Clin Oncol*. 2011;29:3263–3269.
262. Mols F, Lemmens V, Bosscha K, et al. Living with the physical and mental consequences of an ostomy: a study among 1-10-year rectal cancer survivors from the population-based PROFILES registry. *Psychooncology*. 2014;23:998–1004.
263. Thong MSY, Koch-Gallenkamp L, Jansen L, et al. Age-specific health-related quality of life in long-term and very long-term colorectal cancer survivors versus population controls - a population-based study. *Acta Oncol*. 2019;58:801–810.
264. Brown KGM, Solomon MJ, Lau YC, et al. Sciatic and Femoral Nerve Resection During Extended Radical Surgery for Advanced Pelvic Tumours: Long-term Survival, Functional, and Quality-of-life Outcomes. *Ann Surg*. . Epub ahead of print June 7, 2019. DOI: 10.1097/SLA.0000000000003390.
265. Overview | Colorectal cancer | Quality standards | NICE Available from: https://www.nice.org.uk/guidance/qs20. Accessed June 5, 2025.
266. Leong K, Hartley J, Karandikar S. Association of Coloproctology of Great Britain & Ireland (ACPGBI): Guidelines for the Management of Cancer of the Colon, Rectum and Anus (2017) – Follow Up, Lifestyle and Survivorship. *Colorectal Disease*. 2017;19:67–70.
267. Oronsky B, Reid T, Larson C, et al. Locally advanced rectal cancer: The past, present, and future. *Semin Oncol*. 2020;47:85–92.
268. Van Kessel CS, Solomon MJ. Understanding the Philosophy, Anatomy, and Surgery of the Extra-TME Plane of Locally Advanced and Locally Recurrent Rectal Cancer; Single Institution Experience with International Benchmarking. *Cancers 2022, Vol 14, Page 5058*. 2022;14:5058.
269. Rödel C, Graeven U, Fietkau R, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): Final results of the multicentre, open-label, randomised, phase 3 trial. *Lancet Oncol*. 2015;16:979–989.
270. De Felice F, Archetti L, D'Ambrosio G, et al. Intensified Total Neoadjuvant Therapy in Patients With Locally Advanced Rectal Cancer: Long-term Results of a Prospective Phase II Study. *Clin Oncol*. 2025;37:103698.
271. Hackett NJ, De Oliveira GS, Jain UK, et al. ASA class is a reliable independent predictor of medical complications and mortality following surgery. *Int J Surg*. 2015;18:184–190.
272. Kang B, Zhao ZQ, Liu XY, et al. Effect of hypoalbuminemia on short-term outcomes after colorectal cancer surgery: A propensity score matching analysis. *Front Nutr*. 2022;9:925086.

273. Guthrie GJK, Charles KA, Roxburgh CSD, et al. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol*. 2013;88:218–30.
274. Riley RD, Moons KGM, Snell KIE, et al. A guide to systematic review and meta-analysis of prognostic factor studies. *BMJ*. 2019;364:k4597.
275. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev*. 2021;10:89.
276. Platt E, Dovell G, Smolarek S. Systematic review of outcomes following pelvic exenteration for the treatment of primary and recurrent locally advanced rectal cancer. *Tech Coloproctol*. 2018;22:835–845.
277. Hayden JA, van der Windt DA, Cartwright JL, et al. Assessing Bias in Studies of Prognostic Factors. *Ann Intern Med*. 2013;158:280.
278. Wiig JN, Poulsen JP, Larsen S, et al. Total pelvic exenteration with preoperative irradiation for advanced primary and recurrent rectal cancer. *European Journal of Surgery*. 2002;168:42–48.
279. Jimenez RE, Shoup M, Cohen AM, et al. Contemporary Outcomes of Total Pelvic Exenteration in the Treatment of Colorectal Cancer. *Dis Colon Rectum*. 2003;46:1619–1625.
280. Koda K, Shuto K, Matsuo K, et al. Layer-oriented total pelvic exenteration for locally advanced primary colorectal cancer. *Int J Colorectal Dis*. 2016;31:59–66.
281. Kazi M, Kumar NAN, Rohila J, et al. Minimally invasive versus open pelvic exenterations for rectal cancer: a comparative analysis of perioperative and 3-year oncological outcomes. *BJS Open*.;5 . Epub ahead of print 2021. DOI: 10.1093/bjsopen/zrab074.
282. Culcu S, Yüksel C, Onur Kültüroğlu M, et al. Pelvic Exenteration for Recurrent Rectal Cancer: a Single Institution Experience. *Turkish Journal of Colorectal Disease*. 2021;31:20–24.
283. Bhangu A, Ali SM, Brown G, et al. Indications and outcome of pelvic exenteration for locally advanced primary and recurrent rectal cancer. *Ann Surg*. 2014;259:315–22.
284. Ike H, Shimada H, Yamaguchi S, et al. Outcome of total pelvic exenteration for primary rectal cancer. *Dis Colon Rectum*. 2003;46:474–480.
285. Quyn AJ, Austin KKS, Young JM, et al. Outcomes of pelvic exenteration for locally advanced primary rectal cancer: Overall survival and quality of life. *European Journal of Surgical Oncology*. 2016;42:823–828.
286. Hsu T-W, Chiang F-F, Chen M-C, et al. Pelvic exenteration for men with locally advanced rectal cancer: A morbidity analysis of complicated cases. *Asian J Surg*. 2011;34:115–120.
287. Radwan RW, Jones HG, Rawat N, et al. Determinants of survival following pelvic exenteration for primary rectal cancer. *British Journal of Surgery*. 2015;102:1278–1284.
288. Ishiguro S, Akasu T, Fujita S, et al. Pelvic exenteration for clinical T4 rectal cancer: Oncologic outcome in 93 patients at a single institution over a 30-year period. *Surgery*. 2009;145:189–195.
289. Ghouti L, Pereira P, Filleron T, et al. Pelvic exenterations for specific extraluminal recurrences in the era of total mesorectal excision: Is there still a chance for cure?: A single-center review

