Complication profiling and Evolution of pelvic exenteration surgery performed in high volume tertiary referral centres over thirty years.

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A thesis submitted in fulfilment of the requirements for the degree of Master of Medical Science

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STATEMENT OF ORIGINALITY

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. In writing this thesis I have been involved in every step from conception of ideas to execution of manuscript publication. I have examined areas in exenterative surgery where a paucity of data exists and with the hypothesis set for my thesis I constructed a database including patients from two major referral centres. In addition to entering data and compiling the database, I analysed and performed statistical analysis for each study/chapter, wrote the submitted/published manuscripts and performed corrections where required for final publication which now make up the individual chapters of this thesis. I hereby declare that this material has not been submitted, either in full or in part, for a degree at this or any other institution.

Jacob J McCormick 26/11/2019

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Journal articles:

PUBLICATIONS submitted from this thesis

1. **Evolution of pelvic exenteration surgery: resectional trends and oncological outcomes over three decades.**
   P Waters*, O Peacock*, SK Warrier, C Wakeman, T Eglinton, AC Lynch, FA Frizelle, AG Heriot, J McCormick
   Submitted to European journal of surgical oncology –Decision: - accepted pending changes

2. **Excision of urological organs impacts surgical and survival outcomes following exenterative surgery for locally advanced and recurrent pelvic malignancies.**
   O Peacock, PS Waters, JC Kong, SK Warrier, C Wakeman, T Eglinton, DG Murphy, AG Heriot, FA Frizelle, JJ McCormick
   Submitted to Colorectal disease – under review.

3. **Complications after pelvic exenteration for locally advanced and recurrent pelvic malignancies: A 25-year experience.**
   O Peacock, PS Waters, JC Kong, SK Warrier, C Wakeman, T Eglinton, AG Heriot, FA Frizelle, JJ McCormick
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Introduction:

How big is the problem of rectal cancer?

The ultimate goal of surgical treatment for cancer is to be able to cure the disease while maintaining acceptable risks to the patient from the intervention required. Colorectal cancer is a frequent malignancy reported to cancer registries, being the second-most common in female patients and third-most common in male patients. In 2015 there were 15,604 new cases of colorectal cancer diagnoses in Australia and 3081 in New Zealand (1). About a third of these cases occur in the rectum. Invasion of an adjacent organ, defined as T4b disease, occurs in 10-20% of cases (2). In order to achieve long-term survival it is critical that resection of the tumour with clear surgical margins be achieved. In the setting of T4b disease to achieve this will require a multi-visceral resection (MVR). Multi-visceral resection involves the en bloc resection of the tumour along with the invaded surrounding organ (3). It may range from a partial cystectomy or hysterectomy to a total pelvic exenteration (TPE) with resection of the rectum, anus, urogenital organs +/- boney and/or vascular resection.

Early treatments

Early management of rectal cancer involved attempts at resection via a perineal approach. As understanding of anatomy, anaesthesia and post-operative care improved surgery was to become more radical. The introduction of the abdomino-perineal resection by Miles in 1923 changed rectal cancer surgery by introducing the concept of a clear margin of resection. Sugarbaker published the first reported series of pelvic exenteration in 1946 (4). Here he presented 42 patients where there "*was either known involvement of the structure adjacent to the bowel or*

such firm fixation to it that dissection between them was felt to entail too great a risk of entering disease". He found that the patients treated with the multi-visceral resection were slightly younger (56y vs 61y), had much higher incidence of pre-operative weight loss and had a higher peri-operative mortality of 19% vs 9%. Given they had had a similar duration of symptoms to the standard-resection group he postulated that they had a more aggressive form of disease.

Understanding of Total Mesorectal Excision and neoadjuvant therapies

Heald's popularisation of the concept of total mesorectal excision (TME) through the 1980s had a significant impact on the rate of local recurrence for rectal cancer (5). Prior to this local recurrence rates were as high as 27% as highlighted by the non-radiation arm of the Swedish rectal cancer trial (6). This awareness of TME-surgery through the 1980s and 1990s occurred in conjunction with trials looking at the use of radiotherapy for rectal cancer. Pre-operative radiation, be that short-course radiotherapy or long-course chemo-radiotherapy has shown to reduce rates of local recurrence and improve overall and disease-free survival (7-9). Although it comes with an increased risk of peri-operative complications and a worse functional outcome (10). For these reasons it is usually reserved for locally advanced rectal cancer, be that node-positive disease or cases where the circumferential resection margin may be at risk. With a multidisciplinary approach to treatment, including improved preoperative imaging, judicious use of preoperative chemoradiation and standardisation of surgery, as well as adoption of total mesorectal excision (TME) the local recurrence rates in many tertiary centres has dropped below 5 percent.

Recurrence

For rectal cancer patients the majority will have recurrences at or within 2 years of primary surgery (11). Heriot and colleagues reported that 43% of local recurrences were detected following 48 months from primary surgery, while Sagar and colleagues showed that 40% of LR occurred after 36 months (12). The risk profile for the primary tumours can predict the chance of recurrence. Patients with a threatened or involved circumferential resection margin (CRM), poorly differentiated adenocarcinoma, lympho-vascular invasion, venous invasion, perineural invasion, obstruction and perforation are at increased risk of local recurrence (13, 14). If preoperative Chemoradiation has been used prior to primary surgical resection then the recurrence may be delayed. While the majority of patients who undergo exenterative surgery are for rectal cancer, there are other indications for this surgery.

These include:

- Primary gynaecological cancers- advanced endometrial, ovarian, cervical and vaginal
- Primary urological and sarcoma patients.
- Lateral Lymph Nodes

Lateral pelvic lymph nodes fall outside of the normal plane of dissection for rectal cancer. Modern imaging techniques, particularly MRI scans, are much better at identifying abnormal lateral pelvic lymph nodes on initial staging (15). The approach to abnormal lateral pelvic lymph nodes has not been standardised. Japanese studies suggest that the addition of lateral lymph-node dissection could reduce lateral recurrence. Other approaches have been to include the lateral pelvic sidewall in the radiation field. A multi-centre, retrospective cohort-study was performed by Ogura et al which looked at the role of lateral pelvic sidewall dissection for radiologically-

abnormal lateral pelvic sidewall lymph nodes. This showed a lateral pelvic sidewall recurrence rate of 5.7% in those that had radiation, followed by TME + lateral pelvic sidewall resection, compared to 19.5% for those that did not undergo the lateral pelvic sidewall resection (16). Kim et al have subsequently performed a retrospective review of their management of pelvic-sidewall lymph nodes. This group routinely performed post-radiation MRI scans. Their results showed that, even in patients who had appeared to have responded on imaging, if resected, 16% of these patients still had viable tumour in their lateral pelvic nodes (17). In their patient-cohort the worst survival was in patients who had no response to neoadjuvant treatment, followed by those who had a good response and subsequently did not undergo sidewall dissection and finally the best results were in the group that had a good response and underwent a pelvic sidewall dissection.

Direct invasion of tumour into the pelvic sidewall is difficult to manage. Due to the technical difficulties in achieving a clear margin when the tumour abuts or involves the major neurovascular structures of the pelvic sidewall many units would consider this un-resectable disease. In 1967 Barber and Brunschwig first reported 55 patients who underwent pelvic exenteration with en bloc common or external iliac vessel excision. Due to pelvic contamination and local factors only 5 of these 55 patients underwent graft reconstruction. 30-day mortality was high and only 5 patients remained alive at 5 years, all 5 of whom had only undergone venous excision (18). These initial poor results discouraged en bloc vascular resections for a generation of surgeons however we are starting to see some more-favourable results from large, modern units (19).

Lateral Pelvic Sidewall Dissection in Pelvic Exenteration:

Study	Year	Location	No. of patient	Vascular reconstruction	EBL (L)	Operating time (hrs)	R0 Resection rate (%)	Morbidity (%)	Mortality (%)	Overall 5-yr Survival (%)
Barber/Brunschwig *et al*	1967	New York, USA	55	5	-	-	-	-	35%	11
Yamada *et al*	2001	Kagoshima, Japan	17	0	-	-	-	-	3	0
Moore *et al*	2004	New York, USA	12	0	-	-	17	-	9	-
Austin/Solomon *et al*	2009	Sydney, Australia	36	8	6.6[a]	9	53	70	0	69 (19 month F/U)
Solomon *et al*	2015	Sydney, Australia	200	23	3.5	10.25	67	82	0.5	35
Tekkis *et al*	2017	London, UK	41		1.5	9	71	24	0	61

[a]estimated from transfusion requirements (adapted from a table by Brown et al (22))

Predicting locally invasive disease

Not all surgeons are comfortable performing multi-visceral resections as it often requires operating outside of an area of familiarity. Mohan et al proposed three main reasons for this (20). It is not always possible to identify the need for MVR pre-operatively, intraoperatively it is difficult to identify true invasion from inflammatory adhesions, and MVR is associated with significant morbidity (20-22). Govindarajan et al found that the majority of patients with locally advanced rectal cancer in the USA did not receive a MVR, despite improved survival shown with MVR (23). In their analysis of the SEER database they found only 33% of patients with locally advanced colon and rectal cancers underwent MVR. They found an overall survival benefit for undergoing a MVR with no increase in short-term mortality compared to the group who did not undergo MVR (23).

Intra-operative identification of true tumour invasion is difficult. Mohan et al performed a systematic review of 1575 patients across 22 studies where MVR was performed for colorectal cancer. 15 studies (1047 patients) differentiated between true tumour invasion and inflammatory adhesions with a true invasion rate of only 54.1% (20). Interestingly true invasion, versus inflammatory adherence was not seen to be an independent prognostic factor for survival in any of these studies on multivariate analysis.

Complications

The Clavien-Dindo classification system, modified in 2004 from the original complication classification proposal by Clavien in 1992 aims to create an objective and reproducible complication system for the post-operative course (24). Grade 1 and 2 complications are classed as "minor", while grade 3 and 4 are classed as "major". Deaths are classed as grade 5. Grade 1 and 2 complications are able to be dealt with at the bedside +/- pharmacological intervention. Grade 3 (further subdivided into 3a and 3b) require invasive procedures, while grade 4a/b complications require ICU-level management. Previous publications regarding multi-visceral resections have reported overall complication rates ranging from 37-87% (20). Few have reported on the grade of complication and there is scarce data on the pattern or impact of complications on survival.

The learning curve: Does volume matter?

This area is slightly controversial. In general, it is believed that complex extended resections are best performed in specialised centres so that theatre staff are familiar with the nuances of the surgery and specialised equipment (25). Centralisation has been a theme in Europe with some healthcare systems centralising rectal cancers to maintain experience. The PelvEX collaborative recently reviewed 1,170 patients who had undergone a pelvic exenteration for locally recurrent

rectal cancer (LRRC) (3). Centres were split into low volume and high volume centres using a cut-off of 20 cases per-year. The results showed there was no significant difference between high volume and low volume centres in overall outcomes and that the R0 resection margin rates in both low and high volume centres (51% to 60%, 49-65%) improved over the 10 years of the study period (3). It should be noted, however, that these are specialised centres contributing to a multi-national dataset.

Clear Margins and lymph nodes

The ability to achieve clear resection (R0) margins is predictive of survival and should be the goal for colo-rectal cancer surgery. Harris et al reviewed 583 patients with recurrent rectal cancer and found overall survival were affected by the resection status with 5-yr OS rates of 44%, 26% and 10% for R0, R1, and R2 respectively (26). The PelvEX collaborative reported 3-yr OS rates of 48.1% (R0), 33.9% (R1) and 15% (R2) (10). Radwan et al reported on their experience with 174 T4 primary rectal cancers and likewise showed improved 5-yr OS of 59.3% for R0, compared to 23% for R1 resection (27). Advanced-stage primary disease and pathologically positive lymph nodes are predictive factors for both local and distant relapse and reduced overall survival.

Urology

Urinary reconstruction may range from partial cystectomy with primary closure or ureteric re-implantation through to cysto-prostatectomy with ileal-conduit urinary diversion with up to 53% of patients undergoing a pelvic exenteration requiring en bloc cystectomy (28). Nephro-uretectomy may be required for direct invasion of the proximal ureter or kidney. These procedures are performed quite frequently for urological malignancies. Brown et al has reported higher rates of urological complications when performing urological resection and reconstruction

as part of a multivisceral resection when compared to reconstructions performed for primary urological cause (29). Most-typically involvement of the prostate has necessitated a cysto-prostatectomy due to concerns about breakdown of a cysto-urethral anastomosis in the setting of previous irradiation. However, Turner and colleagues have shown that post-irradiation cysto-urethral anastomosis may be performed with acceptable morbidity (30).

Thesis Questions

Based on perceived gaps in the literature we sought to assess three specific questions relating to pelvic exenteration across 2 large quaternary high-volume centres.

In **Chapter One,** an assessment is made of the changes in the nature of the surgery over three decades focusing on the surgical complexity, organs that are resected and the complication profile over that time frame. It will show that over time our outcomes for rectal cancer and non-rectal cancer patients have improved and that the complexity of the surgery has increased. All of these factors are discussed in detail.

Chapter Two examines ways to assess the overall outcomes and in particular the 1 and 5-year survival of patients who undergo this procedure. Univariate and multivariate analysis are performed to assess whether tumour type, patient factors or treatment factors influence disease free surgical and overall survival.

Chapter Three, takes an in depth look into the complication profile of undertaking such major surgery. In particular, complications are graded according to the Clavien-Dindo classification system for surgical complications. Other important KPI's are focused on as well including anastomotic leaks, sepsis, intra-abdominal collections and death within 30 days. A logistic

regression analysis is performed to assess independent predictors of morbidity. This chapter will show that the major morbidity is acceptable and the mortality is negligible for patients undertaking exenterative surgery in high volume centres.

Chapter Four, will specifically look at urological complications. Many of the exenterative procedures that are undertaken involve removing part of the urogenital system and hence a whole chapter is devoted to this subject. Again, this will look at predictors of poor outcomes, but also compare the non-urological with the urological intervention group.

It is hoped that in addressing these questions around the evolution and complication profile of exenterative surgery that we as a specialist colorectal community can better inform our patients of the path we have taken, the trajectory we are on, as well as the measured and significant risks that this surgery poses. I also hope that the thesis will show that our outcomes are good and that ultimately that undertaking such surgery can give them a significant prospect of cure.

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Chapter 1

Evolution of Pelvic exenteration surgery– resectional trends and survival outcomes over three decades.

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Abstract

Objective: To examine the changes in exenterative surgery over three decades analysing oncological outcomes and whether changes in surgical approach have led to improved patient outcomes

Background: Advances in surgical technology, perioperative care and pattern of disease recurrence have coincided with an evolutionary change in exenterative surgery.

Methods: A review of prospectively maintained databases of pelvic exenteration surgery from 1988 – 2018 at two high volume specialised institutions. The total cohort was divided into three major time points (1988- 2004, 2005-2010 and 2011 to 2018) to allow comparative analysis. Primary endpoints were overall survival in primary and recurrent disease at each time point. Secondary endpoints included anastomotic leak, blood transfusion, ileus, wound infection rates and evolution of case complexity. Data were analysed using R with a $p<0.05$ considered significant.

Results: Six hundred and seventy patients underwent exenterative surgery. In 2011–2018 there was an increase in resection of recurrent malignancy with a continuous increase in gastro-intestinal malignancies resected over each time period($p<0.001$,<0.01) and a reduction in gynaecological malignancy($p<0.001$). A significant increase in sacrectomy, pelvic sidewall resection and ileal conduit reconstruction was observed ($p<0.01$,<0.001). In 2005–2010 patients had increased rates of ileus and anastomotic leak($p<0.05$). Patients undergoing resection for primary disease had improved overall survival at time points 1998-2004 and 2011–2018 compared to those with recurrent disease($p=0.007$,<0.001). Overall survival was significantly improved in patients with primary versus recurrent disease($p=0.022$).

Conclusion: There has been a significant improvement in survival in patients undergoing pelvic exenteration surgery from primary disease. Case complexity has increased without significant morbidity.

Key Words: Pelvic exenteration, rectal cancer, pelvic malignancy, recurrent rectal cancer, gynaecological malignancy, Evolution of exenteration,

Introduction

Achieving a complete resection with clear margins for pelvic malignancy has been well documented in the literature as the most important prognostic factor (1, 2). Pelvic exenteration is a procedure that allows en bloc multivisceral resection of contiguous locally advanced or recurrent pelvic malignancy. First described in the literature in 1948, it involves the resection of pelvic viscera in non disseminated pelvic lesions where radical margins are difficult to achieve due to tumour growth in close relation to or involving adjacent organs with reconstruction of gastrointestinal and genito-urinal tracts where necessary (3). To date, survival data suggests long term survival in greater than 50% of patients after exenterative surgery for rectal, gynaecological and urological malignancy (4). Due to the radical nature of the resection and reconstruction process there are inherently increased rates of morbidity and mortality when compared to standard isolated organ resection (5, 6). Mortality rates in excess of 20% have been outlined with perioperative morbidity ranging from approximately 30 – 80% (7-10).

With the advent of neoadjuvant therapies, patient optimisation strategies, advances in surgical techniques, imaging and technology; pelvic exenteration surgery has been largely adapted since first inception. Improved oncological and patient post-operative outcomes have been reported with such adaptations (11). The development and application of total mesorectal excision (TME) surgery and use of radiation for rectal cancer has coincided with a significant decline in the incidence of local pelvic recurrence over the last decade from 30% to rates as low as 5 – 10% (12-15). Furthermore, local failure and pattern of disease recurrence has also changed with diminishing central and TME component recurrences. Similar patterns have been recognised in gynaecological malignancy with improved multidisciplinary treatment. All these

recent changes have led to the evolutionary customisation of exenteration surgery and reconstructive techniques for curative rather than palliative intent (16, 17).

Such advances have taken place in a carefully coordinated approach with improved oncological and procedural outcomes reported to be possibly related to surgeon and hospital volume (18). Moreover the development of specialist centres has produced good oncological and patient outcomes for extended radical resection for rectal cancers beyond the TME plane (19,20). The PelvEX collaborative highlighting outcomes in such centres globally has recently reported a 3-year overall survival of 56.4% in patients with clear margins (21). Despite these improved figures exenteration surgery is not commonly practiced and slow to be adopted into many surgical units. This is possibly due to many studies such as PelvEX reporting short term oncological outcomes and also the lack of reported data highlighting changes in the evolution of exenteration surgery over a prolonged period of time. Furthermore with such marked adaptations in approach and technique there have been scant studies reporting associated oncological outcomes with such customisation of surgery over time. The authors propose that it is imperative that such changes in resection and reconstructive technique are not at the patient's detriment. Therefore the aims of this study to examine the changes in exenterative surgery over three decades analysing oncological outcomes in different histological subtypes of pelvic malignancies in primary and recurrent disease. Changes in primary pathology excised with exenteration surgery, compartments resected, case complexity measured by resection and reconstructive patterns and patient complications are reported throughout the study period to assess whether changes in surgical approach over time have led to improved patient outcomes.