of patients with extraluminal pelvic recurrence for rectal cancer from March 2004 to November 201. *Am J Surg*. 2015;209:352–362.

290. Kusters M, Austin KKS, Solomon MJ, et al. Survival after pelvic exenteration for T4 rectal cancer. *British Journal of Surgery*. 2015;102:125–131.
291. Domes TS, Colquhoun PHD, Taylor B, et al. Total pelvic exenteration for rectal cancer: Outcomes and prognostic factors. *Canadian Journal of Surgery*. 2011;54:387–393.
292. Pellino G, Biondo S, Cazador AC, et al. Pelvic exenterations for primary rectal cancer: Analysis from a 10-year national prospective database. *World J Gastroenterol*. 2018;24:5144–5153.
293. Yang HY, Park SC, Hyun JH, et al. Outcomes of pelvic exenteration for recurrent or primary locally advanced colorectal cancer. *Ann Surg Treat Res*. 2015;89:131–7.
294. Moriya Y, Akasu T, Fujita S, et al. Total Pelvic Exenteration With Distal Sacrectomy for Fixed Recurrent Rectal Cancer in the Pelvis. *Dis Colon Rectum*. 2004;47:2047–2054.
295. Kuhrt MP, Chokshi RJ, Arrese D, et al. Retrospective review of pelvic malignancies undergoing total pelvic exenteration. *World J Surg Oncol*. 2012;10:110.
296. Vermaas M, Ferenschild FTJ, Verhoef C, et al. Total pelvic exenteration for primary locally advanced and locally recurrent rectal cancer. *European Journal of Surgical Oncology*. 2007;33:452–458.
297. Nielsen MB, Rasmussen PC, Lindegaard JC, et al. A 10-year experience of total pelvic exenteration for primary advanced and locally recurrent rectal cancer based on a prospective database. *Colorectal Dis*. 2012;14:1076–83.
298. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73:2680–6.
299. PelvEx Collaborative P. Changing outcomes following pelvic exenteration for locally advanced and recurrent rectal cancer. *BJS Open*. 2019;3:516–520.
300. Steffens D, Young JM, Solomon M, et al. Preliminary evidence for physical activity following pelvic exenteration: a pilot longitudinal cohort study. *BMC Cancer*. 2019;19:661.
301. West MA, Astin R, Moyses HE, et al. Exercise prehabilitation may lead to augmented tumor regression following neoadjuvant chemoradiotherapy in locally advanced rectal cancer. *Acta Oncol (Madr)*. 2019;58:588–595.
302. Dolan RD, McSorley ST, Park JH, et al. The prognostic value of systemic inflammation in patients undergoing surgery for colon cancer: comparison of composite ratios and cumulative scores. *Br J Cancer*. 2018;119:40–51.
303. Mendis S, To YH, Tie J. Biomarkers in Locally Advanced Rectal Cancer: A Review. *Clin Colorectal Cancer*. . Epub ahead of print November 20, 2021. DOI: 10.1016/J.CLCC.2021.11.002.

304. Malnutrition Universal Screening Tool Available from: www.bapen.org.uk. Accessed September 15, 2025.
305. Siddiqui MRS, Simillis C, Hunter C, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *British Journal of Cancer 2017 116:12*. 2017;116:1513–1519.
306. Bugg WG, Andreou AK, Biswas D, et al. The prognostic significance of MRI-detected extramural venous invasion in rectal carcinoma. *Clin Radiol*. 2014;69:619–623.
307. Nagtegaal ID, Glynne-Jones R. How to measure tumour response in rectal cancer? An explanation of discrepancies and suggestions for improvement. *Cancer Treat Rev*. 2020;84:101964.
308. Fletcher J, Drami I, Burns E, et al. Open sidewall excision for recurrent rectal cancer with gluteal flap reconstruction - a video vignette. *Colorectal Dis*. 2022;24:1252–1253.
309. Fletcher JA, Drami I, West MA, et al. Inferior gluteal artery perforator flap reconstruction of the perineum: A Video Vignette. *Colorectal Dis*. 2022;24:1098.
310. Drami I, Fletcher JA, Corr A, et al. Total pelvic exenteration with “high and wide” sacrectomy for recurrent rectal cancer: A video vignette. *Colorectal Dis*. 2022;24:1625–1626.
311. Definition | Background information | Hypertension | CKS | NICE Available from: https://cks.nice.org.uk/topics/hypertension/background-information/definition/. Accessed August 9, 2022.
312. Definition | Background information | Anaemia - iron deficiency | CKS | NICE Available from: https://cks.nice.org.uk/topics/anaemia-iron-deficiency/background-information/definition/. Accessed August 9, 2022.
313. Definition of CVD | Background information | CVD risk assessment and management | CKS | NICE Available from: https://cks.nice.org.uk/topics/cvd-risk-assessment-management/background-information/definition-of-cvd/. Accessed August 9, 2022.
314. Chiang S-F, Hung H-Y, Tang R, et al. Can neutrophil-to-lymphocyte ratio predict the survival of colorectal cancer patients who have received curative surgery electively? *Int J Colorectal Dis*. 2012;27:1347–57.
315. Wan S, Lai Y, Myers RE, et al. Preoperative platelet count associates with survival and distant metastasis in surgically resected colorectal cancer patients. *J Gastrointest Cancer*. 2013;44:293–304.
316. Wilkins B. Standards and datasets for reporting cancers Dataset for histopathological reporting of colorectal cancer Available from: https://www.rcpath.org/uploads/assets/c8b61ba0-ae3f-43f1-85ffd3ab9f17cfe6/G049-Dataset-for-histopathological-reporting-of-colorectal-cancer.pdf. 2018. Accessed August 16, 2022.

317. Hagemans JAW, van Rees JM, Alberda WJ, et al. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. *Eur J Surg Oncol*. 2020;46:448–454.
318. Bhangu A, Ali SM, Cunningham D, et al. Comparison of long-term survival outcome of operative vs nonoperative management of recurrent rectal cancer. *Colorectal Dis*. 2013;15:156–163.
319. Heriot AG, Byrne CM, Lee P, et al. Extended radical resection: the choice for locally recurrent rectal cancer. *Dis Colon Rectum*. 2008;51:284–91.
320. Hansen MH, Balteskard L, Dørum LM, et al. Locally recurrent rectal cancer in Norway. *Br J Surg*. 2009;96:1176–82.
321. MB N, PC R, JC L, et al. A 10-year experience of total pelvic exenteration for primary advanced and locally recurrent rectal cancer based on a prospective database. *Colorectal Dis*.;14 . Epub ahead of print 2012. DOI: 10.1111/J.1463-1318.2011.02893.X.
322. Bhangu A, Ali SM, Brown G, et al. Indications and outcome of pelvic exenteration for locally advanced primary and recurrent rectal cancer. *Ann Surg*. 2014;259:315–22.
323. Sasikumar A, Bhan C, Jenkins JT, et al. Systematic Review of Pelvic Exenteration With En Bloc Sacrectomy for Recurrent Rectal Adenocarcinoma: R0 Resection Predicts Disease-free Survival. *Dis Colon Rectum*. 2017;60:346–352.
324. Melton GB, Paty PB, Boland PJ, et al. Sacral resection for recurrent rectal cancer: analysis of morbidity and treatment results. *Dis Colon Rectum*. 2006;49:1099–107.
325. I S, I H, W A, et al. High subcortical sacrectomy: a novel approach to facilitate complete resection of locally advanced and recurrent rectal cancer with high (S1-S2) sacral extension. *Colorectal Dis*.;18 . Epub ahead of print 2016. DOI: 10.1111/CODI.13226.
326. Milne T, Solomon MJ, Lee P, et al. Assessing the impact of a sacral resection on morbidity and survival after extended radical surgery for locally recurrent rectal cancer. *Ann Surg*. 2013;258:1007–13.
327. Kim NK. Anatomic Basis of Sharp Pelvic Dissection for Curative Resection of Rectal Cancer. *Yonsei Med J*. 2005;46:737–749.
328. Lee DJK, Sagar PM, Sadadcharam G, et al. Advances in surgical management for locally recurrent rectal cancer: How far have we come? *World J Gastroenterol*. 2017;23:4170–4180.
329. Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg*. 2013;100:1009–14.
330. Sahakitrungruang C, Chantra K, Dusitanond N, et al. Sacrectomy for primary sacral tumors. *Dis Colon Rectum*. 2009;52:913–8.