METHODS:

A review of prospectively maintained databases was undertaken to assess the outcome of patients who had undergone pelvic exenteration surgery. The primary objectives were to analyse changes in resections performed in exenteration surgery and assess oncological and patient outcomes. Two tertiary referral centres with specialist experience in the surgical management of advanced rectal cancer and similar surgical approaches to exenterative surgery were included. These institutions were Christchurch Hospital (Christchurch, New Zealand) and Peter MacCallum Cancer Centre (Melbourne, Australia). All patients were routinely discussed at a dedicated colorectal cancer multidisciplinary meeting. The diagnosis of all cancers was based on preoperative radiological imaging and clinical assessment. Data were prospectively collected at individual institutions. Patient demographics (age, sex), neoadjuvant & adjuvant regimen, use of intraoperative radiotherapy (IORT), surgical intent, type of surgery including extended resections and the need for bony resection or flap reconstruction and complications were recorded. Histopathological assessment included margin status (R status), lymph node positivity, presence of lympho-vascular invasion (LVI) and degree of differentiation. Centralised data were evaluated independently and analysed at the Peter MacCallum Cancer Centre, Melbourne, Australia.

Definitions:

The total cohort was divided into three major time points to allow for equal cohort numbers over each decade of surgery for comparative analysis. The cohorts were divided in those operated on from 1988- 2004, 2005-2010 and 2011 to 2018 respectively. Patients analysed included pathologies of Gastrointestinal (GI), gynaecological, squamous cell carcinoma (SCC) and Other (Melanoma, Prostate, Sarcoma, GIST, Chordoma) and had surgically resected organs recorded

prospectively. Type of exenteration performed was defined by the seven intrapelvic compartments demonstrating the organs that are included in each compartment. They were classified as Anterior above peritoneal reflection (PR), Anterior below PR, Central, Posterior, Lateral, Inferior and Peritoneal Reflection (22). Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause. Resection of primary disease was defined as newly diagnosed malignant process requiring up front pelvic exenteration based on clinical and radiological assessment. Recurrent disease was defined as newly diagnosed disease of similar histological characteristics as previously resected tumour with a RO margin. Histopathological evaluation considered a R0 resection as a circumferential resection margin (CRM) of >1mm. R1 resection was the presence of microscopic residual disease defined as a CRM of ≤1mm, whereas R2 resection was the presence of macroscopic residual disease. Complexity of exenteration was defined by type of organs resected or the requirement of organ reconstruction. Complications were compiled prospectively. A wound infection is defined by the US Centre for Disease Control and Prevention (CDC) as surgical site infection (SSI) (23). This is further defined as superficial incisional SSI (recorded as grade1) deep incisional SSI (grade 2) organ/space SSI (grade3). Ileus was defined as functional obstruction of the gastrointestinal tract and especially the small intestine that is marked by the absence of peristalsis, is usually accompanied by abdominal pain, bloating, and sometimes nausea and vomiting, and typically occurs following abdominal surgery. Anastomotic leakage was defined as a defect of the intestinal wall at the anastomotic site to a communication between the intra- and extraluminal compartments (24).

Endpoints:

The primary endpoints were overall survival primary and recurrent disease and by histological subtype at each time point. Secondary endpoints included complication rates of anastomotic leak, blood transfusion requirement, ileus and wound infection rates and evolution of case complexity.

Statistical Analysis:

Data were analysed using R (version 3.0.3; R Development Core Team 2009). Baseline characteristics were summarised using descriptive statistics, with the mean and standard deviation (SD) used for categorical variables and the median and range for continuous variables. Comparison of outcomes between two groups was performed using paired t-test and one-way Anova was used to analyse the means of three or more factors within the study with a p-value of less than 0.05 ($p<0.05$) considered significant. Univariate and multivariate analysis was performed to examine the impact of one or multiple factors on outcome. The Kaplan-Meier method was used to estimate the OS curves for each histological subtype and in primary and recurrent disease and associated 95% confidence intervals were reported. Univariate analysis of possible prognostic variables on OS was assessed using the log-rank test (or exact log-rank test for small group numbers) with hazard ratios obtained from the Cox proportional hazards model used to estimate hazard ratio (HR) for death.

Results

Patients were divided into three time points dependent on timing of exenterative surgery, 1988 – 2004 (n=193), 2005 – 2010 (n=250) and 2011 – 2018 (n= 265, Table 1, Figure 1). A significantly increased number of males underwent exenteration surgery in the latest time period. Age, ASA scores and co-morbidities remained similar throughout all time points. A significant increase in resections performed for recurrent disease was observed in 2011 -2018 ($p<0.01$). The number of

node positive tumours (N1 & N2) resected have significantly increased over time ($p>0.05$). There has been an increase in sacrectomy and prostatectomy over time with significant reduction in anal, ovarian and uterine resections. Furthermore, a significant increase in lateral, central and central with posterior compartments were resected with a similar decrease in central with inferior compartment resection ($p<0.01$). Margin (R) status was accurately collected for 361 patients within this thesis. In patients undergoing exenteration for primary disease R0 (clear margin) was achieved 81.6% of cases with R1 (microscopic margin) achieved in 17.6% and R2 (macroscopic) in 0.8% of cases. In recurrent cancer patients requiring exenteration – R0 margin was 70.1% followed by R1 margin of 24.8% and R2 of 4.9%.

	1988 - 2004		2005 - 2010		2011 -2018		Total	
N	193	29%	212	32%	265	40%	670	
Gender								
Male	66	34%	67	32%	142	54%	275	41%
Female	127	66%	145	68%	99	37%	371	55%
Unknown					24	9%	24	4%
Age								
Mean (SD)	62.9 (13.5)		62.4 (13.0)		60.8 (12.9)		61.9 (13.1)	
Median (Range)	64.8 (26.4 - 111.0)		64.7 (22.1 - 89.2)		61.9 (19.0 - 87.0)		63.6 (19.0 - 111.0)	
ASA Grade								
1	11	5.60%	25	11.79%	16	6.03%	52	7.76%
2	108	55.90%	104	49%	102	38.49%	314	46.86%
3	57	29.50%	63	29.71%	58	21.88%	178	26.56
4	5	2.59%	5	2.35%	6	2.26%	16	2.38%
x	11	5.60%	15	7.07%	59	22.26%	85	12.68%
Co-morbidity								

MI	15	7.77%	11	5.18%	16	6.03%	42	6.26%
Stroke	7	3.62%	8	3.77%	6	2.26%	21	3.13%
PVD	2	1%	2	0.94	3	1.13%	7	1.04%
Asthma	11	5.60%	14	6.60%	8	3.01%	33	4.92%
COPD	16	8.20%	6	2.83%	3	1.13%	25	3.73%
Renal failure	6	3.10%	7	3.30%	5	1.88%	18	2.68%
Diabetes	22	11.39%	22	10.37%	21	7.92%	65	9.70%
Psychiatric disorder	12	6.21%	12	5.66%	9	3.39%	33	4.92%
Smoker	23	11.91%	31	14.62%	24	9.05%	78	11.64%
Tumour								
Primary	142	74%	166	78%	115	43%	423	63%
Recurrent	51	26%	46	22%	150	57%	247	37%
T								
0	105	54%	109	51%	9	3%	223	33%
1	2	1%	0	0%	4	2%	6	1%
2	6	3%	7	3%	18	7%	31	5%
3	20	10%	22	10%	84	32%	126	19%
4	60	31%	73	34%	92	35%	225	34%
X	0	0%	1	0%	58	22%	59	9%
N								
0	158	82%	161	76%	122	46%	441	66%
1	25	13%	30	14%	42	16%	97	14%
2	10	5%	17	8%	36	14%	63	9%
X	0	0%	4	2%	65	25%	69	10%
M								
0	181	94%	196	92%	225	85%	602	90%
1	12	6%	16	8%	39	15%	67	10%
Organs Resected								
Colon	29	15%	51	24%	52	20%	132	20%
Rectum	148	73%	140	66%	180	68%	468	70%
Anus	75	39%	40	19%	31	12%	146	22%
Small intestine	26	13%	43	20%	65	25%	134	20%
Vagina	49	25%	37	17%	50	19%	136	20%

Uterus	59	31%	73	34%	53	20%	185	28%
Ovaries FP tubes	66	34%	101	48%	41	15%	208	31%
Prostate	29	15%	31	15%	65	25%	125	19%
Bladder	54	28%	50	24%	78	29%	182	27%
Sacrum	30	16%	24	11%	60	23%	114	17%
Compartments Resected								
Central	6	3%	7	3%	38	14%	51	8%
central with posterior	29	15%	20	9%	70	26%	119	18%
anterior above PR with anterior below PR	25	13%	46	22%	24	9%	95	14%
central with anterior below PR	66	34%	89	42%	62	23%	217	32%
anterior below PR	5	3%	8	4%	21	8%	34	5%
anterior above PR with anterior below PR	4	2%	7	3%	10	4%	21	3%
lateral	3	2%	4	2%	34	13%	41	6%
central inferior	55	28%	31	15%	6	2%	92	14%

Table 1: Patient demographics, co-morbidities, tumour characteristics and organ/compartments resected.

From 1998 to 2004 a significant proportion of patients (n=142) underwent exenterative surgery for primary disease compared to those with recurrent disease (n=51). A significant similar pattern was observed from 2005 – 2010 (n=183, n=67 respectively ($p<0.01$). There was a change in 2011 – 2018 with a significantly higher proportion of patients undergoing exenterative surgery for recurrent disease (n=150) rather than primary disease (n=115, $p<0.001$).

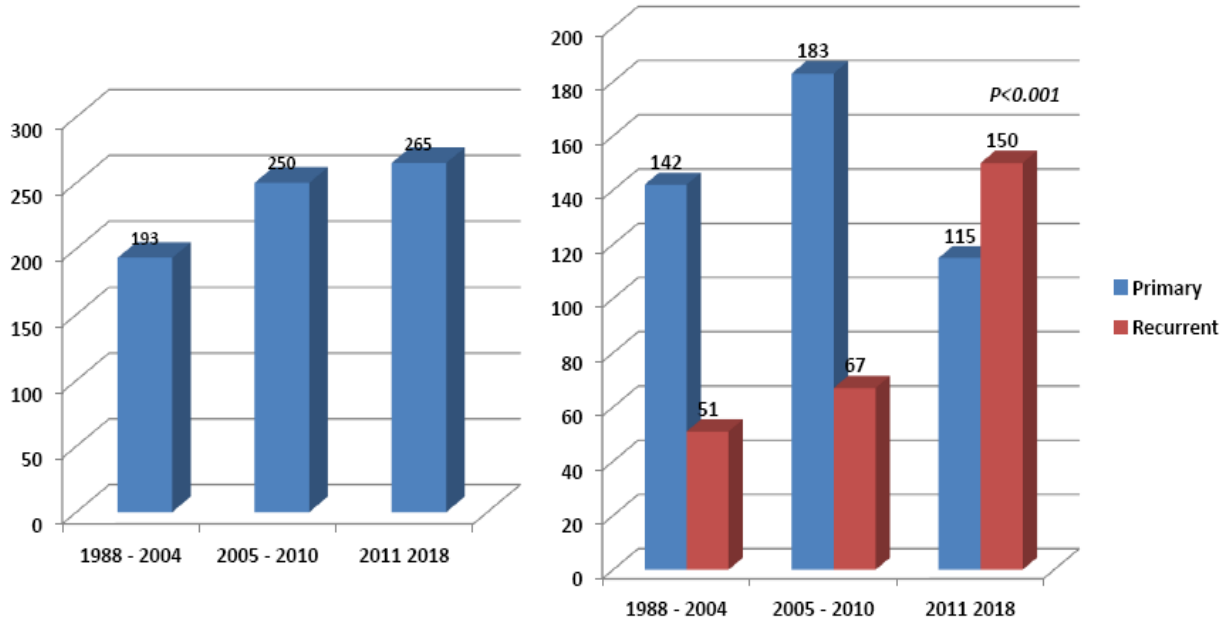

Figure 1: Total patient cohort at each time point and resection of primary or recurrent disease: *There was a significantly higher proportion of primary diagnosed malignancy undergoing pelvic exenteration in 1998 – 2004 and 2005 – 2010 (p<0.01). In 2011 – 2018 there has been a significant shift in resection of recurrent malignancy compared to primary disease (P<0.001).*

Throughout the study period there was a significant increase in exenteration surgery performed for GI related malignancies over each time point (1988 – 2004 n= 135, 2005 – 2010 n=161, 2011 – 2018 n=225, p<0.01, Figure 2). There was no statistical increase in patients undergoing exenterative surgery for SCC and other malignancies at each time point (p=0.6872, p=0.6319 respectively). There was a significant decrease in exenterative surgery being performed for patients with gynaecological related malignancies in 2005 – 2010 (n=99) and 2011 – 2018 (n=10, p<0.001).

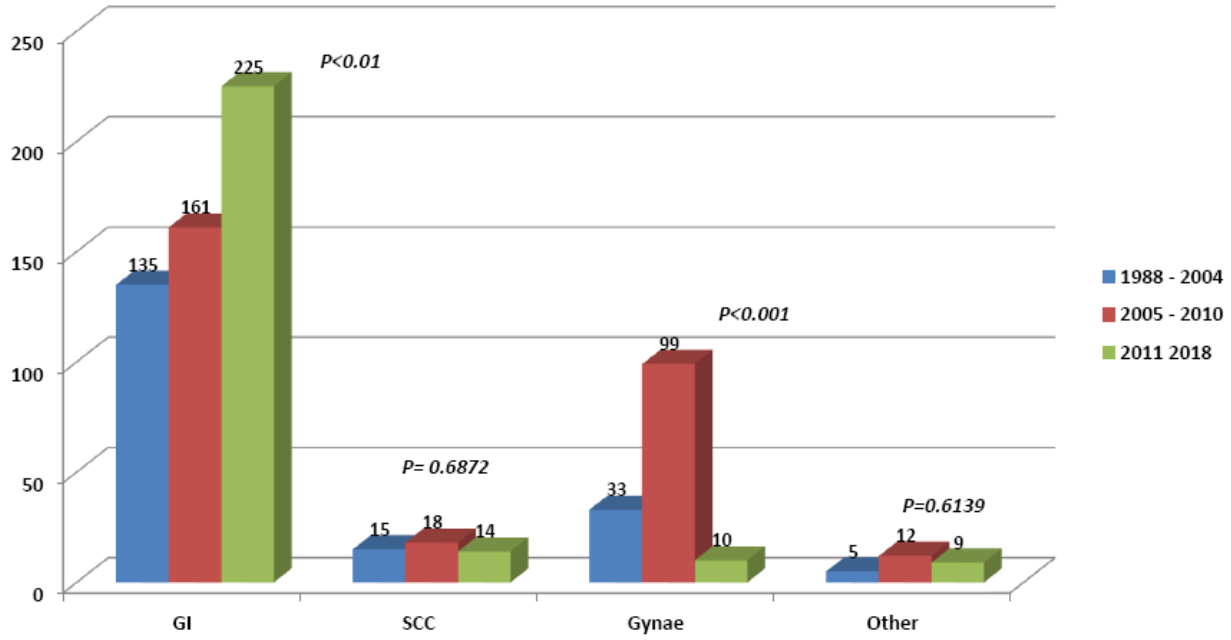

Figure 2: Primary pathology resected: *there has been a continuous increase in GI malignancies resected over each time period (p<0.01). There has been a similar amount SCC and Other malignancies (Melanoma, Prostate, Sarcoma, GIST, Chordoma) resected at each time point during the study period (p=0.687, p=0.61 respectively). Gynaecological related malignancies have significantly reduced from 2005 – 2010 time point to 2011 – 2018 (p<0.001).*

Case complexity has increased over the study period. There has been a significant increase in patients undergoing sacrectomy in 2011 – 2018 (n=60, p<0.01, Figure 3). Urinary diversion and reconstruction with ileal conduit has also significantly increased in the latest time period (n=81, p<0.001). Similarly a significantly increased proportion of patients in 2011 – 2018 had pelvic sidewall resection performed (n=34, p<0.001). The number of patients undergoing flap reconstruction of the perineum remained similar throughout each time point (p=0.142).

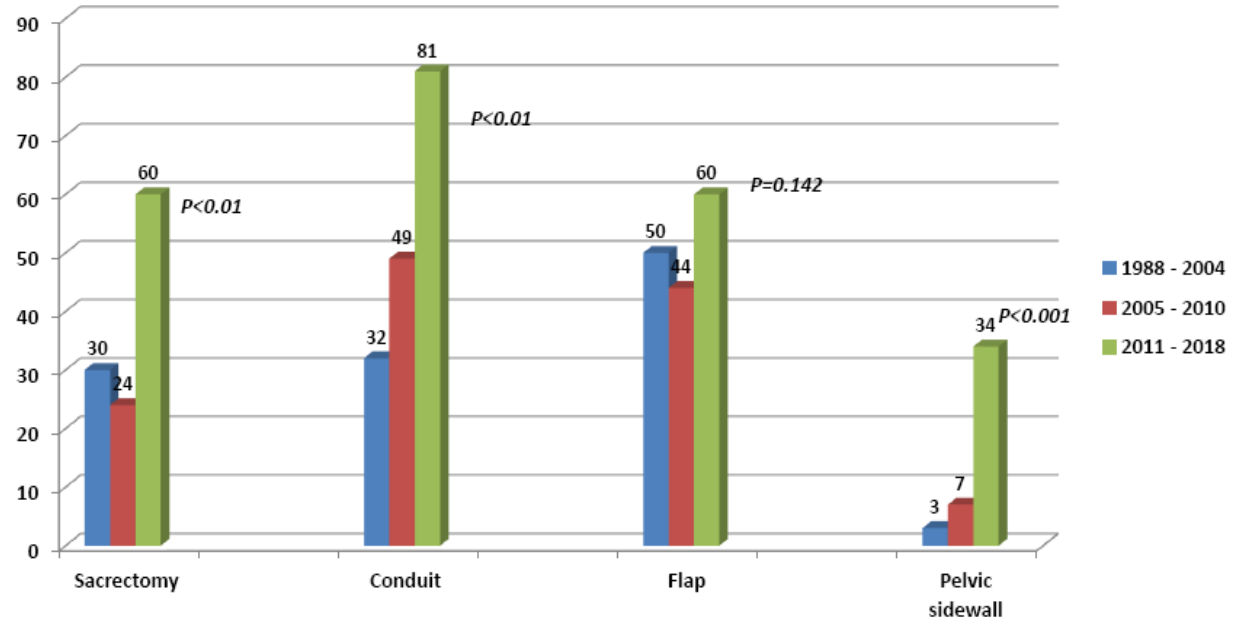

Figure 3: Case complexity outlined by boney and sidewall resection and reconstruction. *Throughout the study period there has been a significant increase in sacrectomy and pelvic sidewall resection ($p<0.01$ and <0.001 respectively). Patients undergoing flap reconstruction has remained similar throughout the study period ($p=0.142$). Ileal conduit reconstruction has significantly increased in the most recent time point 2011 – 2018 ($p<0.01$).*

Complications were recorded prospectively within the database during the study period. There was a significant increase in patients with postoperative ileus during 2005 – 2010 time point compared to other time points ($p<0.001$, Table 2). 25% of patients (n=52) experienced post-operative ileus compared to 18% in 1988- 2004 and 17% in 2011 to 2018. Of the total cohort, 20% of patients developed post-operative ileus. A significantly higher proportion of patients experienced an anastomotic leak during the same time period (n=10, p=0.006). Of patients that had a gastro-intestinal anastomosis performed (n=127) the anastomotic leak rate was 5%. The overall wound infection rate for the cohort was 19%. Wound infection rates were significantly higher in 2011 – 2018 (n=50, $p<0.001$). Superficial wound infections were significantly higher during this time period with less deep organ spaced infection (14% & 1% respectively). Deep

organ space infections were highest in 1988 – 2004 and 2005 – 2010. Blood transfusion requirement was significantly lower in 2005 – 2010 compared to other time points ($p<0.01$, Table 2). Mean transfusion was 0.943 of a unit (range 0-27units).