331. Kido A, Koizumi M, Honoki K, et al. Extent and contraindications for sacral amputation in patients with recurrent rectal cancer: a systematic literature review. *Journal of Orthopaedic Science*. 2011;16:286–290.
332. Clair B Ordway NR Damron T Lavelle WF. Sacral Insufficiency Fracture After Partial Sacrectomy | MDedge Surgery. *Am J Orthop*. 2014;43:E272–E274.
333. Yu B, Zheng Z, Zhuang X, et al. Biomechanical Effects of Transverse Partial Sacrectomy on the Sacroiliac Joints. *Spine (Phila Pa 1976)*. 2009;34:1370–1375.
334. Lau YC, Jongerius K, Wakeman C, et al. Influence of the level of sacrectomy on survival in patients with locally advanced and recurrent rectal cancer. *British Journal of Surgery*. 2019;106:484–490.
335. Melton GB, Paty PB, Boland PJ, et al. Sacral resection for recurrent rectal cancer: analysis of morbidity and treatment results. *Dis Colon Rectum*. 2006;49:1099–107.
336. PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *British Journal of Surgery*. 2018;105:650–657.
337. Yamada K, Ishizawa T, Niwa K, et al. Pelvic Exenteration and Sacral Resection for Locally Advanced Primary and Recurrent Rectal Cancer. *Dis Colon Rectum*. 2002;45:1078–1084.
338. McCarthy ASE, Solomon MJ, Koh CE, et al. Quality of life and functional outcomes following pelvic exenteration and sacrectomy. *Colorectal Disease*. 2020;22:521–528.
339. Steffens D, Solomon MJ, Young JM, et al. Cohort study of long-term survival and quality of life following pelvic exenteration. *BJS Open*. 2018;2:328–335.
340. Mughal M, Baker RJ, Muneer A, et al. Reconstruction of perineal defects. *Ann R Coll Surg Engl*. 2013;95:539–44.
341. Witte DYS, van Ramshorst GH, Lapid O, et al. Flap Reconstruction of Perineal Defects after Pelvic Exenteration: A Systematic Description of Four Choices of Surgical Reconstruction Methods. *Plast Reconstr Surg*. 2021;147:1420–1435.
342. Moraru DC, Scripcariu V. Decisional Algorithms for the Reconstruction of Pelviperineal Defects After Total Pelvic Exenteration : A Review Available from: https://www.semanticscholar.org/paper/Decisional-Algorithms-for-the-Reconstruction-of-%3A-A-Moraru-Scripcariu/4265df83a7c5982f6f6b644966a49a0d26b30b10. 2018. Accessed March 7, 2019.
343. Woodfield J, Hulme-Moir M, Ly J. A comparison of the cost of primary closure or rectus abdominis myocutaneous flap closure of the perineum after abdominoperineal excision. *Colorectal Dis*. 2017;19:934–941.
344. Drami I, Fletcher JA, Corr A, et al. Total pelvic exenteration with “high and wide” sacrectomy for recurrent rectal cancer: A video vignette. *Colorectal Disease*. . Epub ahead of print June 22, 2022. DOI: 10.1111/codi.16230.

345. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240:205–13.
346. Hainsworth A, Al Akash M, Roblin P, et al. Perineal reconstruction after abdominoperineal excision using inferior gluteal artery perforator flaps. *British Journal of Surgery*. 2012;99:584–588.
347. Yang XY, Wei MT, Yang XT, et al. Primary *vs* myocutaneous flap closure of perineal defects following abdominoperineal resection for colorectal disease: a systematic review and meta-analysis. *Colorectal Disease*. 2019;21:138–155.
348. Johnstone MS. Vertical Rectus Abdominis Myocutaneous Versus Alternative Flaps for Perineal Repair After Abdominoperineal Excision of the Rectum in the Era of Laparoscopic Surgery. *Ann Plast Surg*. 2017;79:101–106.
349. Copeland-Halperin LR, Stewart T, Chen Y, et al. Perineal reconstruction following abdominoperineal resection: Comprehensive review of the literature. *J Plast Reconstr Aesthet Surg*. 2020;73:1924–1932.
350. Read T, Morrison EJ, Lonie S, et al. Treatment outcomes after pelvic exenteration with IGAM or VRAM flap reconstruction: Review of 130 consecutive cases. *Journal of Plastic, Reconstructive and Aesthetic Surgery*. 2025;103:140–147.
351. Pule ML, Buckley E, Niyonsenga T, et al. The effects of comorbidity on colorectal cancer mortality in an Australian cancer population. *Sci Rep*. 2019;9:8580.
352. Hagemans JAW, Rothbarth J, Kirkels WJ, et al. Total pelvic exenteration for locally advanced and locally recurrent rectal cancer in the elderly. *European Journal of Surgical Oncology*. 2018;44:1548–1554.
353. Radwan RW, Evans MD, Davies M, et al. Pelvic exenteration for advanced malignancy in elderly patients. *Br J Surg*. 2016;103:e115-9.
354. Van Rees JM, Visser E, Van Vugt JLA, et al. Impact of nutritional status and body composition on postoperative outcomes after pelvic exenteration for locally advanced and locally recurrent rectal cancer. *BJS Open*.;5 . Epub ahead of print October 1, 2021. DOI: 10.1093/BJSOPEN/ZRAB096.
355. Watt A, Kaushik V, Harris C, et al. Nutrition-related predictors of complications and length of hospital stay following total pelvic exenteration surgery. *Clin Nutr ESPEN*. 2024;62:88–94.
356. Kang B, Zhao ZQ, Liu XY, et al. Effect of hypoalbuminemia on short-term outcomes after colorectal cancer surgery: A propensity score matching analysis. *Front Nutr*. 2022;9:925086.
357. Braun LH, Baumann D, Zwirner K, et al. Neutrophil-to-Lymphocyte Ratio in Rectal Cancer-Novel Biomarker of Tumor Immunogenicity During Radiotherapy or Confounding Variable? *Int J Mol Sci*.;20 . Epub ahead of print May 17, 2019. DOI: 10.3390/ijms20102448.