Complications	**1998 - 2004**		**2005-2010**		**2011-2018**		**Total cohort**		***P Value***
Ileus									***0.001***
No	159	82%	160	75%	197	74%	516	77%	
Yes	34	18%	52	25%	44	17%	130	20%	
Anastomotic Leak									***P=0.006***
No	190	98%	202	95%	250	94%	632	94%	
Yes	3	2%	10	5%	15	6%	14	6%	
Wound Infection									***P<0.001***
No	150	78%	173	82%	191	72%	514	77%	
Grade 1	11	6%	14	6%	37	14%	62	9%	
Grade 2	25	13%	19	9%	10	4%	54	8%	
Grade 3	7	4%	6	3%	3	1%	16	2%	
Transfusion									
Mean (SD) Median (Range)	1.68 (5.88) 0 (0- 55)		0.943 (3.24) 0 (0-27)		1.67 (3.24) 0 (0-20)		1.41 (4.19) 0 (0-55)		***P<0.01***

Table 2: ***Complications* encountered during each time point and total cohort***: Patients undergoing pelvic exenteration surgery during 2005 – 2010 had significantly increased rates of ileus compared to other time points ($p<0.001$). There were also increased rates of anastomotic leak at this during this time point. Incidence of total wound infections were significantly lower in 2005 – 2010 time point ($p<0.001$). Blood transfusion requirement was significantly higher during 1984 – 2004 and 2011 – 2018 time points ($p<0.01$).*

Overall survival for patients with primary and recurrent disease undergoing exenterative surgery was recorded during each time period and also for the total cohort. Patients with primary disease undergoing resection had a significantly improved survival in 1998 – 2004 and 2011 – 2018 than those undergoing operative intervention for recurrent disease ($p=0.007$, $p<0.001$, Figure 4).

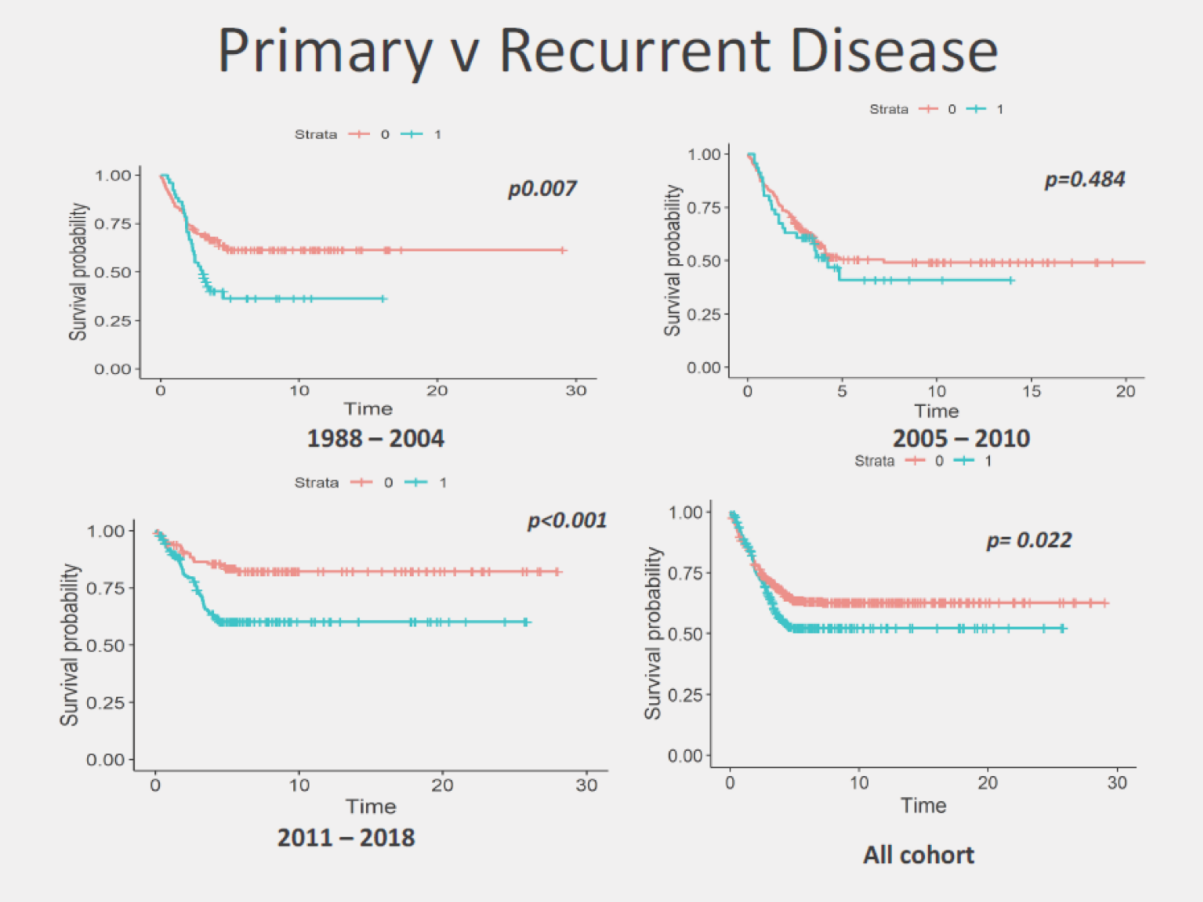

Figure 4: Overall survival in primary (Red) and recurrent disease (Green): *Patients undergoing resection for Primary disease had significantly improved overall survival at time points 1988-2004 and 2011 – 2018 compared to those with recurrent disease (p=0.007, p<0.001 respectively). Overall survival for the total cohort was significantly improved in patients undergoing resection for primary disease versus recurrent disease (p=0.022).*

There was no significant difference in survival observed in those with primary versus recurrent disease during 2005 – 2010 (p=0.484). Within the total cohort those with primary resected disease had significantly improved survival than those with recurrent disease (p=0.022). Survival probability for each major histological subtype undergoing exenteration at each time point was measured. Those patients with gastrointestinal malignancy undergoing exenteration in 2011 – 2018 had significantly improved survival compared to those undergoing surgery in 1988-2004 and 2005 – 2010 (p<0.01, Figure 5). A similar pattern was observed in patients with

gynaecological malignancy having a significantly improved survival when undergoing resection in 2011-2018 compared to those in 1988 – 2004 and 2005 – 2011 ($p<0.05$). Patients with SCC and other malignancy (Melanoma, Prostate, Sarcoma, GIST, Chordoma) did not display any difference in survival when operated in each time point ($p=0.793$, $p=0.667$).

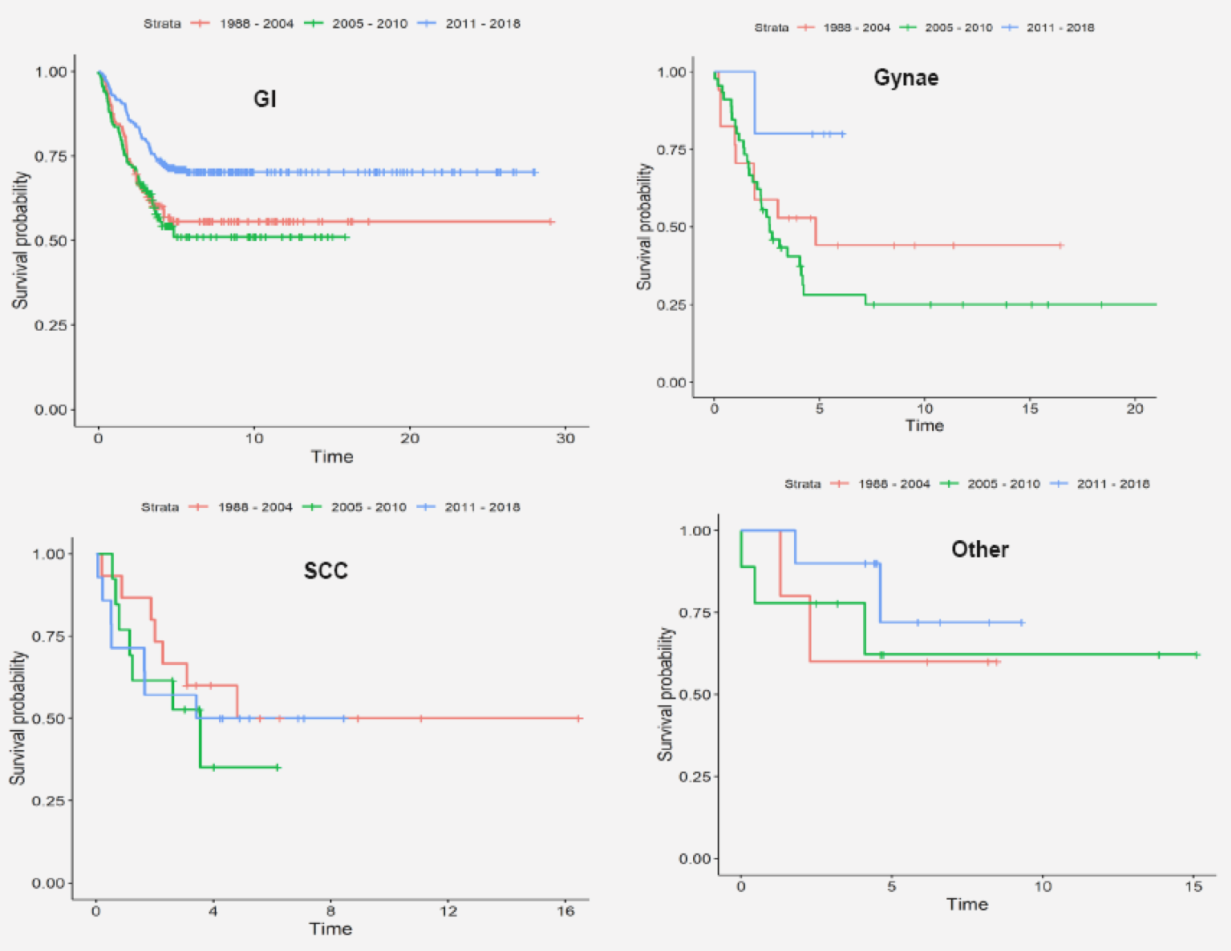

Figure 5: Overall survival in each histological subtype at each time point*. Patients undergoing pelvic exenteration with GI and Gynae diagnosed malignancy had significant overall improved survival in 2011 to 2018 compared to other time points ($p<0.01$ and $p<0.05$ respectively). SCC and other* malignancy (Melanoma, Prostate, Sarcoma, GIST and Chordoma) *did not have improved survival at each time point.*

Discussion

This large international combined series from established centres, specialising in pelvic exenterative surgery, presents good outcomes and describes the evolution of this technique for locally advanced pelvic tumours. Surgical intervention to treat locally advanced pelvic tumours has steadily been gaining momentum. During the course of the last three decades, this study demonstrates advances in the operative strategies implemented and the types of pathology encountered. There was a tendency towards performing exenterative surgery for recurrent disease during the latter years of this study (2011 to 2018) compared with the preceding time points. The increasing complexity of the pathology encountered is also reflected by the expanding number of surgical components performed. This correlation is demonstrated by the increasing number of sacrectomy, ileal conduits and lateral pelvic sidewall dissections performed.

These increasing trends might mirror overcoming the surgical learning curve and therefore the technical challenges of the operative interventions evolve with increasing familiarity of the procedures. As surgeons become more comfortable with the techniques of exenterative surgery, the boundaries have been pushed, performing more radical surgery including cystectomy, sacrectomy and now lateral pelvic side wall resections. The complexity management of the disease has also increased (recurrent versus primary) and an increasing willingness to perform exenterative surgery on higher risk patients (less ASA 1 & 2 patients).

The surgery has also become more bespoke, with the aim to improve patient's quality of life. During this study period, there has been an increasing trend towards sphincter preserving surgery, reflected by the downward trend in resecting the anus (39% to 12%) as exenterative surgery has evolved. This might explain the slight increase in anastomotic leak rate between 2005 to 2010 (5%) compared with 1988 to 2004, which corresponds with the initial downward

trend in resecting the anus. As this technique has evolved and further reduction in resecting the anus, the anastomotic leak rate has decreased to the baseline. Other efforts to improve patient's quality of life are reflected in the development of techniques to resect the prostate enbloc and leave the bladder in situ and functioning (25). This strategy has been enabled by the development in the techniques for radical prostate surgery in prostate cancer.

The increasing familiarity and expertise in exenterative surgery might also be reflected in the decrease utilisation of blood transfusion in the middle period of this study. However, the adoption of expanding operative complexity, particularly with increasing pelvic side wall dissection and sacrectomy between 2010 to 2018, may also explain the increase in blood transfusion requirements during this time period, similar to the initial period (1988 to 2004).

This current study also reports a significant overall survival in patients undergoing exenteration surgery for primary compared to recurrent disease. This improved survival was observed in patients undergoing resection in 1998 – 2004 and 2011 – 2018 and further borne out in the total cohort despite no difference in survival observed in patients operated within 2005 – 2010. This observation could be reflected on the fact that there has been improved patient selection over the last decade despite the significant increase in patients with recurrent disease undergoing surgery within the two units. Throughout all time points there has been increased numbers of patients with GI pathology being resected however within the 2005- 2010 period there was a significant increase in operative intervention in patients with gynaecological related malignancy followed by a significant decline in the last decade. The authors postulate that this significant increase could potentially lead to worse survival in patients undergoing resection within the primary malignancy group during this time point. The literature to date has documented inferior survival in patients with gynaecological malignancy undergoing

exenterative surgery than primary organ resection or resection of other pathologies. A study by Westin et al reported five-year overall survival after pelvic exenteration was 40% in patients with gynaecological malignancy (26). The authors report that survival outcomes have not significantly improved despite improvements in technique and patient selection undergoing exenteration. Moreover, they state that non-modifiable factors associated with gynaecological malignancy at the time of exenteration are associated with poor survival. These outcomes have been mirrored in other studies (27, 28) A recent study reported an overall survival of 40.7% and cumulative 5-year overall survival of 38% in patients under exenterative surgery for primary and recurrent cervical carcinoma. In contrast patients undergoing exenterative surgery for GI related malignancies have superior overall oncological and survival outcomes.

This analysis documents a sustained increase in survival at each time point in patients undergoing intervention for primary and recurrent disease with an overall 5-year survival of greater than 75% or primary resected malignancy in the latest time point. These findings are reflected in other smaller studies analysing survival outcomes in primary and recurrent disease. Ferenschild et al report overall 5-year survival for primary locally advanced rectal cancer, recurrent rectal cancer, and cervical cancer was 66%, 8%, and 45% respectively (29). Furthermore a more recent study comparing outcomes in rectal cancer patients under exenteration surgery highlight a significant reduced disease free survival in patients with recurrent rectal cancer compared to those with primary locally advanced disease (30). Recurrent rectal cancer patients continued to have significant worse DFS even after patients with R1 resections were excluded. A study examining outcomes of 40 consecutive exenterations over a nine year period for locally advanced versus locally recurrent colorectal malignancy reported that 5-year overall survival was significantly inferior in recurrent disease as apposed to upfront

advanced disease (58.7% vs. 11.8%, P = 0.022) (31). Similar to contemporary work from the PelvEX collaborative group and other centres, the authors report worse outcomes in recurrent disease and the importance of achieving an RO resection (1, 30, 32, 33).

The five-year survival probability of each primary pathology was analysed at each time point to assess survival outcomes. The analysis demonstrates that patients operated on during this current time point (2011 – 2018) had significantly improved five-year survival in GI malignancy compared to other time points. There was no change in survival in those operated in 1988 – 2004 and 2005 – 2010. Moreover, patients with SCC and Other malignancy had similar five year survivals regardless of time point of operation. Interestingly however the current study documents improved survival in patients undergoing exenteration for gynaecological malignancy during 2011 – 2018. With a significant reduction in the number of patients in the time point the authors postulate that improved patient selection for curative intent is likely to be the underlying reason for such a significant improved survival.

There are limitations to this study, which need to be considered. Firstly, interpretations of these results are limited somewhat by the degree of heterogeneity, both within each and between centres. This includes the degree of heterogeneity of the patient populations, pathology, variations in the treatment strategies and surgical technique. It is also important to acknowledge that the data is collected over a long time period (1988-2018), which may also introduce a degree of inherent bias, given the evolving treatment strategies over time, which have been described. However, there is a previous collaborative history (35, 36), with also a high degree of consistency of approach across the centres included in this study.