358. Chittleborough T, Beadel G, Frizelle F. Extended Exenterative Resections Involving Bone. *Surgical Management of Advanced Pelvic Cancer*. 2021;97–109.
359. Höcht S, Mann B, Germer CT, et al. Pelvic sidewall involvement in recurrent rectal cancer. *Int J Colorectal Dis*. 2004;19:108–113.
360. Gould LE, Pring ET, Moorghen M, et al. Pathological determinants of outcome following resection of locally advanced or locally recurrent rectal cancer. *European Journal of Surgical Oncology*. 2023;49:106971.
361. Corr A, Fletcher J, Jenkins JT, et al. Image-guided pelvic exenteration-preoperative and intraoperative strategies. *Eur J Surg Oncol*. 2022;48:2263–2276.
362. Roxburgh CS, McMillan DC. Role of systemic inflammatory response in predicting survival in patients with primary operable cancer. *Future Oncology*. 2010;6:149–163.
363. Malietzis G, Johns N, Al-Hassi HO, et al. Low Muscularity and Myosteatosis Is Related to the Host Systemic Inflammatory Response in Patients Undergoing Surgery for Colorectal Cancer. *Ann Surg*. 2016;263:320–325.
364. Johnstone CSH, Roberts D, Mathieson S, et al. Pain, pain management and related outcomes following pelvic exenteration surgery: a systematic review. *Colorectal Dis*. 2023;25:562–572.
365. McCarthy ASE, Solomon MJ, Koh CE, et al. Quality of life and functional outcomes following pelvic exenteration and sacrectomy. *Colorectal Dis*. 2020;22:521–528.
366. Fleming M, Ravula S, Tatishchev SF, et al. Colorectal carcinoma: Pathologic aspects. *J Gastrointest Oncol*. 2012;3:153.
367. Roxburgh CSD, McMillan DC. The role of the in situ local inflammatory response in predicting recurrence and survival in patients with primary operable colorectal cancer. *Cancer Treat Rev*. 2012;38:451–466.
368. Templeton AJ, Ace O, McNamara MG, et al. Prognostic Role of Platelet to Lymphocyte Ratio in Solid Tumors: A Systematic Review and Meta-Analysis. *Cancer Epidemiology Biomarkers & Prevention*. 2014;23:1204–1212.
369. Zhao M, Feng L, Zhao K, et al. An MRI-based scoring system for pretreatment risk stratification in locally advanced rectal cancer. *British Journal of Cancer 2023 129:7*. 2023;129:1095–1104.
370. Cui Y, Wang G, Ren J, et al. Radiomics Features at Multiparametric MRI Predict Disease-Free Survival in Patients With Locally Advanced Rectal Cancer. *Acad Radiol*. 2022;29:e128–e138.
371. Maudsley J, Clifford RE, Aziz O, et al. A systematic review of oncosurgical and quality of life outcomes following pelvic exenteration for locally advanced and recurrent rectal cancer. *Ann R Coll Surg Engl*.;107 . Epub ahead of print February 1, 2025. DOI: 10.1308/RCSANN.2023.0031.
372. Brown KGM, Pisaniello J, Ng KS, et al. Variation in outcome measurement and reporting in studies of pelvic exenteration for locally advanced and recurrent rectal cancer: a systematic review. *Colorectal Dis*. 2024;26:272–280.