Conclusion

Pelvic exenterative surgery has undergone dramatic changes over the last three decades with its indications now expanding to include significantly increased cases of recurrent disease. Despite increased case complexity over time there has been no significant change in the associated complication profile. Patients undergoing upfront exenteration for primary disease continue to have improved survival compared to those undergoing resection of recurrent malignancy. Finally, patients with GI and gynaecological primaries have seen significant improved survival in the last decade.

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Chapter 2

Complications after pelvic exenteration for locally advanced and recurrent pelvic malignancies: A 25-year experience

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Short running head: Complications after pelvic exenteration

Mini-Abstract: Our series adds to the increasing evidence that good outcomes can be achieved for pelvic exenterative surgery in locally advanced and recurrent pelvic malignancies. A coordinated approach in specialist centres for beyond TME surgery demonstrates this is a safe and feasible procedure, offering low major complication rates.

ABSTRACT

BACKGROUND: The oncological role of pelvic exenteration for locally advanced and recurrent pelvic malignancies arising from the anorectum, gynaecological or urological systems is now well established. Despite this, the surgical community has been slow to accept pelvic exenteration, undoubtedly owing to concerns about high morbidity and mortality rates based on historical data. Therefore, the aims of this study were to assess the general major complications and predictors of morbidity following exenterative surgery for locally advanced and recurrent pelvic malignancies.

METHODS: Data were collected from prospective databases at two high-volume institutions specialising in beyond TME surgery for locally advanced and recurrent pelvic malignancies between 1990 and 2015. The primary outcome measures were major complications (Clavien-Dindo 3 or above) and predictors for morbidity.

RESULTS: A total of 646 consecutive patients requiring exenterative surgery for local advanced pelvic malignancies were identified. The median age was 63 years (range 19-89 years), and the majority were female patients (371; 57.4%). Five hundred and forty patients did not suffer a major complication (83.6%) following pelvic exenterative surgery. One or more major complications were observed in the remaining 106 patients (16.4%). The most common major complications were intra-abdominal collection (43.7%; n=59/135) and wound infection (14.1%; n=19/135). The overall inpatient mortality rate was 0.46% (n=3/646). Independent predictors for major morbidity following exenterative surgery for locally advanced or recurrent pelvic malignancies were squamous cell carcinoma of anus, sacrectomy, past history of peripheral vascular disease and requirement for blood transfusion.

CONCLUSION: Our series adds to the increasing evidence that good outcomes can be achieved for pelvic exenterative surgery in locally advanced and recurrent pelvic malignancies. A coordinated approach in specialist centres for beyond TME surgery demonstrates this is a safe and feasible procedure, offering low major complication rates.

KEYWORDS: Pelvic exenteration, malignancy, 30-day morbidity & mortality, complications

INTRODUCTION:

The oncological role of pelvic exenteration for locally advanced and recurrent pelvic malignancies arising from the anorectum, gynaecological or urological systems is now well established(1-3). The beyond TME collaborative provides consensus on the definitions and principles of management of these complex patients, advocating an extended surgical resection beyond the TME plane to achieve a pathological R0 resection(1). Extensive multi-visceral resection is often required to achieve clear resection margins (R0), which is the key predictor of long-term survival for locally advanced pelvic tumours(4, 5). It is the only curative option for patients with locally advanced or recurrent pelvic malignancy.

Since pelvic exenteration was first described in 1948, advances in healthcare have brought dramatic oncological improvements and reduced morbidity from what was previously deemed a palliative procedure(6, 7). In recent decades, an attempt to offer a chance of cure to greater numbers of patients with more advanced disease has enabled the development of techniques for increasingly radical lateral neurovascular and bony pelvic excisions(8). Current data demonstrate that long-term survival after pelvic exenteration is achievable in more than 50 per cent of selected patients with an acceptable quality of life(8, 9).

Although pelvic exenteration clearly represents the treatment of choice in the modern era of medicine, accessibility to surgery for those with potentially curative local recurrence remains a concern(10). Also, despite the encouraging figures, which are comparable to outcomes of hepatic metastasectomy, the surgical community has been slow to accept pelvic exenteration, undoubtedly owing to concerns about high morbidity and mortality rates based on historical data(7, 8). Therefore, the aims of this study were to assess the general major complications and

predictors of morbidity following exenterative surgery for locally advanced and recurrent pelvic malignancies.

METHODS:

A retrospective review of prospectively maintained databases was undertaken to assess the outcome of patients who have undergone pelvic exenterative surgery for locally advanced or recurrent pelvic malignancies. The primary objectives were to identify the general major complications and predictive factors for morbidity following pelvic exenterations. Two tertiary referral centres with specialist experience in the surgical management of advanced pelvic tumours, similar surgical approaches to beyond TME surgery and previous collaborative experience(2, 11) were included. These institutions were Christchurch Hospital (Christchurch, New Zealand) and Peter MacCallum Cancer Centre (Melbourne, Australia). All patients were routinely discussed at a dedicated pelvic exenterative surgery multidisciplinary meeting. The diagnosis of locally advanced pelvic tumour was based on preoperative radiological imaging and clinical assessment. Data were prospectively collected at individual institutions. Patient demographics (age, sex, ASA), comorbidities, primary or recurrent tumour, tumour type, neoadjuvant & adjuvant regimen, organs resected and type of surgery including the need for urological or bony resection or flap reconstruction were recorded. Furthermore, the type of general complications (number of major complications: wound infection, pneumonia, urinary tract infection, sepsis, myocardial infarction, arrhythmias, pulmonary embolus, stroke, acute kidney injury, acute respiratory distress syndrome, anastomotic leak, intra-abdominal collection, post-operative bleeding and small bowel obstruction) were recorded.

Definitions:

Operations were considered exenterative when the primary organ and at least one of the surrounding organs was removed en-bloc (rectum, bladder, prostate, uterus, vagina, sacrum, small bowel, ureter, iliac vessels, ovary and fallopian tube removal)(11).

Patients analysed included the following pathologies; gastrointestinal adenocarcinoma, anal squamous cell carcinoma (SCC), gynaecological (ovarian, cervical, uterine or vaginal) and other malignancy (melanoma, prostate, sarcoma, GIST and chordoma) and had surgically resected organs recorded prospectively.

Resection of primary disease was defined as newly diagnosed malignant process requiring up front pelvic exenteration based on clinical and radiological assessment. Recurrent disease was defined as newly diagnosed disease of similar histological characteristics as previously resected tumour with an R0 margin.

Complications occurring within 30-days postoperatively or during the inpatient care for the index operation were graded according to the Clavien-Dindo classification system for surgical complications(12). A major complication was defined as Grade III, IV or V of the Clavien-Dindo classification. A wound infection was defined as per the United States Centre for Disease Control and Prevention (CDC) for surgical site infection (SSI)(13). Anastomotic leak was defined as an intestinal wall defect at the site of the anastomosis with a direct communication between the intra- and extraluminal compartments(14). Sepsis was defined as proof of bacteraemia or clinical suspicion of sepsis, as well as signs and symptoms of systemic inflammatory response syndrome(15). An intra-abdominal collection was defined as an organised collection of fluid or pus diagnosed on imaging(16). Inpatient mortality was defined as a death occurring within 30-days of the index procedure.

Endpoints:

The primary endpoints were the general major complications and predictive factors for major morbidity following pelvic exenterative surgery for locally advanced and recurrent pelvic malignancies.

Statistical Analysis:

Baseline characteristics were summarised using descriptive statistics. All categorical data were analysed using either Fisher's exact or Pearson-chi square test and continuous data using the student t-test. The Kaplan-Meier method was used to estimate the 5-year overall survival, with a sub-analysis performed assessing patients' survival by comparing pelvic exenteration for primary and recurrent pelvic tumours and major complications. Logistic regression analysis was performed to identify independent risk factors for major morbidity. All analysis was undertaken using IBM Corporation Released 2017, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corporation. A $p<0.05$ was considered significant.

RESULTS:

A total of 646 consecutive patients requiring exenterative surgery for local advanced or recurrent pelvic malignancies between 1990 and 2015 were identified from the combined databases of two tertiary surgical institutions. The median age for this cohort of patients was 63 years (range 19-89 years), and the majority were female patients (371; 57.4%). The baseline patient characteristics are outlined in Table 1. The majority of exenterations were performed for primary disease (64.4%) and gastrointestinal adenocarcinoma histological subtype (70.0%).

Patient Characteristic	**Total N = 646 (%)**
Sex	
Male	275 (42.6%)
Female	371 (57.4%)
Age	
<60	263 (40.7%)
>60	383 (59.3%)
ASA Score	
1	62 (9.6%)
2	374 (57.9%)
3	195 (30.2%)
4	15 (2.3%)
Prior Chemotherapy	
Yes	378 (58.5%)
No	268 (41.5%)
Prior Radiotherapy	
Yes	343 (53.1%)
No	303 (46.1%)
Disease Type	
Primary	416 (64.4%)
Recurrent	230 (35.6%)
Tumour Type	
GI Adenocarcinoma	452 (70.0%)

Anal SCC	42 (6.5%)
Gynaecological	72 (11.1%)
Other	80 (12.4%)

Table 1: Baseline patient and tumour characteristics.

Five hundred and forty patients did not suffer a major complication (83.6%) following pelvic exenterative surgery. The major complications observed in the remaining 106 patients (16.4%) are outlined in Table 2. Some patients experienced more than one major complication. The most common major complications were intra-abdominal collection (43.7%; n=59/135) and wound infection (14.1%; n=19/135). The frequency of anastomotic leak (1.5%; n=10/646) and post-operative bleeding (0.93%; n=6/646) requiring intervention were very low in this series. The overall inpatient mortality rate was 0.46%, occurring in 3 patients within this series. One patient died from a pulmonary embolus and the other two patients died from septicaemia.

Variables	**Total**
Major complications	106 patients (16.4%)
Wound Infection	19 (14.1%)
Pneumonia	4 (3.0%)
UTI	3 (2.2%)
Septicaemia	5 (3.7%)
Myocardial infarction	3 (2.2%)
Arrythmia	3 (2.2%)
Pulmonary embolus	3 (2.2%)
Stroke	1 (0.7%)
Acute kidney injury	10 (7.4%)
Acute respiratory distress syndrome	5 (3.7%)
Intestinal anastomotic leak	10 (7.4%)
Intra-abdominal collection	59 (43.7%)
Post-operative bleeding	6 (4.4%)
Small bowel obstruction	4 (3.0%)

Table 2: Major complications following pelvic exenterative surgery in 106 patients. Some patients suffered more than one major complication. Total number of major complications were 135 with wound complications accounting for the majority.

There was no difference in major morbidity between age, ASA, primary or recurrent tumour, number of organs resected, radiotherapy and chemotherapy (Table 3). Certain medical comorbidities, types of organs resected, formation of an ileal conduit and requirement for a blood transfusion were all associated with major morbidity on univariate analysis (Table 3).

Characteristics	**No Morbidity (%) N=540**	**Major Morbidity (%) N=106**	**p-value**
Sex			
Male	218 (40.4)	57 (53.8)	
Female	322 (59.6)	49 (46.2)	0.013
Age			
<60	219 (40.6)	44 (41.5)	
≥60	321 (59.4)	62 (58.5)	0.829
ASA score			
I	37 (8.5)	3 (3.3)	
II	250 (57.3)	54 (58.7)	
III	134 (30.7)	33 (35.9)	
IV	15 (3.4)	2 (2.2)	0.287
Co-morbidities			
Myocardial Infarction	32 (5.9)	10 (9.4)	0.195
Peripheral Vascular Disease	4 (0.7)	3 (2.8)	0.091
Respiratory Disease	20 (3.7)	9 (8.5)	0.039
Chronic Renal Failure	12 (2.2)	6 (5.7)	0.096
Psychiatric history	24 (4.4)	10 (9.4)	0.053

Tumour			
Primary	351 (65)	65 (61.3)	
Recurrent	189 (35)	41 (38.7)	0.506
Tumour type			
GI Adenocarcinoma	381 (70.6)	71 (67)	
Anal SCC	30 (5.6)	12 (11.3)	
Gynaecological	62 (11.4)	10 (9.4)	
Others	67 (12.4)	13 (12.3)	0.072
Types of Organ Removed			
Colon	92 (17)	18 (17)	NS
Rectum	376 (70.9)	75 (70.8)	NS
Anus	98 (18.5)	27 (25.5)	NS
Small bowel	99 (18.3)	21 (19.8)	NS
Vagina	110 (20.4)	25 (23.6)	NS
Uterus	161 (29.8)	16 (15.1)	0.002
Ovaries	188 (34.8)	21 (19.8)	0.002
Prostate	93 (17.2)	32 (30.2)	0.003
Bladder	141 (26.1)	41 (38.7)	0.013
Sacrum	78 (14.4)	30 (28.3)	0.001
Other Procedures			
Ileal conduit	109 (20.2)	40 (37.7)	<0.001
Rectus flap	110 (20.4)	31 (29.2)	0.053

Number of Organ Removed			
1	80 (14.8)	9 (8.5)	
2	147 (27.2)	29 (27.4)	
3	165 (30.6)	39 (36.8)	
4	104 (19.3)	15 (14.2)	
5	23 (4.3)	10 (9.4)	
6	6 (1.1)	2 (1.9)	
Missing	15 (2.8)	2 (1.9)	0.114
Radiotherapy			
No	258 (47.8)	45 (42.5)	
Yes	282 (52.2)	61 (57.5)	0.339
Chemotherapy			
No	222 (41.1)	46 (43.4)	
Yes	318 (58.9)	60 (56.6)	0.668
Mean red blood cell packs (SD)	1.18 (3.2)	2.6 (7.3)	<0.001

Table 3: Patient, tumour, surgical and medical factors examined for an associated with major morbidity.

Independent predictors for major morbidity following exenterative surgery for locally advanced or recurrent pelvic malignancies were squamous cell carcinoma of anus, sacrectomy, past history of peripheral vascular disease and requirement for blood transfusion (Table 4).

Variables	OR	OR 95%CI		p-value
		Lower	Upper	
Squamous cell cancer	2.21	1.06	4.62	0.035
Sacrectomy	1.81	1.08	3.05	0.026
Peripheral vascular disease	5.19	1.04	25.82	0.044
Hx of respiratory disease	2.34	0.99	5.48	0.051
Blood transfusion	1.05	1.01	1.10	0.015

Table 4: Logistic regression analysis – independent predictors for major morbidity highlighting that SCC, sacrectomy, PVD and blood transfusions are predictors for major morbidity.

DISCUSSION:

Complex major surgery is usually associated with significant complications(17) and this radical surgery is performed in the setting of advanced tumour growth and frequently irradiated tissue, thus exenterative surgery is commonly associated with major morbidity(18). A systematic review of pelvic exenteration reported complication rates between 37% and 100%, whilst perioperative mortality rates ranged from 0% to 25%(19). More recently, the PelvEx collaborative reported a 30-day major complication rate of 37.8% and 1.5% 30-day mortality rate following pelvic exenteration for locally advanced rectal cancer. Furthermore, other high-volume centres have reported improved serious complication rates (27%) following exenterative surgery for gynaecological malignancies(20). This large study of exenterative surgery for locally advanced and recurrent pelvic malignancies has shown good short-term outcomes can be achieved in specialist centres with a coordinated approach. The low 30-day major morbidity (16.4%) and inpatient mortality rates (0.46%) demonstrate this to be safe and feasible, supporting the argument that specialist centres with centralised care pathways are key to improving patient outcomes. Moreover, it is noted that appropriate patient selection is critical to improved outcomes which coincides with a thorough MDT process and stringent documentation of morbidity and morbidity.

A common potential complication for the ever-expanding complex oncological surgery is the risk of massive intra-operative and postoperative haemorrhage and the subsequent blood transfusion requirement(21). Several factors, including tumour characteristics, neoadjuvant chemoradiotherapy, anatomical features of the surgical area (eg. vascular proximity), complexity of surgery, explain the significant risk of bleeding and transfusion requirements in oncology patients(21). The mean red blood pack cell transfusion requirement was 2.6 (SD+/- 7.3) in the

major morbidity group compared to 1.18 (SD+/- 3.2) in the non-major morbidity group ($p<0.001$). Blood transfusion requirement was shown to be an independent predictor for major complication (OR 1.05; 95%CI 1.01-1.10; p=0.015) in this study. This is supported by a study analysing 18,891 patients that underwent coronary artery bypass graft surgery, which showed that greater blood transfusion was independently associated with increased risk of mortality and major morbidity after adjusting for potential cofounders(22). Moreover, a meta-analysis investigating the effects of blood transfusion on clinical outcomes in patients undergoing colorectal cancer surgery, demonstrated blood transfusions were associated with adverse clinical outcomes(23). It is the effect of allogeneic transfusions inducing immune suppression, which explains the independent predictor of morbidity and mortality(24-26).

Moreover, the definition of resectability has changed in the management of advanced pelvic malignancy(27), with more radical resections showing benefits in overall survival(5, 8). This complexity of surgery includes en-bloc sacral excisions to ensure clear margins, which are now performed routinely in specialist centres(28). However, the wider excision required to improve oncological outcomes comes at a cost, creating a larger defect and this increased complexity in surgery correlates with major postoperative morbidity(20). Sacrectomy was shown to be an independent predictor for major complication (OR 1.81; 95% CI 1.08-3.05; p=0.026) in this study.

Salvage surgery for residual or recurrent anal squamous cell carcinoma after primary treatment, although uncommon, when it is necessary, the residual/recurrent disease pattern requires a locally extensive operation to avoid positive margins(29). The extensive surgery often required to achieve a clear margin is also likely reflected by the multifocality and more aggressive tumour biology of anal squamous cell carcinoma(30, 31). These aspects likely explain the predictive

factor of anal squamous cell carcinoma for major morbidity after exenterative surgery (OR 2.21; 95% CI 1.06-4.62; p=0.035), which is associated with high morbidity in other reported series(29, 32, 33).

There are several limitations to this study, which need to be considered. Firstly, the study is retrospective, albeit based on data collected prospectively from two centres. Interpretation of these results are limited somewhat by the degree of heterogeneity, both within each and between centres. This includes, the degree of heterogeneity of the patient populations and variations in the treatment strategies and surgical technique. It is also important to acknowledge that the data is collected over a long time period (1990-2015), which may also introduce a degree of inherent bias, given the evolving treatment strategies over time. However, there is a previous collaborative history(2, 11, 28), with also a high degree of consistency of approach across the centres included in this study. Therefore, in the absence of prospective studies, this report provides further data on the short-term complications and predictors following exenterative surgery for locally advanced and recurrent pelvic malignancies.

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Chapter 3

Excision of urological organs impacts surgical and survival outcomes following exenterative surgery for locally advanced and recurrent pelvic malignancies.

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Short running head: Complications after urological procedures in pelvic exenteration

Mini-Abstract: The aims were to analyse the major morbidity and factors predicting complications and long-term outcomes following a urological procedure within exenterative surgery. Six hundred and forty-six patients from two specialist centres were evaluated. The

major complication rate following a urological procedure was 28.3%. Urological procedures were associated with more major morbidity that impacted on 5-year overall survival.

BACKGROUND: Extensive multi-visceral resection, including components of the urinary tract, is often required to achieve clear resection margins, which is now well established as a key predictor of long-term survival for locally advanced pelvic tumours. The aims of this study were to analyse the major morbidity and factors predicting complications and long-term outcomes following a urological procedure within exenterative surgery.

METHODS: Data were collected from prospective databases at two high-volume institutions specialising in exenterative surgery for locally advanced and recurrent pelvic malignancies between 1990 and 2015. The primary endpoints were general complications following urological and non-urological procedures in exenterative surgery and factors influencing complications and overall survival.

RESULTS: A total of 646 consecutive patients requiring exenterative surgery for local advanced or recurrent pelvic malignancies were identified. The median age was 63 years (range 19-89 years), the majority were female (371; 57.4%). A urological intervention was performed in 226 patients (35.0%). The overall 30-days major complication rate was significantly higher in the urological intervention group (28.3%; n=64) compared to the non-urological group (12.4%; n=52 patients; p=0.001). Intestinal anastomotic leak (p=0.005) and intra-abdominal collections (p=0.001) were more common in the urological cohort. Poor independent prognostic markers for 5-year overall survival following a urological procedure were recurrent tumour, cardiovascular disease, previous thromboembolic event and post-operative PE. A positive survival benefit was demonstrated in patients that received neo-adjuvant radiotherapy (HR 0.54; 95% CI 0.34-0.85; p=0.007).

CONCLUSION: Major complications, particularly intestinal anastomotic leak and intra-abdominal collection, are more common in patients undergoing a urological procedure within pelvic exenterative surgery, impacting on 5-year overall survival.

KEYWORDS: Urological intervention, pelvic exenteration, ileal conduit, malignancy, 30-day morbidity.

INTRODUCTION:

The oncological role of pelvic exenteration for locally advanced and recurrent pelvic malignancies arising from the anorectum, gynaecological or urological systems is now well established(1-3).

The beyond TME collaborative provides consensus on the definitions and principles of management of these complex patients, advocating an extended surgical resection beyond the TME plane to achieve a pathological R0 resection(1). Extensive multi-visceral resection is often required to achieve clear resection margins (R0), which is now well established as a key predictor of long-term survival for locally advanced pelvic tumours(4, 5). To achieve an R0 resection, an en-bloc multi-visceral resection with partial or complete cystectomy or resection of the ureter/s may be required in 20-53% of patients undergoing a pelvic exenteration(6-8).

Urinary tract reconstruction after both cystectomy and partial ureter resection is associated with more specific complications in the context of locally advanced colorectal cancer surgery compared with primary urothelial cancer surgery(9, 10). Prior pelvic radiotherapy and extent of surgical resection are two factors suggested for this increased urological morbidity(9, 11). However, there appears to be some disparity in reported specific morbidity outcomes following urological procedures in this context(12). There is also a paucity of literature on general complications and outcomes following a urological procedure within exenterative surgery for locally advanced or recurrent pelvic malignancies.

The aims of this study were to assess the general major morbidity related to urological procedures following exenterative surgery for locally advanced and recurrent pelvic malignancies. Moreover, to evaluate the frequency of major complications in exenterative

surgery between urological and non-urological procedures. Finally, to investigate potential patient and surgical factors predicting complications and long-term outcomes.

METHODS:

A retrospective review of prospectively maintained databases was undertaken to assess the outcome of patients who have undergone pelvic exenterative surgery for locally advanced pelvic malignancies. The primary objectives were to identify the types of general complications following urological procedures compared with non-urological procedures, patient and surgical factors predicting complications and long-term outcomes following exenterative surgery for locally advanced pelvic tumours. Two tertiary referral centres with specialist experience in the surgical management of advanced pelvic tumours, similar surgical approaches to beyond TME surgery and previous collaborative experience(2, 13) were included. These institutions were Christchurch Hospital (Christchurch, New Zealand) and Peter MacCallum Cancer Centre (Melbourne, Australia). All patients were routinely discussed at a dedicated pelvic exenterative surgery multidisciplinary meeting. The diagnosis of locally advanced pelvic tumour was based on preoperative radiological imaging and clinical assessment. Data were prospectively collected at individual institutions. Patient demographics (age, sex, ASA), comorbidities, primary or recurrent tumour, tumour type, neoadjuvant & adjuvant regimen, organs resected and type of surgery including the need for urological or bony resection or flap reconstruction were recorded. Furthermore, the type of general complications (number of major complications: wound infection, pneumonia, urinary tract infection, sepsis, myocardial infarction, arrhythmias, pulmonary embolus, stroke, acute renal failure, acute respiratory distress syndrome, anastomotic leak, intra-abdominal collection, post-operative bleeding and small bowel obstruction) were recorded.

Definitions:

Overall survival (OS) was defined as the time from the date of surgery to the date of death from any cause.

Operations were considered exenterative when the primary organ and at least one of the surrounding organs was removed en-bloc (rectum, bladder, prostate, uterus, vagina, sacrum, small bowel, ureter, iliac vessels, ovary and fallopian tube removal)(13).

Patients analysed included the following pathologies; gastrointestinal adenocarcinoma, anal squamous cell carcinoma (SCC), gynaecological (ovarian, cervical, uterine or vaginal) and other malignancy (melanoma, prostate, sarcoma, GIST and chordoma) and had surgically resected organs recorded prospectively.

Resection of primary disease was defined as newly diagnosed malignant process requiring up front pelvic exenteration based on clinical and radiological assessment. Recurrent disease was defined as newly diagnosed disease of similar histological characteristics as previously resected tumour with an R0 margin.

A urological intervention was defined as a partial or complete excision of any genitourinary organ in men and any urinary tract organ in women, +/- urinary tract reconstruction (eg. ileal conduit). Incontinent ileal conduits were constructed as per Bricker and the ureteroenteric anastomoses according to either the Bricker or Wallace techniques(14).

Complications occurring within 30-days postoperatively or during the inpatient care for the index operation were graded according to the Clavien-Dindo classification system for surgical complications(15). A major complication was defined as Grade III, IV or V of the Clavien-Dindo classification. A wound infection was defined as per the United States Centre for Disease Control and Prevention (CDC) for surgical site infection (SSI)(16). Anastomotic leak was defined as an intestinal wall defect at the site of the anastomosis with a direct communication

between the intra- and extraluminal compartments(17). Sepsis was defined as proof of bacteraemia or clinical suspicion of sepsis, as well as signs and symptoms of systemic inflammatory response syndrome(18). An intra-abdominal collection was defined as an organised collection of fluid or pus diagnosed on imaging(19). Inpatient mortality was defined as a death occurring within 30-days of the index procedure.

Endpoints:

The primary endpoints were the general complications following urological and non-urological procedures in pelvic exenterative surgery and factors influencing complications and overall survival for locally advanced and recurrent pelvic malignancies.

Statistical Analysis:

Baseline characteristics were summarised using descriptive statistics. All categorical data were analysed using either Fisher's exact or Pearson-chi square test and continuous data using the student t-test. The Kaplan-Meier method was used to estimate the 5-year overall survival, with a sub-analysis performed assessing patients' survival by comparing pelvic exenteration for primary and recurrent pelvic tumours and major complications. Cox regression analysis was performed to identify independent risk factors for short- and long-term survival. This included entering post-operative complications as part of the analysis to assess its effect on survival after adjusting for patient, pathological and operative factors. All analysis was undertaken using IBM Corporation Released 2017, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corporation. A $p<0.05$ was considered significant.

RESULTS:

A total of 646 consecutive patients requiring exenterative surgery for local advanced or recurrent pelvic malignancies between 1990 and 2015 were identified from the combined databases of two tertiary surgical institutions. The median age for this cohort of patients was 63 years (range 19-89 years), and the majority were female patients (371; 57.4%). A urological intervention was performed in 226 patients (35.0%). The baseline characteristics of urological intervention and non-urological intervention are outlined in Table 1.

Patient Characteristic	**Urological intervention N = 226 (%)**	**Non-Urological intervention N = 420 (%)**	**Total**
Sex			
Male	158 (69.9%)	117 (27.9%)	275
Female	68 (30.1%)	303 (72.1%)	371
Age			
<60	93 (41.2%)	170 (40.5%)	263
>60	133 (58.8%)	250 (59.5%)	383
ASA Score			
1	18 (8.0%)	44 (10.4%)	62
2	130 (57.5%)	244 (58.1%)	374
3	75 (33.2%)	120 (28.6%)	195
4	3 (1.3%)	12 (2.9%)	15
Prior Chemotherapy			
Yes	144 (63.7%)	234 (55.7%)	378
No	82 (36.3%)	186 (44.3%)	268
Prior Radiotherapy			
Yes	131 (58.0%)	212 (50.5%)	343
No	95 (42.0%)	208 (49.5%)	303
Disease Type			
Primary	167 (73.9%)	249 (59.3%)	416
Recurrent	59 (26.1%)	171 (40.7%)	230
Tumour Type			
GI Adenocarcinoma	161 (71.2%)	291 (69.3%)	452
Anal SCC	13 (5.8%)	29 (6.9%)	42

Gynaecological	22 (9.7%)	50 (11.9%)	72
Other	30 (13.3%)	50 (11.9%)	80

Table 1. Patient demographics of urological and non-urological interventions

Operative details

In the urological intervention group, a total cystectomy was performed in 149 patients (65.9%) and all had an incontinent ileal conduit formed. Twenty-seven patients (11.9%) underwent a rectal resection and prostatectomy without cystectomy as part of the pelvic exenteration, a technique previously described(20). The remaining urological procedures were a variety of ureteric resections and/or partial cystectomy (n=50; 22.1%).

Overall complications

The overall 30-day major complication rate for the urological intervention group was 28.3% (n=64 patients) and the type of major complications are outlined in Table 2. The rate of overall 30-days major complication rate was significantly higher in the urological intervention group compared to the non-urological group (12.4%; n=52 patients; p=0.001). Acute renal failure (p=0.038), intestinal anastomotic leak (p=0.005) and intra-abdominal collections (p=0.001) were more common in the urological intervention cohort compared to the non-urological group (Table 2). There was no difference in the inpatient mortality rates between the two groups. There was one death in the urological intervention group (0.4%) from a pulmonary embolus and two inpatient deaths in the non-urological cohort (0.5%) from septicaemia. There was no association between major complications and requirement for a blood transfusion within the urological intervention group (p=0.86).

Variables	Urological Procedure	Non-urological Procedure	p-value
Major complications			
No	162 (71.7%)	368 (87.6%)	
Yes	64 (28.3%)	52 (12.4%)	0.001
Wound Infection			
No	220 (97.3%)	407 (96.9%)	
Yes	6 (2.7%)	13 (3.1%)	0.813
Pneumonia			
No	224 (99.1)	418 (99.5)	
Yes	2 (0.9)	2 (0.5)	0.615
UTI			
No	224 (99.1)	419 (99.8)	
Yes	2 (0.9)	1 (0.2)	0.281
Septicaemia			
No	224 (99.1)	417 (99.3)	
Yes	2 (0.9)	3 (0.7)	1
Myocardial infarction			
No	224 (99.1)	419 (99.8)	
Yes	2 (0.9)	1 (0.2)	0.281
Arrythmia			
No	225 (99.6)	418 (99.5)	
Yes	1 (0.4)	2 (0.5)	1
Pulmonary embolus			
No	224 (99.1)	419 (99.8)	
Yes	2 (0.9)	1 (0.2)	0.281
Stroke			
No	225 (99.6)	420 (100)	
Yes	1 (0.4)	0	0.35
Acute renal failure			
No	219 (96.9)	417 (99.3)	
Yes	7 (3.1)	3 (0.7)	0.038
Acute respiratory distress syndrome			
No	225 (99.6)	416 (99.0)	
Yes	1 (0.4)	4 (1.0)	0.662

Intestinal anastomotic leak			
No	218 (96.5)	418 (99.5)	
Yes	8 (3.5)	2 (0.5)	0.005
Intra-abdominal collection			
No	193 (85.4)	394 (93.8)	
Yes	33 (14.6)	26 (6.2)	0.001
Post-operative bleeding			
No	226 (100)	414 (98.6)	
Yes	0	6 (1.4)	0.096
Small bowel obstruction			
No	223 (98.7)	419 (99.8)	
Yes	3 (1.3)	1 (0.2)	0.126

Table 2: Major complications associated with urological and non-urological procedures. A total of 64 patients suffered one or more major complications in the urological procedure group, compared with 52 patients with one or more major complications in the non-urological group.

Outcomes analysis

The overall 1-year mortality rate in the urological intervention cohort was 14.2% (n=32 patients). Table 3 outlines the patient, tumour and operative characteristics for this cohort of patients. A past medical history of cardiovascular disease, previous malignant diagnosis or thromboembolic event were significant patient factors for 1-year mortality on univariate analysis (Table 3). Anal squamous cell carcinoma pathology and the requirement of a small bowel resection were also significant factors (Table 3). There was a tendency towards major morbidity in the group requiring an ileal conduit, but this was not statistically significant (p=0.067). Independent predictors for 1-year mortality in the urological procedure group were anal squamous cell carcinoma, small bowel resection and acute renal failure post-surgical intervention (Table 4).

Variables	Survivors	Mortalities	p-value	No Major Morbidity	Major Morbidity	p-value
Sex						
Male	148 (76.3)	22 (68.8)		131 (75.3)	39 (75.0)	
Female	46 (23.7)	10 (31.3)	0.380	43 (24.7)	13 (25.0)	NS
Age						
<60	82 (42.5)	11 (34.4)		72 (41.6)	21 (40.4)	
≥60	111 (57.5)	21 (65.6)	0.442	101 (58.4)	31 (59.6)	NS
Past Medical History						
Myocardial infarction	18 (9.3)	2 (6.3)	NS	13 (7.5)	7 (13.5)	0.263
Stroke	8 (4.1)	2 (6.3)	NS	8 (4.6)	2 (3.8)	NS
Peripheral vascular disease	1 (0.5)	0	NS	1 (0.6)	0	NS
COPD	6 (3.1)	1 (3.1)	NS	6 (3.4)	1 (1.9)	NS
Cardiovascular Disease	25 (12.9)	9 (28.1)	0.034	24 (13.8)	10 (19.2)	0.377
Respiratory Disease	11 (5.7)	1 (3.1)	NS	8 (4.6)	4 (7.7)	NS
Previous thromboembolic event	6 (3.1)	4 (12.5)	0.038	6 (3.4)	4 (7.7)	0.244
Chronic renal disease	8 (4.1)	3 (9.4)	0.192	7 (4.0)	4 (7.7)	0.282
Diabetes	23 (11.9)	0	0.052	20 (11.5)	3 (5.8)	0.302
Previous malignancy diagnosis	22 (11.2)	8 (25.0)	0.047	22 (12.6)	8 (15.4)	NS
Smoker	29 (14.9)	2 (6.3)	0.269	23 (13.2)	8 (15.4)	NS
Tumour						
Primary	125 (64.4)	16 (50)		110 (63.2)	31 (59.6)	
Recurrent	69 (35.6)	16 (50)	0.167	64 (36.8)	21 (40.4)	NS
Tumour type						
GI Adenocarcinoma	151 (77.8)	24 (75.0)		134 (77.0)	41 (78.8)	
Anal SCC	10 (5.2)	6 (18.8)		11 (6.3)	5 (9.6)	
Gynaecological	10 (5.2%)	0		7 (4.0)	3 (5.8)	
Other	23 (11.9)	2 (6.2)	NS	22 (12.7)	3 (5.8)	NS
Types of Organ Removed						
Colon	28 (14.4)	5 (15.6)	NS	22 (12.6)	11 (21.2)	0.177
Rectum	139 (71.6)	21 (65.6)	NS	128 (73.6)	32 (61.5)	0.117
Anus	32 (16.6)	5 (15.6)	NS	28 (16.2)	9 (17.3)	NS
Small bowel	46 (23.7)	15 (46.9)	0.009	47 (27.0)	14 (26.9)	NS
Vagina	21 (10.9)	7 (21.9)	0.089	18 (10.4)	10 (19.2)	0.098
Uterus	15 (7.7)	5 (15.6)	0.173	17 (9.8)	3 (5.8)	NS
Ovaries	21 (10.8)	5 (15.6)	0.384	22 (12.6)	4 (7.7)	NS
Prostate	108 (55.7)	17 (53.1)	NS	93 (53.4)	32 (61.5)	NS
Bladder	153 (78.9)	29 (90.6)	0.151	141 (81.0)	41 (78.8)	NS
Sacrum	38 (19.6)	4 (12.5)	NS	32 (18.4)	10 (19.2)	NS
No of Organs Removed						
1	6 (3.1)	1 (3.1)		6 (3.4)	1 (1.9)	

2	42 (21.6)	6 (18.8)		37 (21.3)	11 (21.2)	
3	83 (42.8)	8 (25.0)		69 (39.7)	22 (42.3)	
4	45 (23.2)	11 (34.4)		47 (27.0)	9 (17.3)	
5	14 (17.2)	4 (12.5)		11 (6.3)	7 (13.5)	
6	2 (1.0)	2 (6.3)		3 (1.7)	1 (1.9)	
Missing	2 (1.0)	0	0.164	1 (0.6)	1 (1.9)	NS
Other Procedures						
Stoma	153 (78.9)	29 (90.6)	0.151	136 (78.2)	46 (88.5)	0.113
Ileal conduit	124 (63.9)	25 (78.1)	0.158	109 (62.6)	40 (76.9)	0.067
Rectus flap	42 (21.6)	10 (31.3)	0.258	41 (23.6)	11 (21.2)	NS
Radiotherapy						
No	70 (36.1)	17 (53.1)		69 (39.7)	18 (34.6)	
Yes	124 (63.9)	15 (46.9)	0.079	105 (60.3)	34 (65.4)	0.626
Chemotherapy						
No	69 (35.6)	14 (43.8)		66 (37.9)	17 (32.7)	
Yes	125 (64.6)	18 (56.3)	0.430	108 (62.1)	35 (67.3)	NS

Table 3: 1-year mortality patient, tumour, and operative characteristics in the urological intervention group.