373. Rokan Z, Wale A, Day N, et al. Pelvic exenteration for locally advanced rectal cancer and associated outcomes in England between 1995 and 2016: Analysis of a national database. *Colorectal Dis*.;26 . Epub ahead of print October 1, 2024. DOI: 10.1111/CODI.17137.
374. Stocks T, Van Hemelrijck M, Manjer J, et al. Blood pressure and risk of cancer incidence and mortality in the Metabolic Syndrome and Cancer Project. *Hypertension*. 2012;59:802–10.
375. Yu H-C, Luo Y-X, Peng H, et al. Association of perioperative blood pressure with long-term survival in rectal cancer patients. *Chin J Cancer*. 2016;35:38.
376. Balkrishnan R, Desai RP, Narayan A, et al. Associations between initiating antihypertensive regimens on stage I–III colorectal cancer outcomes: A Medicare SEER cohort analysis. *Cancer Med*. 2021;10:5347–5357.
377. Chok AY, Oliver A, Rasheed S, et al. Perioperative management and anaesthetic considerations in pelvic exenterations using Delphi methodology: results from the PelvEx Collaborative. *BJS Open*.;5 . Epub ahead of print January 8, 2021. DOI: 10.1093/bjsopen/zraa055.
378. McSorley ST, Johnstone M, Steele CW, et al. Normocytic anaemia is associated with systemic inflammation and poorer survival in patients with colorectal cancer treated with curative intent. *Int J Colorectal Dis*. 2019;34:401–408.
379. Ward WH, Goel N, Ruth KJ, et al. Predictive Value of Leukocyte- and Platelet-Derived Ratios in Rectal Adenocarcinoma. *J Surg Res*. 2018;232:275–282.
380. Sato T, Ueno H, Mochizuki H, et al. Objective criteria for the grading of venous invasion in colorectal cancer. *Am J Surg Pathol*. 2010;34:454–62.
381. Guinney J, Dienstmann R, Wang X, et al. The consensus molecular subtypes of colorectal cancer. *Nat Med*. 2015;21:1350–1356.
382. Perez-Villamil B, Romera-Lopez A, Hernandez-Prieto S, et al. Colon cancer molecular subtypes identified by expression profiling and associated to stroma, mucinous type and different clinical behavior. *BMC Cancer*. 2012;12:260.
383. Pring ET, Malietzis G, Gould LE, et al. Tumour grade and stage are associated with specific body composition phenotypes with visceral obesity predisposing the host to a less aggressive tumour in colorectal cancer. *European Journal of Surgical Oncology*. 2022;48:1664–1670.
384. Malietzis G, Currie AC, Johns N, et al. Skeletal Muscle Changes After Elective Colorectal Cancer Resection: A Longitudinal Study. *Ann Surg Oncol*. 2016;23:2539–2547.
385. Pring ET, Gould LE, Malietzis G, et al. Sarcopenia in colorectal cancer is related to socio-economic deprivation and Body Mass Index alone misrepresents underlying muscle loss in the deprived. *Clin Nutr ESPEN*. 2024;63:13–19.
386. Malietzis G, Currie AC, Athanasiou T, et al. Influence of body composition profile on outcomes following colorectal cancer surgery. *British Journal of Surgery*. 2016;103:572–580.

387. Prado CMM, Baracos VE, McCargar LJ, et al. Body Composition as an Independent Determinant of 5-Fluorouracil-Based Chemotherapy Toxicity. *Clinical Cancer Research*. 2007;13:3264–3268.
388. Shen W, Punyanitya M, Wang Z, et al. Total body skeletal muscle and adipose tissue volumes: estimation from a single abdominal cross-sectional image. *J Appl Physiol*. 2004;97:2333–2338.
389. Martin L, Birdsell L, Macdonald N, et al. Cancer cachexia in the age of obesity: skeletal muscle depletion is a powerful prognostic factor, independent of body mass index. *J Clin Oncol*. 2013;31:1539–47.
390. Doyle SL, Bennett AM, Donohoe CL, et al. Establishing computed tomography–defined visceral fat area thresholds for use in obesity-related cancer research. 2013;33:171–179.
391. Baracos VE, Martin L, Korc M, et al. Cancer-associated cachexia. *Nat Rev Dis Primers*. 2018;4:17105.
392. Martin L, Hopkins J, Malietzis G, et al. Assessment of Computed Tomography (CT)-Defined Muscle and Adipose Tissue Features in Relation to Short-Term Outcomes After Elective Surgery for Colorectal Cancer: A Multicenter Approach. *Ann Surg Oncol*. . Epub ahead of print 2018. DOI: 10.1245/s10434-018-6652-x.
393. Swan L, Warters A, O'Sullivan M. Socioeconomic Disadvantage is Associated with Probable Sarcopenia in Community-Dwelling Older Adults: Findings from the English Longitudinal Study of Ageing. *Journal of Frailty & Aging*. 2022;11:398–406.
394. Yang PF, Ang ZH, Badiani S, et al. Impact of obesity on patients undergoing surgery for rectal cancer in Australia and New Zealand. *Int J Colorectal Dis*. 2023;38:163.
395. Ellulu MS, Patimah I, Khaza'ai H, et al. Obesity and inflammation: the linking mechanism and the complications. *Arch Med Sci*. 2017;13:851–863.
396. Pathak S, Pandanaboyana S, Daniels I, et al. Obesity and colorectal liver metastases: Mechanisms and management. *Surg Oncol*. . Epub ahead of print 2016. DOI: 10.1016/j.suronc.2016.05.021.
397. Lopez-Kostner F, Fazio VW, Vignali A, et al. Locally recurrent rectal cancer: predictors and success of salvage surgery. *Dis Colon Rectum*. 2001;44:173–8.
398. Zhao J, Du C-Z, Sun Y-S, et al. Patterns and prognosis of locally recurrent rectal cancer following multidisciplinary treatment. *World J Gastroenterol*. 2012;18:7015–20.
399. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell*. 2011;144:646–74.
400. Väyrynen SA, Väyrynen JP, Klintrup K, et al. Clinical impact and network of determinants of tumour necrosis in colorectal cancer. *Br J Cancer*. 2016;114:1334–42.
401. Richards CH, Roxburgh CSD, Anderson JH, et al. Prognostic value of tumour necrosis and host inflammatory responses in colorectal cancer. *British Journal of Surgery*. 2012;99:287–294.