Variables	**HR**	**95%CI for OR**		**p-value**
		Lower	**Upper**	
Squamous cell cancer	4.54	1.43	14.35	0.010
Small bowel resection	2.90	1.29	6.50	0.010
Acute kidney injury	8.04	1.60	40.44	0.011

Table 4: Independent predictors for 1-year mortality

There was no difference in the 5-year overall survival between the urological and non-urological intervention group (Figure 1). However, analysis of 5-year overall survival in the urological group showed a difference between patients that suffered a major complication and those that did not (Figure 2). Poor independent prognostic markers following proportional hazards regression analysis for 5-year overall survival in the urological procedure group were recurrent tumour (Figure 3), joint anal surgery, previous malignant diagnosis, cardiovascular disease, previous thromboembolic event and post-operative PE (Table 5). A positive survival benefit was demonstrated in patients that received neo-adjuvant radiotherapy (HR 0.54; 95% CI 0.34-0.85; p=0.007).

Variables	HR	95%CI HR		p-value
		Lower	Upper	
Recurrent tumour resection	2.56	1.59	4.14	<0.001
Radiation therapy	0.54	0.34	0.85	0.007
Joint anal surgery	2.01	1.19	3.37	0.009
Hx of cardiovascular disease	1.91	1.10	3.34	0.022
Previous thromboembolic event	6.17	2.70	14.1	<0.001
Previous malignant diagnosis	1.83	1.03	3.24	0.039
Post-operative PE	7.83	1.02	60.16	0.048

Table 5: Cox Regression Analysis on 5-year overall survival in the urological procedures group.

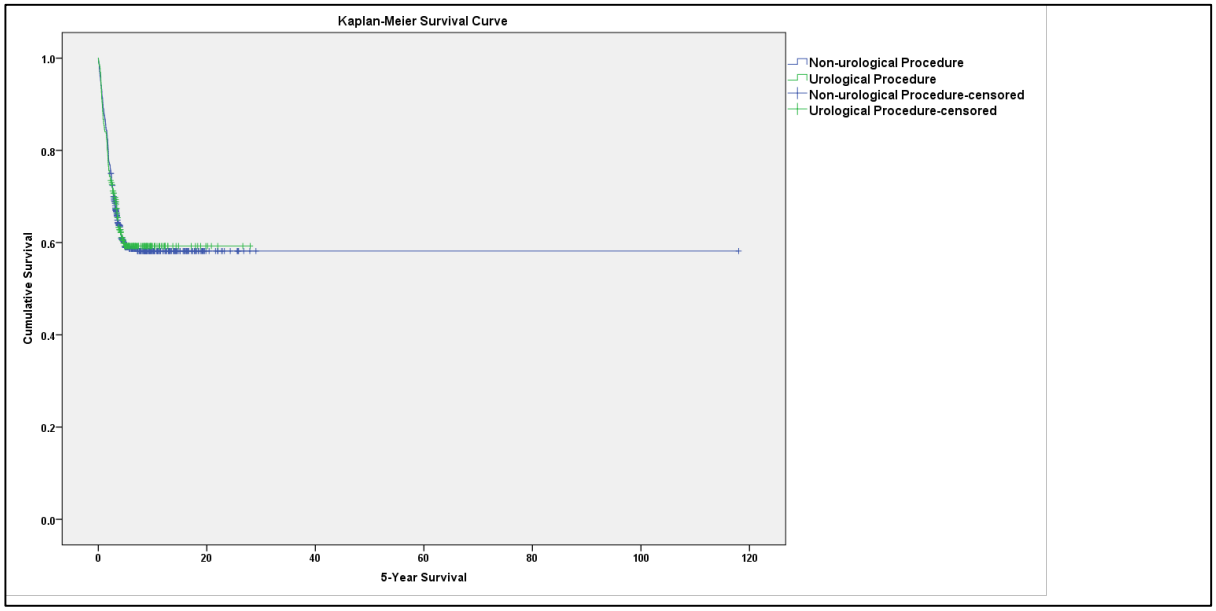

Figure 1: Five-year overall survival between urological and non-urological interventions

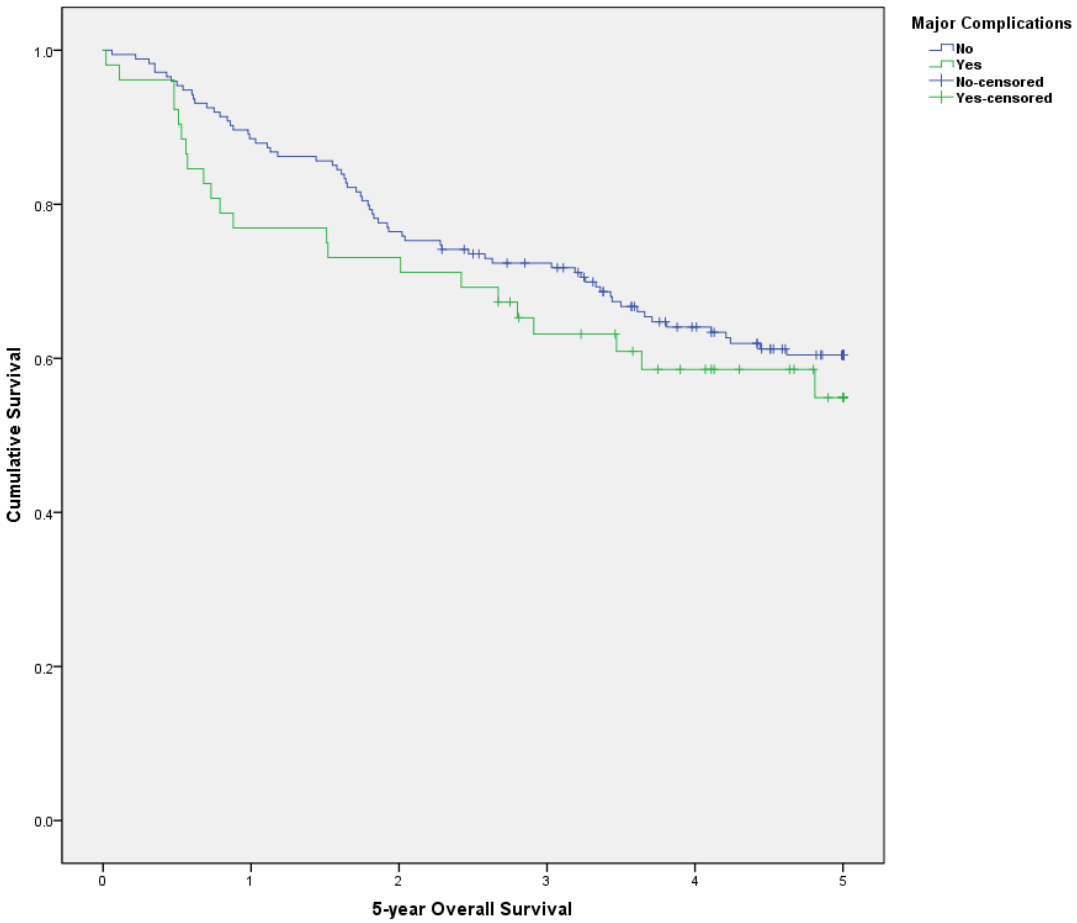

Figure 2: Five-year overall survival between major complications and no major complications within the urological intervention group.

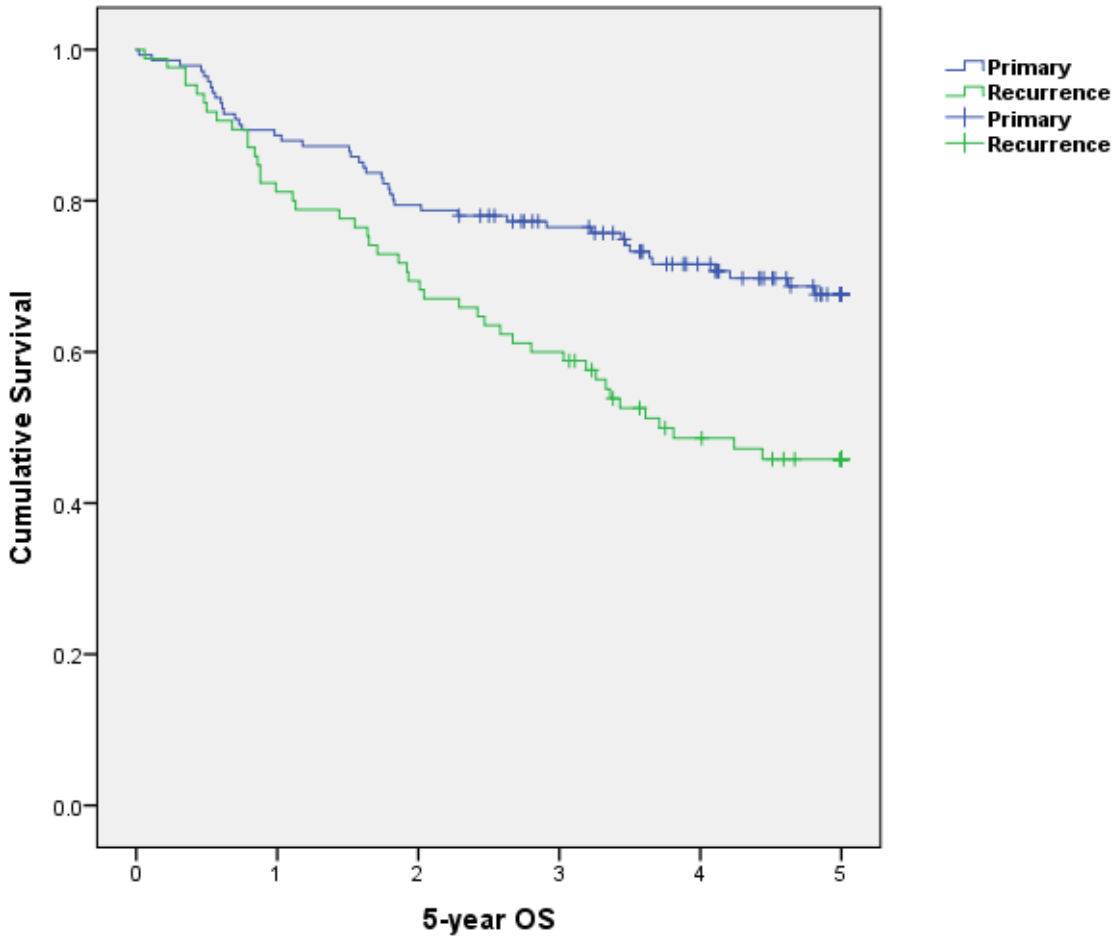

Figure 3: Five-year overall survival of primary versus recurrent disease in the urological intervention group.

DISCUSSION:

This large international combined series from established centres, specialising in pelvic exenterative surgery, describes the patterns of general complications and presents good overall outcomes for urological procedures performed as part of the management of locally advanced and recurrent pelvic malignancies. Overall, 35.0% (n=226 patients) of all patients required a urological procedure as part of the pelvic exenteration, which is a similar frequency to other large series(6, 8, 12).

Pelvic exenteration has previously been associated with a high incidence of perioperative complications with rates ranging from 32% to 84%(3). However, evolution in the surgical techniques has steadily been gaining momentum, with improved outcomes(21, 22), therefore it is no longer deemed a palliative procedure(23). Recently, the PelvEx Collaborative reported a 30-day major complication rate of 37.8% among all patients undergoing exenteration for locally advanced rectal cancer(5). Moreover, a study investigating the patterns of complications following urological intervention in pelvic exenterative surgery demonstrated a major complication rate of 35% (67/189 patients)(24). This study presents favourable 30-day major general morbidity rates of 28.3% for the urological intervention group and 12.4% for the non-urological intervention group. The inpatient mortality rate was also lower in this study compared with rates ranging from 1.5% to 15.6%(5, 7, 24).

The major general complication rate was significantly higher in the urological intervention group compared with the non-urological group (p=0.001), which was reflected predominantly by the increased frequency of intestinal anastomotic leak and intra-abdominal collections (Table 2). A recent study evaluating short-term outcomes following pelvic exenteration for gynaecological malignancy demonstrated a similar serious morbidity rate (27%)(25). Surgical complexity is a

main driver of complications, with urological procedures being associated with significantly more complications(25). The increase in intra-abdominal collections within the urological intervention group might reflect the nature of the surgery performed, particularly ileal conduit formation or reconstruction following ureteric resection, representing urine leaks. However, this can only be postulated as the database did not capture this specific information on urine leaks. The increased dead space within the pelvic inlet following a total pelvic exenteration may also further explain this observed outcome(26). The frequency of major intra-abdominal collections were similar to other reported series of 13.7%(27).

The increased number of intestinal anastomotic leaks in the urological intervention group (3.5% n=8) likely reflects the increased frequency of anastomoses performed in relation to ileal conduits formation. An ileal conduit was the method of choice for reconstruction of the urinary tract following total cystectomy because the majority of patients receive neoadjuvant radiotherapy, limiting the option of orthotopic bladder substitutes(28). Also, continent urinary reconstruction options do not consistently provide improved quality of life(29). The intestinal anastomotic leak rate has been reported as high as 9% following a urological procedure(24). Possible risk factors for increased morbidity in pelvic exenterative surgery include prior pelvic irradiation, however, this remains uncertain(6, 9, 11, 30). In this study, neoadjuvant radiotherapy did not impact on major general complications in the urological intervention group ($p=0.626$).

An association between poorer overall survival and post-surgical complications has been observed in colorectal cancer patients(31). This study also showed that development of a major complication impacted 5-year overall survival (Figure 2) in the urological intervention group. This effect might be explained by the systemic consequence of the complication on the patient and/or causing delay or rendering the patient unsuitable for further adjuvant therapies(28).

Two independent poor prognostic markers for 5-year overall survival were pulmonary embolus and previous thromboembolic events. The long-term consequence of pulmonary embolus is well known, due to nearly 50% of the patients are likely to continue suffering from serious adverse events, such as recurrent venous thromboembolism, cardiovascular events, chronic pulmonary hypertension and death(32). Assessment of patient comorbidities prior to surgical intervention is an integral part of risk-stratification because of the direct correlation between the increasing mean age of cancer patients and the presence of one or more comorbidities(33). In cancer patients above the age of 65, approximately 60% will have one or more comorbidity; in which 23% were associated with cardiovascular disease(34). Cardiovascular disease was also an independent poor prognostic predictor for 5-year overall survival in this study, consistent with other studies showing it to be a significant predictor of in-patient mortality(35) and poorer 5-year overall survival(36).

This highlights that patient comorbidities and specific complications can influence long-term survival, emphasising the importance of an individualised discussion and treatment plan for patients requiring pelvic exenterative surgery. Patients must be counselled accordingly when considering surgical intervention and this study further aids in the process of informed consent for patients, explaining the pathological, technical complexities and patient factors leading to poorer outcomes and affecting survival.

There are several limitations to this study, which need to be considered. Firstly, the study is retrospective, albeit based on data collected prospectively from two centres. Interpretation of these results are limited somewhat by the degree of heterogeneity, both within each and between centres. This includes, the degree of heterogeneity of the patient populations and variations in the treatment strategies and surgical technique. It is also important to acknowledge that the data

is collected over a long-time period (1990-2015), which may also introduce a degree of inherent bias, given the evolving treatment strategies over time. However, there is a previous collaborative history(2, 13, 37), with also a high degree of consistency of approach across the centres included in this study. Therefore, in the absence of prospective studies, this report provides further data to the paucity of literature on general complications and prognostic outcomes following urological procedures as part of pelvic exenterative surgery for locally advanced pelvic malignancies.

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Chapter 4

Title: Predictors of overall survival following extended radical resections for locally advanced and recurrent pelvic malignancies

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Background:

In an era of personalised medicine, there is an overwhelming effort for predicting patients that will benefit from extended radical resections for locally advanced pelvic malignancy. However, there is paucity of data on the effect of comorbidities and post-operative complications on long-term overall survival (OS). The aim of this study was to define predictors of one-year and five-year OS.

Methods:

Data were collected from prospective databases at two high-volume institutions specialising in beyond TME surgery for locally advanced and recurrent pelvic malignancies between 1990 and 2015. The primary outcome measures were 1-year and 5-year OS.

Results:

A total of 646 consecutive extended radical resections were performed between 1990 and 2015. The majority were female patients (371, 57.4%) and the median age was 63 years (range 19-89 years). One-year OS, primary rectal adenocarcinoma had the best survival whilst recurrent colon cancer had the worse survival (p=0.047). The 5-year OS between primary and recurrent cancers were 64.7% and 53% respectively (p=0.004). Poor independent prognostic markers for 5-year OS were; increasing ASA score, cardiovascular disease, recurrent cancers, ovarian cancers, pulmonary embolus and acute respiratory distress syndrome. A positive survival benefit was demonstrated with pre-operative radiotherapy (HR 0.55; 95%CI 0.4-0.75, p<0.001).

Conclusion:

Patient comorbidities and specific complications can influence long-term survival following extended radical resections. This study highlights important predictors, enabling clinicians to

better inform patients of the potential short and long-term outcomes in the management of locally advanced and recurrent pelvic malignancy.

Introduction

Pelvic exenteration was first described as an en-bloc removal of the pelvic organs for advanced or recurrent cancers(1). Previously, such a radical approach have significant post-operative consequence, with reported 30-day mortality rate of 17.2%, 2-year overall survival (OS) of 27% and 5-year OS of 17%.(2) Subsequently, through improvements in perioperative care and surgical technique, current accepted mortality rates are 1.1-2% and 5-year OS of 40-48.6%.(3-6) Therefore, pelvic exenteration has shifted from a palliative surgical approach to providing appropriately selected patients with a chance for cure.

In an era of personalised medicine, there is an overwhelming effort for predicting those that will benefit most from extended radical resections(4, 6, 7). This will not only aid in patient selection for such a morbid procedure, but informed consent. However, most studies have only assessed surgical and pathological variables as significant influence on long-term outcomes. There is paucity of data on the effect of comorbidities and post-operative complications on long-term OS.

The aim of this study was to define predictors of one-year and five-year OS based on patient comorbidities, pathological characteristics, blood transfusion and post-operative complications.

Methods

This was a retrospective observational study of a prospectively maintained database from two tertiary teaching hospitals, Peter MacCallum Cancer Centre, Australia and Christchurch Hospital, Canterbury District Health Board, New Zealand. All patients were routinely discussed at a dedicated pelvic exenterative surgery multidisciplinary meeting. The diagnosis of locally advanced or recurrent pelvic tumour was based on preoperative radiological imaging and clinical assessment.