402. Wan S, Lai Y, Myers RE, et al. Preoperative Platelet Count Associates with Survival and Distant Metastasis in Surgically Resected Colorectal Cancer Patients. *J Gastrointest Cancer*. 2013;44:293–304.
403. Li X, Sun K, Liao X, et al. Colorectal carcinomas with mucinous differentiation are associated with high frequent mutation of KRAS or BRAF mutations, irrespective of quantity of mucinous component. *BMC Cancer*. 2020;20:400.
404. Pietras K, Östman A. Hallmarks of cancer: Interactions with the tumor stroma. *Exp Cell Res*. 2010;316:1324–1331.
405. Dekker TJA, van de Velde CJH, van Pelt GW, et al. Prognostic significance of the tumor-stroma ratio: validation study in node-negative premenopausal breast cancer patients from the EORTC perioperative chemotherapy (POP) trial (10854). *Breast Cancer Res Treat*. 2013;139:371–9.
406. Almangush A, Alabi RO, Troiano G, et al. Clinical significance of tumor-stroma ratio in head and neck cancer: a systematic review and meta-analysis. *BMC Cancer*. 2021;21:480.
407. Kemi N, Eskuri M, Kauppila JH. Tumour-stroma ratio and 5-year mortality in gastric adenocarcinoma: a systematic review and meta-analysis. *Sci Rep*. 2019;9:16018.
408. Mei Z, Liu Y, Liu C, et al. Tumour-infiltrating inflammation and prognosis in colorectal cancer: systematic review and meta-analysis. *Br J Cancer*. 2014;110:1595–605.
409. WHO classification of tumours of the digestive system. Available from: https://www.cabdirect.org/cabdirect/abstract/20113051318. Accessed December 20, 2022.
410. Kim SH, Shin SJ, Lee KY, et al. Prognostic Value of Mucinous Histology Depends on Microsatellite Instability Status in Patients with Stage III Colon Cancer Treated with Adjuvant FOLFOX Chemotherapy: A Retrospective Cohort Study. *Ann Surg Oncol*. 2013;20:3407–3413.
411. Green JB, Timmcke AE, Mitchell WT, et al. Mucinous carcinoma--just another colon cancer? *Dis Colon Rectum*. 1993;36:49–54.
412. Li X, Sun K, Liao X, et al. Colorectal carcinomas with mucinous differentiation are associated with high frequent mutation of KRAS or BRAF mutations, irrespective of quantity of mucinous component. *BMC Cancer*. 2020;20:400.
413. Yan C, Yang H, Chen L, et al. Clinical significance of mucinous component in colorectal adenocarcinoma: a propensity score-matched study. *BMC Cancer*. 2021;21:1286.
414. Swinson DEB, Jones JL, Richardson D, et al. Tumour necrosis is an independent prognostic marker in non-small cell lung cancer: correlation with biological variables. *Lung Cancer*. 2002;37:235–40.
415. Pichler M, Hutterer GC, Chromecki TF, et al. Histologic Tumor Necrosis Is an Independent Prognostic Indicator for Clear Cell and Papillary Renal Cell Carcinoma. *Am J Clin Pathol*. 2012;137:283–289.

416. Hiraoka N, Ino Y, Sekine S, et al. Tumour necrosis is a postoperative prognostic marker for pancreatic cancer patients with a high interobserver reproducibility in histological evaluation. *Br J Cancer*. 2010;103:1057–65.
417. Gilchrist KW, Gray R, Fowble B, et al. Tumor necrosis is a prognostic predictor for early recurrence and death in lymph node-positive breast cancer: a 10-year follow-up study of 728 Eastern Cooperative Oncology Group patients. *J Clin Oncol*. 1993;11:1929–35.
418. Väyrynen SA, Väyrynen JP, Klintrup K, et al. Clinical impact and network of determinants of tumour necrosis in colorectal cancer. *Br J Cancer*. 2016;114:1334–1342.
419. Karsch-Bluman A, Feiglin A, Arbib E, et al. Tissue necrosis and its role in cancer progression. *Oncogene*. 2019;38:1920–1935.
420. Vakkila J, Lotze MT. Inflammation and necrosis promote tumour growth. *Nat Rev Immunol*. 2004;4:641–648.
421. Pollheimer MJ, Kornprat P, Lindtner RA, et al. Tumor necrosis is a new promising prognostic factor in colorectal cancer. *Hum Pathol*. 2010;41:1749–57.
422. Väyrynen JP, Tuomisto A, Klintrup K, et al. Detailed analysis of inflammatory cell infiltration in colorectal cancer. *Br J Cancer*. 2013;109:1839–1847.
423. Simillis C, Baird DLH, Kontovounisios C, et al. A systematic review to assess resection margin status after abdominoperineal excision and pelvic exenteration for rectal cancer. *Ann Surg*. 2017;265:291–299.
424. Magrini S, Nelson H, Gunderson LL, et al. Sacropelvic resection and intraoperative electron irradiation in the management of recurrent anorectal cancer. *Dis Colon Rectum*. 1996;39:1–9.
425. Koh CE, Solomon MJ, Brown KG, et al. The Evolution of Pelvic Exenteration Practice at a Single Center. *Dis Colon Rectum*. 2017;60:627–635.
426. Maudsley J, Clifford RE, Aziz O, et al. A systematic review of oncosurgical and quality of life outcomes following pelvic exenteration for locally advanced and recurrent rectal cancer. *Ann R Coll Surg Engl.*;106 . Epub ahead of print February 1, 2024. DOI: 10.1308/RCSANN.2023.0031/ASSET/IMAGES/RCSANN.2023.0031.05.JPG.
427. Hugen N, van de Velde CJ, Bosch SL, et al. Modern Treatment of Rectal Cancer Closes the Gap Between Common Adenocarcinoma and Mucinous Carcinoma. *Ann Surg Oncol*. 2015;22:2669–2676.
428. Koëter T, Stijns RCH, van Koeverden S, et al. Poor response at restaging MRI and high incomplete resection rates of locally advanced mucinous rectal cancer after chemoradiation therapy. *Colorectal Disease*. 2021;23:2341.
429. McGranahan N, Swanton C. Clonal Heterogeneity and Tumor Evolution: Past, Present, and the Future. *Cell*. 2017;168:613–628.
430. Zafari N, Khosravi F, Rezaee Z, et al. The role of the tumor microenvironment in colorectal cancer and the potential therapeutic approaches. *J Clin Lab Anal*. 2022;36:e24585.