Clinical data was entered into an electronic database; which includes patient comorbidities (age, American Society of Anaesthesiologist (ASA) score, myocardial infarction, stroke, peripheral vascular disease, asthma, chronic obstructive pulmonary disease, cardiovascular disease, respiratory disease, thromboembolic events, chronic renal failure, diabetes, previous malignancy, smoker), surgical procedure (number of organs removed and reconstructive method), type of treatment (blood transfusion, pre-operative chemotherapy and radiotherapy), pathology and complications (number of major complications, pneumonia, urinary tract infection, sepsis, myocardial infarction, arrhythmias, pulmonary embolus, stroke, acute renal failure, acute respiratory distress syndrome, anastomotic leak, intra-abdominal collection, post-operative bleeding, ileus and small bowel obstruction).

Definitions:

Operations were considered extended radical resections when the primary organ and at least one of the surrounding organs was removed en-bloc(8).

Patients analysed included the following pathologies: rectal adenocarcinoma, colonic adenocarcinoma, anal squamous cell carcinoma (SCC), ovarian cancer, other gynaecological

(cervical, uterine or vaginal) malignancy and other malignancy (melanoma, prostate, sarcoma, GIST and chordoma).

Complications occurring within 30-days postoperatively or during the inpatient care for the index operation were graded according to the Clavien-Dindo classification system for surgical complications(9). A major complication was defined as Grade III, IV or V of the Clavien-Dindo classification. A wound infection was defined as per the United States Centre for Disease Control and Prevention (CDC) for surgical site infection (SSI)(10). Anastomotic leak was defined as an intestinal wall defect at the site of the anastomosis with a direct communication between the intra- and extraluminal compartments(11). Sepsis was defined as proof of bacteraemia or clinical suspicion of sepsis, as well as signs and symptoms of systemic inflammatory response syndrome(12). An intra-abdominal collection was defined as an organised collection of fluid or pus diagnosed on imaging(13).

Statistical analysis:

The primary outcome measures were 1-year and 5-year OS. Descriptive analysis was performed accordingly; all categorical data were analysed using either Fisher's exact or Pearson-chi square test and continuous data using the student t-test. A Kaplan-Meir survival curve was performed to ascertain 1-year and 5-year OS, with a sub-analysis performed assessing patients' survival by comparing extended radical resection for primary and recurrent colorectal cancers. Cox regression analysis was performed to identify independent risk factors for short- and long-term survival. This includes entering post-operative complications as part of the analysis to assess its effect on survival after adjusting for patient, pathological and operative factors.

All analysis was undertaken using IBM Corporation Released 2017, IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corporation. A $p<0.05$ was considered significant.

The protocol and methods of this study were reviewed and approved by the institutional ethics committee of the Peter MacCallum Cancer Centre.

Results

There was a total of 646 consecutive extended radical resections between 1990 and 2015. The majority were female patients (371, 57.4%) and the median age was 63 years (range 19-89 years). The pathological characteristics were 416 (64.4%) primary cancers and 230 (35.6%) recurrent cancers, with the majority confirmed to be adenocarcinoma 452 (70%). The median follow-up was 4 years (range 0.2-29.1 years). There was only one death within 30-days and the one-year mortality rate was 12.2% (79 patients).

Univariate analysis for one-year mortality is shown in Tables 1 and 2. Older patients (more than 70 years old; p=0.039), higher ASA score (III and IV; p=0.006), histology confirmation of SCC or ovarian cancer (p=0.015) and known history of cardiovascular disease (p<0.001) were shown to be significant predictors of poorer one-year overall survival.

Variables	**Alive (%)**	**One-year mortality (%)**	**p-value**
Sex			
Male	246 (43.4)	29 (36.7)	
Female	321 (56.6)	50 (63.3)	0.277
Age			
18-29	11 (1.9)	2 (2.5)	
30-49	100 (17.6)	5 (6.3)	
50-69	297 (52.4)	40 (50.6)	
70-79	130 (22.9)	28 (35.4)	
≥80	29 (5.1)	4 (5.1)	0.039
ASA score			
I	37 (7.9)	3 (4.8)	
II	279 (59.9)	25 (40.3)	
III	136 (29.2)	31 (50)	
IV	14 (3.0)	3 (4.8)	
V	0	0	0.006
Missing	101	17	

Tumour			
Primary	363 (64)	53 (67.1)	
Recurrent	204 (36)	26 (32.9)	0.619
Tumour type			
Adenocarcinoma	402 (70.9)	50 (63.3)	
SCC	33 (5.8)	9 (11.4)	
Gynaecological malignancy	15 (2.6)	2 (2.5)	
Ovarian cancer	44 (7.8)	13 (16.5)	
Others	73 (12.9)	5 (6.3)	0.015
Types of Organ Removed			
Colon	90 (15.9)	20 (25.3)	0.054
Rectum	403 (71.1)	48 (60.8)	0.068
Anus	111 (19.9)	14 (17.7)	NS
Small bowel	93 (16.4)	27 (34.2)	<0.001
Vagina	117 (20.7)	18 (22.8)	NS
Uterus	154 (27.2)	23 (29.1)	NS
Ovaries	183 (32.3)	26 (32.9)	NS
Prostate	108 (19.0)	17 (21.5)	NS
Bladder	153 (27.0)	29 (36.7)	0.083
Sacrum	99 (17.5)	9 (11.4)	NS
Other Procedures			
Stoma	391 (69.0)	61 (77.2)	NS
Ileal conduit	124 (21.9)	25 (31.6)	0.063
Rectus flap	125 (22.0)	16 (20.3)	NS

Table 1: Patient, tumour and operative characteristics of all pelvic exenteration patients

The influence of post-operative complications on short-term survival was also assessed, showing a statistically significant negative impact on survival as shown in Table 2. However, blood transfusion did not show any difference between those that had survived compared to those that did not after a year, with a mean transfusion of 1.33 (SD of 4.1) and 2 (SD of 5; p=0.185) respectively.

Variables	Alive (%)	One-year mortality (%)	p-value
Co-morbidities			
History of cardiovascular disease	76 (13.4)	24 (30.4)	<0.001
Previous thromboembolic disease	25 (4.4)	8 (10.1)	0.050
Previous myocardial infarction	34 (6.0)	8 (10.1)	0.218
Previous stroke	18 (3.2)	3 (3.8)	0.734
Peripheral vascular disease	5 (0.9)	2 (2.5)	0.207
Chronic obstructive pulmonary disease	20 (3.5)	5 (6.3)	0.215
Chronic renal failure	15 (2.6)	3 (3.8)	0.474
Diabetes mellitus	58 (10.2)	7 (8.9)	0.843
Previous malignancy	66 (11.6)	14 (17.7)	0.143
Smoker	71 (12.5)	7 (8.9)	0.461
Major Complications			
No	485 (85.5)	55 (69.6)	
Yes	82 (14.5)	24 (30.4)	0.001
Septicaemia			
No	565 (99.6)	76 (96.2)	
Yes	2 (0.4)	3 (3.8)	0.015
Pulmonary embolus			
No	566 (99.8)	77 (97.5)	
Yes	1 (0.2)	2 (2.5)	0.041
Acute Renal Failure			
No	561 (98.9)	75 (94.9)	
Yes	6 (1.1)	4 (5.1)	0.024
Acute Respiratory Distress Syndrome			
No	565 (99.6)	76 (96.2)	
Yes	2 (0.4)	3 (3.8)	0.015
Intra-abdominal Collection			
No	520 (91.7)	67 (84.8)	
Yes	47 (8.3)	12 (15.2)	0.059
Mean red blood cell packs (SD)	1.33 (4.1)	2.00 (5.0)	0.185
Radiotherapy			
No	256 (45.1)	47 (59.5)	
Yes	311 (54.9)	32 (40.5)	0.022
Chemotherapy			
No	226 (39.9)	42 (53.2)	
Yes	341 (60.1)	37 (46.8)	0.028

Table 2: Patient comorbidities, post-operative complications and medical treatment.

In a sub-analysis of recurrent cancers, the majority were adenocarcinoma (173 patients - 75.2%) followed by SCC (24 patients - 10.4%) and gynaecological malignancy (10 patients - 4.3%). Preoperative radiotherapy or chemotherapy were commonly given to recurrent compared to primary cancers as shown in Table 3. There was no difference in major complications; however, blood transfusion more than two units was higher in recurrent compared to primary cancers.

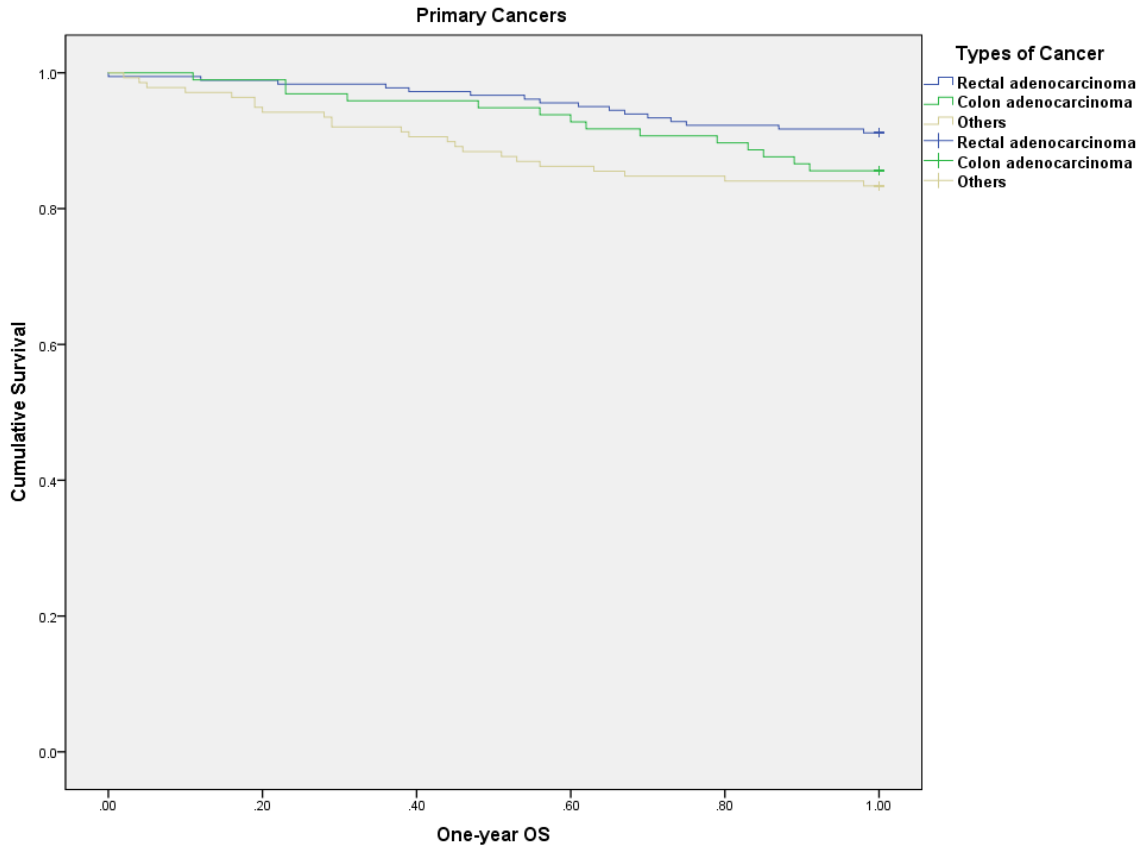
Variables	**Primary cancers (%)**	**Recurrent cancers (%)**	
Sex			
Male	163 (39.2)	112 (48.7)	
Female	253 (60.8)	118 (51.3)	0.020
Age			
18-29	10 (2.4)	3 (1.3)	
30-49	72 (17.3)	33 (14.3)	
50-69	207 (49.8)	130 (56.5)	
70-79	103 (24.8)	55 (23.9)	
≥80	24 (5.8)	9 (3.9)	0.402
Tumour type			
Adenocarcinoma	279 (67.1)	173 (75.2)	
SCC	18 (4.3)	24 (10.4)	
Gynaecological malignancy	7 (1.7)	10 (4.3)	
Ovarian cancer	53 (12.7)	4 (1.7)	
Others	59 (14.2)	19 (8.3)	<0.001
Organ resection			
Colon	85 (20.4)	25 (10.9)	0.002
Rectum	291 (70.0)	160 (69.6)	0.929
Anus	78 (18.9)	47 (21.0)	0.533
Small bowel	62 (14.9)	58 (25.3)	0.001
Vagina	70 (16.9)	65 (28.3)	0.001
Uterus	125 (30.0)	52 (22.6)	0.043
Ovaries	160 (38.5)	49 (21.3)	<0.001
Prostate	82 (19.7)	43 (18.7)	0.754
Bladder	126 (30.3)	56 (24.3)	0.121
Sacrum	37 (8.9)	71 (30.9)	<0.001
Clinical T stage			
T3			
Rectal adenocarcinoma	30 (66.7)	11 (52.4)	
Colon carcinoma	10 (22.2)	2 (9.5)	
Others	5 (11.1)	8 (38.1)	0.030

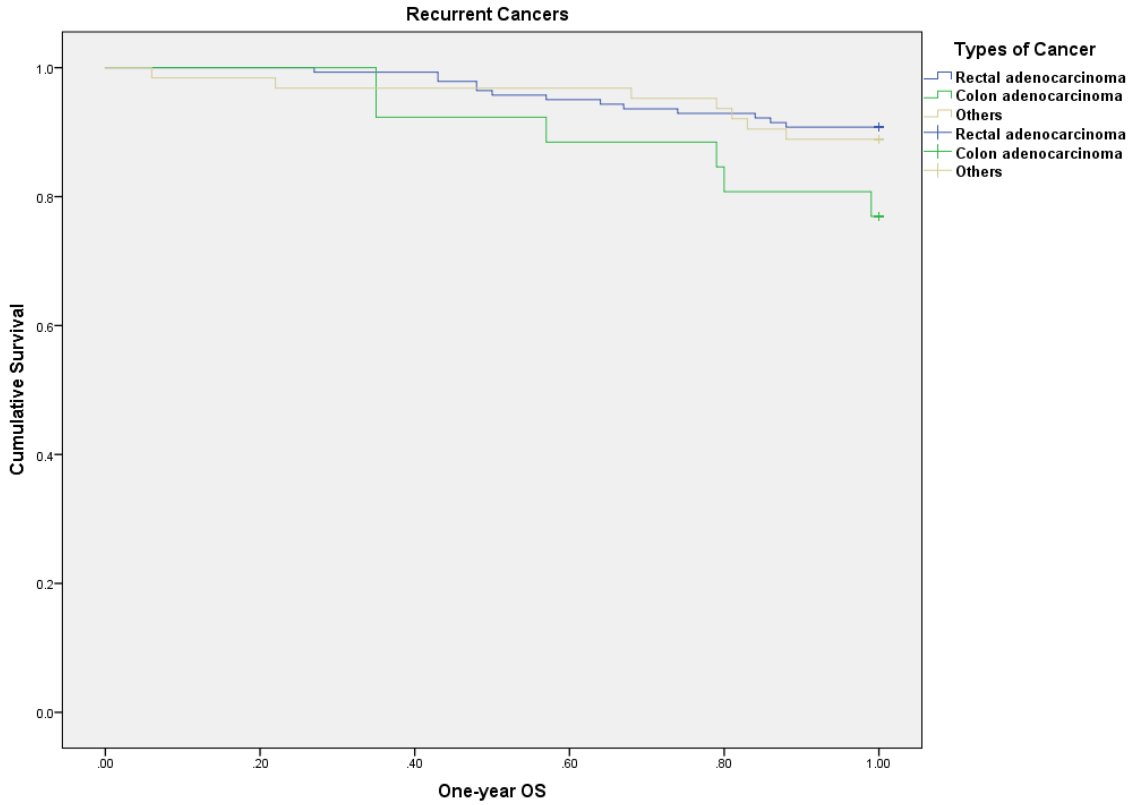
T4			
Rectal adenocarcinoma	117 (65.0)	29 (54.7)	
Colon carcinoma	50 (27.8)	7 (13.2)	
Others	13 (7.2)	17 (32.1)	<0.001
T stage not mentioned	191	156	
Clinical N stage			
N0			
Rectal adenocarcinoma	61 (24.5)	60 (54.5)	
Colon carcinoma	66 (26.5)	11 (10.0)	
Others	122 (49.0)	39 (35.5)	<0.001
N1			
Rectal adenocarcinoma	54 (75.0)	11 (57.9)	
Colon carcinoma	13 (18.1)	2 (10.5)	
Others	5 (6.9)	6 (31.6)	0.013
N2			
Rectal adenocarcinoma	45 (77.6)	3 (100)	
Colon carcinoma	10 (17.2)	0	
Others	3 (5.2)	0	0.652
N stage not mentioned	37	98	
Pre-operative radiation therapy			
No	224 (53.8)	79 (34.3)	
Yes	192 (46.2)	151 (65.7)	<0.001
Rectal cancer pre-operative radiation			
No	45 (24.9)	31 (22.0)	
Yes	136 (75.1)	110 (78.0)	0.598
Colon cancer pre-operative radiation			
No	69 (71.1)	10 (38.5)	
Yes	28 (28.9)	16 (61.5)	0.003
Others			
No	110 (79.7)	38 (60.3)	
Yes	28 (20.3)	25 (39.7)	0.006
Pre-operative chemotherapy			
No	187 (45.0)	81 (35.2)	
Yes	229 (55.0)	149 (64.8)	0.019
Major complications			
No	351 (84.4)	189 (82.2)	
Yes	65 (15.6)	41 (17.8)	0.506

Blood transfusion			
<2 units	347 (83.4)	155 (67.4)	
≥2 units	69 (16.6)	75 (32.6)	<0.001
1-year OS	87.3%	88.7%	0.619
Rectal adenocarcinoma	91.2%	90.8%	
Colon carcinoma	85.6%	76.9%	
Others	83.3%	88.9%	
5-year OS	64.7%	53.0%	0.004
Rectal adenocarcinoma	74.6%	52.5%	
Colon carcinoma	60.8%	50.0%	
Others	54.3%	55.6%	

Table 3: Patient, tumour and operative characteristics between primary and recurrent cancers

One-year OS, primary rectal adenocarcinoma had the best survival whilst recurrent colon cancer had the worse survival as shown in Figure 1(a) and (b) (p=0.047).