431. Uemura M, Kobayashi Y, Ogawa H, et al. Clonal Evolution from Primary to Locally Recurrent Rectal Cancer Uncovered by Targeted Genomic Analysis of Treatment-Naïve Tumors Running Title Clonal Evolution in Locally Recurrent Rectal Cancer Available from: https://ssrn.com/abstract=5409092. Accessed September 16, 2025.
432. Seliger B, Massa C. Immune Therapy Resistance and Immune Escape of Tumors. *Cancers (Basel)*. 2021;13:551.
433. Tufail M, Jiang CH, Li N. Immune evasion in cancer: mechanisms and cutting-edge therapeutic approaches. *Signal Transduction and Targeted Therapy 2025 10:1*. 2025;10:1–49.

Appendices:

Appendix 1: Search strategy for systematic review

Search strategy

EMBASE:

1. tumor recurrence/

2. exp rectum cancer/

3. exp rectum tumor/

4. exp pelvis exenteration/

5. (((locally advanced rectal or advanced rectal) adj3 (adenocarcinoma or carcinoma or neoplasm or cancer or tumour)) or primary rectal beyond TME or beyond TME).mp. or LARC.ti,ab,kw. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

6. (((recurrent rectal or locally recurrent rectal) adj3 (cancer or adenocarcinoma or neoplasm or carcinoma)) or LRRC).mp. or RRC.ti,ab,kw. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword, floating subheading word, candidate term word]

7. (pelvic exenteration or pelvis exenteration or (multiviscer* adj3 resect*) or ((abdominosacral or abdomen* sacral) adj3 resect*) or ((sacropelvic or sacral) adj3 resect*) or extended resect*).ti,ab,kw.

8. 1 or 2 or 3 or 5 or 6

9. 4 or 7

10. 8 and 9

11. remove duplicates from 10

12. (case adj2 (report or study)).ti,kw.

13. 11 not 12

14. limit 13 to "humans only (removes records about animals)"

15. (mice or mouse or animal* or rat* or pig* or porcine or cow* or bovine or horse* or equine or dog* or canine or cat* or feline).ti.

16. 14 not 15

17. Limit 16 to yr= “2001-Current”

MEDLINE

1. (((locally advanced rectal or advanced rectal) adj3 (adenocarcinoma or carcinoma or neoplasm or cancer or tumour)) or primary rectal beyond TME or beyond TME).mp. or LARC.ti,ab,kw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

2. (((recurrent rectal or locally recurrent rectal) adj3 (cancer or adenocarcinoma or neoplasm or carcinoma)) or LRRC).mp. or RRC.ti,ab,kw. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]

3. (pelvic exenteration or pelvis exenteration or (multiviscer* adj3 resect*) or ((abdominosacral or abdomen* sacral) adj3 resect*) or ((sacropelvic or sacral) adj3 resect*) or extended resect*).ti,ab,kw.

4. exp Neoplasm Recurrence, Local/

5. exp Rectal Neoplasms/

6. exp Pelvic Exenteration/

7. 1 or 2 or 4 or 5

8. 3 or 6

9. 7 and 8

10. remove duplicates from 9

11. limit 10 to case reports

12. 10 not 11

13. limit 12 to animals

14. 12 not 13

15. (mice or mouse or animal* or rat* or pig* or porcine or cow* or bovine or horse* or equine or dog* or canine or cat* or feline).ti.

16. 14 not 15
17. Limit 16 to yr= “2001-Current”

Appendix 2: Permission to use table from The 'Pelvic exenteration lexicon': Creating a common language for complex pelvic cancer surgery.

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