Overall Comparisons[a]

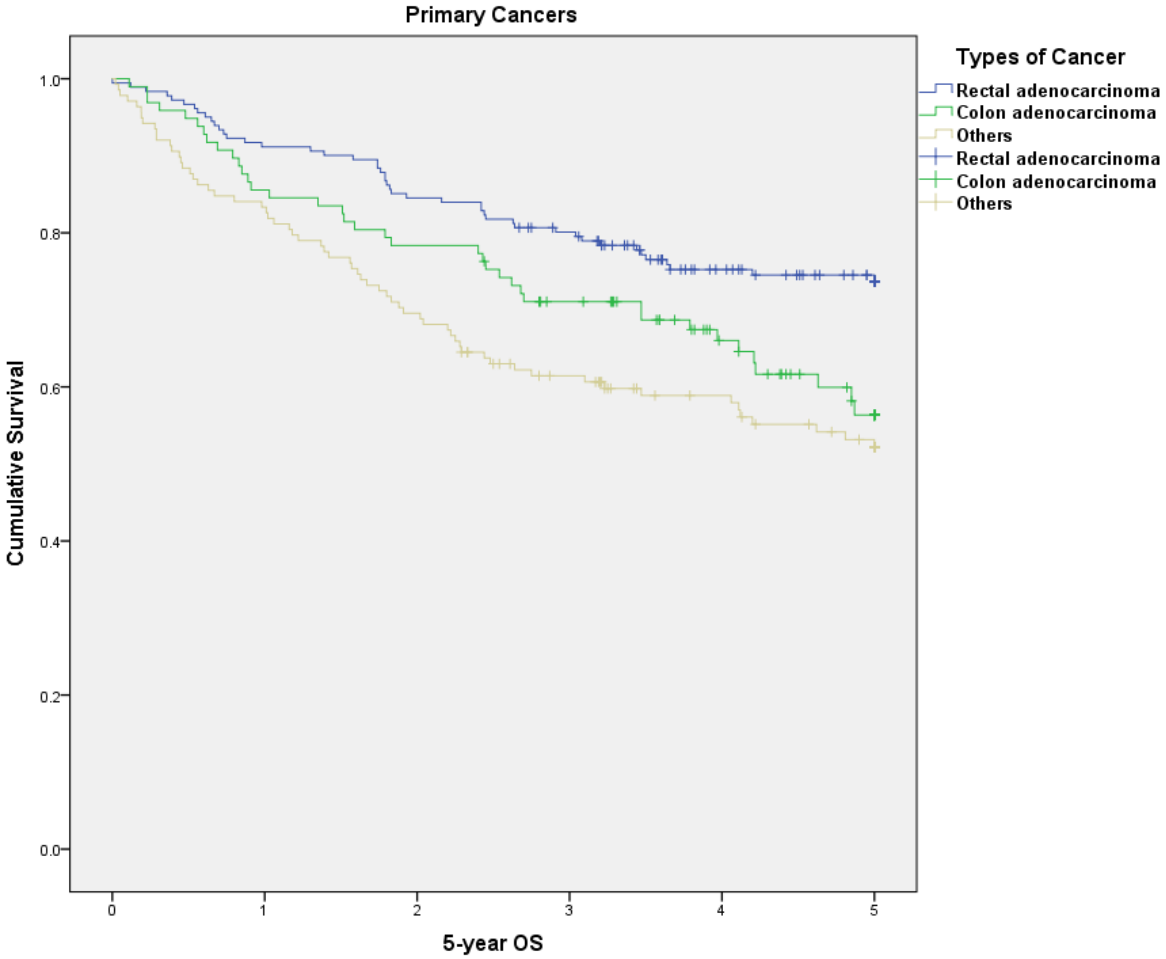
	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	6.076	2	.048
Breslow (Generalized Wilcoxon)	6.111	2	.047
Tarone-Ware	6.105	2	.047

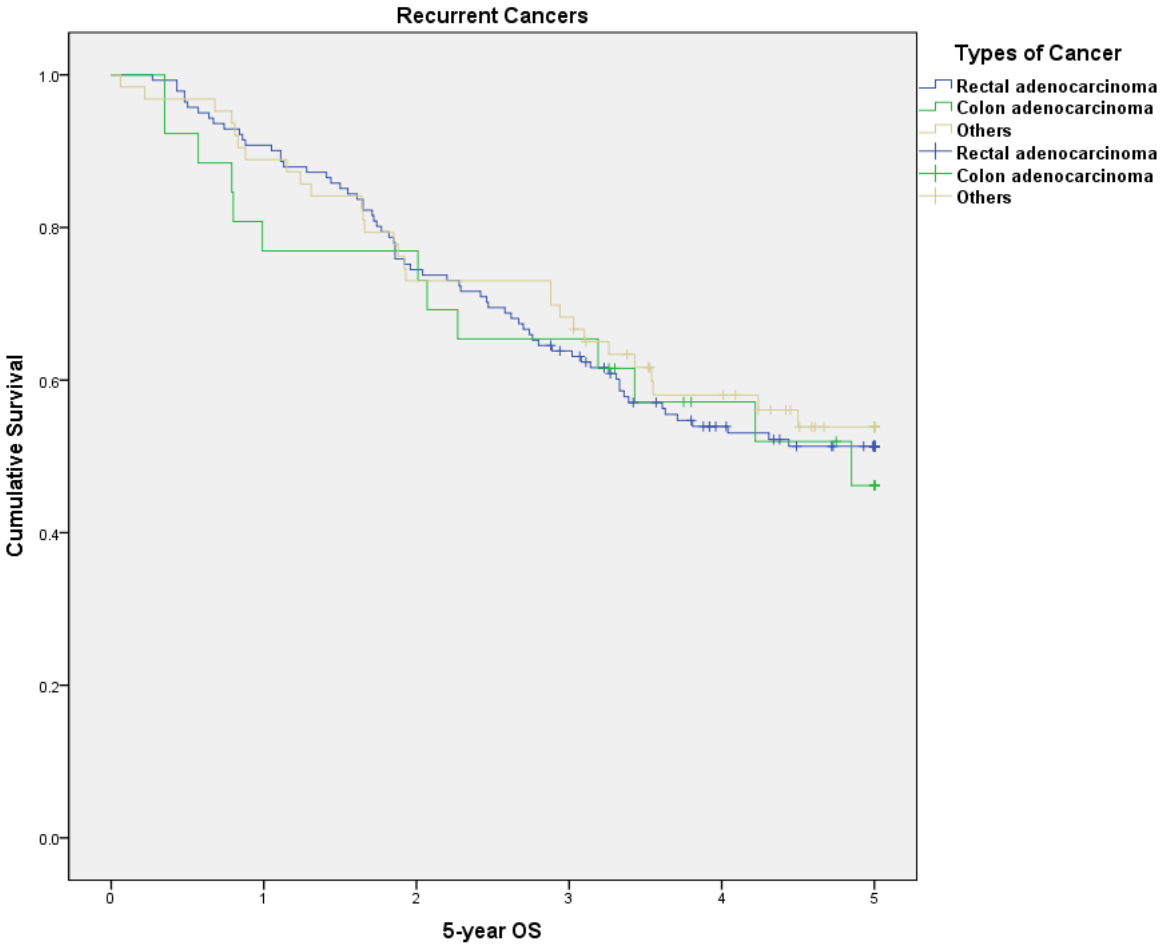
Test of equality of survival distributions for the different levels of AdenoCaSite.

a. Adjusted for Tumour (Primary vs Recurrent).

Figure 1: One-year survival for primary and recurrent cancers

The 5-year OS between primary and recurrent cancers were statistically significant, with an estimated survival of 64.7% and 53% respectively (p=0.004).


Primary Cancers
Types of Cancer
Rectal adenocarcinoma
Colon adenocarcinoma
Others
Rectal adenocarcinoma
Colon adenocarcinoma
Others
Cumulative Survival
1.0
0.8
0.6
0.4
0.2
0.0
0
1
2
3
4
5
5-year OS



Overall Comparisons[a]

	Chi-Square	df	Sig.
Log Rank (Mantel-Cox)	8.405	2	.015
Breslow (Generalized Wilcoxon)	12.704	2	.002
Tarone-Ware	10.798	2	.005

Test of equality of survival distributions for the different levels of AdenoCaSite.

a. Adjusted for Tumour (Primary vs Recurrent).

Figure 2: 5-year overall survival for primary and recurrent cancers

Poor independent prognostic markers for 5-year OS were; increasing ASA score, history of cardiovascular disease, recurrent cancers, ovarian cancers, pulmonary embolus and acute respiratory distress syndrome (see Table 4). A positive survival benefit was demonstrated if patients receive pre-operative radiotherapy with an estimated HR 0.55 (95%CI 0.4-0.75, p<0.001).

Variables	Hazard Ratio	95%CI for OR		p-value
		Lower	Upper	
One-year Overall Survival				
Patient comorbidities				
ASA score				
1	1.00			
2	1.18	0.34	4.07	
3	3.35	0.99	11.37	
4	2.95	0.57	15.12	<0.001
Peripheral vascular disease	5.24	1.21	22.7	0.027
Previous malignancy	2.04	1.06	3.89	0.032
Treatment				
Rectal resection	0.48	0.27	0.82	0.008
Small bowel resection	2.12	1.21	3.71	0.008
Radiation therapy	0.44	0.25	0.78	0.005
Complications				
Septicemia	7.07	1.23	40.7	0.029
Pulmonary embolus	70.59	15.2	327.1	<0.001
ARDS	11.11	3.34	36.95	<0.001
Anastomotic leak	5.00	1.43	17.51	0.012
Post-operative bleeding	6.14	1.40	26.89	0.016
5-year Overall Survival				
Patient comorbidities				
ASA score				
1	1.00			

2	0.79	0.47	1.34	
3	1.43	0.84	2.44	
4	1.22	0.52	2.87	0.004
Cardiovascular disease	1.57	1.11	2.22	0.011
Pathology				
Recurrent cancers	1.84	1.35	2.52	<0.001
Ovarian cancers	2.57	1.73	3.81	<0.001
Treatment				
Pre-operative radiotherapy	0.55	0.40	0.75	<0.001
Complications				
Pulmonary embolus	15.32	3.68	63.7	<0.001
ARDS	3.82	1.38	10.6	0.010
5-year Overall Survival without complications				
Patient comorbidities				
ASA score				
1	1.00			
2	0.76	0.45	1.28	
3	1.31	0.77	2.23	
4	1.29	0.55	3.03	0.007
Cardiovascular disease	1.67	1.19	2.35	0.003
Pathology				
Recurrent cancers	1.76	1.29	2.41	<0.001
Ovarian cancers	3.03	2.01	4.57	<0.001
Treatment				
Pre-operative radiotherapy	0.57	0.42	0.78	<0.001
Anal resection	1.85	1.31	2.60	<0.001
Blood transfusion	1.03	1.01	1.06	0.013

Table 4: Cox regression analysis.

ASA – American Society of Anaesthesiologist, ARDS – acute respiratory distress syndrome

Discussion

In this retrospective analysis of a large dual tertiary hospital database, the risk of 30-day mortality is low, with an overall major complication rate of 16.4% and favourable 5-year OS for primary cancers compared to recurrent cancers. Patient comorbidities and specific complications can influence long-term survival and this study can further aid in patient informed consent, explaining not only the pathological and technical complexities affecting survival but also their comorbidities and potential complications leading to poorer outcomes.

Nonetheless, it was noted for 5-year OS, primary colon cancers had a worse prognosis compared to the rectal cancer cohort. This was despite having more advanced clinical T and N stage, hence the judicious use of pre-operative radiotherapy. This can explain the better long-term outcome, with 75.1% of rectal cancer patients receiving radiotherapy before surgery compared to only 28.9% for patients with advanced colonic cancers. Furthermore, major complications were equivalent between primary and recurrent cancers although blood transfusion requirement was significantly higher in the recurrent cancer cohort.

Although the overall morbidity after surgery was lower than expected compared to the current reported literature,(14-16) it did identify two independent poor prognostic markers for 5-year OS; pulmonary embolus and acute respiratory distress syndrome. The long-term consequence of pulmonary embolus has been clearly defined, in which nearly 50% of the patients will continue to suffer from serious adverse events (within four years) such as recurrent venous thromboembolism, cardiovascular events, chronic pulmonary hypertension and death.(17) Knowing their increased risk of further adverse events, these patients may benefit from close monitoring not only to identify oncological recurrence but subsequent adverse events as a result of pulmonary embolus. This includes individualised assessment of the risk for recurrent venous

thromboembolism for prolonged anticoagulation consideration and effective cardiovascular risk-factor evaluation and preventive treatment measures.(17)

Patient comorbidities should be an integral part of risk stratification for any surgical procedure. As the population ages, so does the mean age of cancer patients and presence of one or more comorbidities.(18) It has been estimated that cancer patients above the age of 65 or older, approximately 60% will have one or more comorbidity; in which 23% were associated with cardiovascular disease.(19) Cardiovascular disease, notably heart failure has been shown to be a significant predictor of in-patient mortality(20) and have poorer 5-year OS.(21)

Therefore, using a comprehensive prospectively collected database, specific patient comorbidities was examined. From our analysis, increasing ASA score and cardiovascular disease were significant predictors for 5-year OS, after adjusting for pathological, treatment and post-operative factors. Several reasons can contribute to poorer survival outcome for patients with known cardiovascular disease; the cardiotoxic and antiangiogenic effects commonly used during systemic and radiation therapies can exacerbate cardiac symptoms, lack of awareness and knowledge about cardiac health and suboptimal access to preventive care maybe the cause for these patients.(22)

Our study is subject to both strengths and limitations. This study represents one of the largest cohorts, with extensive prospectively collected database and durable predictors of short- and long-term outcomes. However, it is based on a well selected group of patients of which surgery was performed in a highly specialised centre, hence the lower morbidity rate. Moreover, we were unable to extrapolate post-operative treatment (adjuvant chemotherapy or radiotherapy) that may be confounders to our current survival analysis. Finally, without knowing the cause of death, it is not possible to associate cause and effect of post-operative complications to long-term survival.

There are several limitations to this study, which need to be considered. Firstly, the study is retrospective, albeit based on data collected prospectively from two centres. Interpretation of these results are limited somewhat by the degree of heterogeneity, both within each and between centres. This includes, the degree of heterogeneity of the patient populations and variations in the treatment strategies and surgical technique. It is also important to acknowledge that the data is collected over a long-time period (1990-2015), which may also introduce a degree of inherent bias, given the evolving treatment strategies over time. However, there is a previous collaborative history(8, 23, 24), with also a high degree of consistency of approach across the centres included in this study. Therefore, in the absence of prospective studies, this report provides further data on the short-term complications and predictors following exenterative surgery for locally advanced and recurrent pelvic malignancies.

There has only been one study examining this clinical research question. Huang et al. showed a none association was identified between patient's comorbidities (for hypertension, pulmonary disease, cardiac disease, diabetes mellitus) with long-term oncological outcomes after pelvic exenteration for gynaecological malignancies.(25) Others have used chronological age or number of comorbidities to better select patients for pelvic exenteration and inconsistent association to survival(14, 16, 26).

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Discussion

In chapter one this large international combined series from established centres specialising in pelvic exenterative surgery, presents good outcomes and describes the evolution of this technique for locally advanced pelvic tumours over thirty years. Surgical innovations over this time have led to multivisceral surgical intervention to treat locally advanced pelvic tumours and this data supports that these approaches have been steadily gaining momentum (1, 2). During the course of the last three decades, this study demonstrates advances in the operative strategies implemented to improve both the potential of gaining an R0 resection margin thus improving oncological and patient outcomes. Moreover, the findings presented within, outline patient survival dependant on the types of pathology encountered. These findings are reported to educate both patients and the surgical community on the potential survival outcomes post-surgical intervention for each pathological subtype. The use of this data is imperative in guiding patient, family and surgical anticipated expectations and outcomes and to aid the pre-operative consent process.

This work documented that there was an increased incidence of patients undergoing exenterative surgery for recurrent disease during the latter years of this study (2011 to 2018) compared with the preceding time points. Furthermore, there was increasing complexity of surgical resections and the pathology encountered which was reflected by the expanding number of surgical compartments resected and operative components performed. This correlation was further demonstrated by the increasing number of sacrectomy, ileal conduits and lateral pelvic sidewall dissections performed during the study period. With regards to survival, patients undergoing exenterative surgery in the most recent time period had significantly improved survival. The data also reported improved survival for primary over recurrent disease at each

specific time point except for 2005 – 2010. However, when examined in the total cohort primary disease undergoing exenteration had superior survival when compared to recurrent disease. These finding were borne out in smaller studies. A study examining outcomes of 40 consecutive exenterations over a nine year period for locally advanced versus locally recurrent colorectal malignancy reported that 5-year overall survival was significantly inferior in recurrent disease as opposed to upfront advanced disease (58.7% vs. 11.8%, P = 0.022) (3). When examining five-year survival data, the latest cohort (2011 – 2018) had greatest survival benefit undergoing surgery for GI and gynaecological related malignancy. There was not a similar survival benefit observed in patents with squamous cell carcinoma and *other* malignancy (Melanoma, Prostate, Sarcoma, GIST and Chordoma). This current work supports smaller studies which have highlighted that non-modifiable factors associated with gynaecological malignancy at the time of exenteration are associated with poor survival (4). These outcomes have been mirrored in other studies (5, 6) A recent study reported an overall survival of 40.7% and cumulative 5-year overall survival of 38% in patients under exenterative surgery for primary and recurrent cervical carcinoma. This combined data together with other smaller studies in the literature provides valuable data which aids in the already complex decision making of patients undergoing exenterative surgery.

In chapter two it is reported through this retrospective analysis the risk of 30-day mortality is low, with an overall major complication rate of 16.4% and favourable 5-year OS for primary cancers compared to recurrent cancers. Complex major surgery has been shown to be associated with significant complications and this radical surgery is performed in the setting of advanced tumour growth and frequently irradiated tissue, thus exenterative surgery is commonly associated with major morbidity (7, 8). Moreover, a systematic review of pelvic exenteration

reported complication rates between 37% and 100%, whilst perioperative mortality rates ranged from 0% to 25% (9). This documents that patient comorbidities and specific complications can influence long-term survival and this study can further aid in patient informed consent, explaining not only the pathological and technical complexities affecting survival but also their comorbidities and potential complications leading to poorer outcomes. Nonetheless, it was noted for 5-year OS, primary colon cancers had a worse prognosis compared to the rectal cancer cohort. This was despite having more advanced clinical T and N stage, hence the judicious use of pre-operative radiotherapy. This can explain the better long-term outcome, with 75.1% of rectal cancer patients receiving radiotherapy before surgery compared to only 28.9% for patients with advanced colonic cancers. Furthermore, major complications were equivalent between primary and recurrent cancers although blood transfusion requirement was significantly higher in the recurrent cancer cohort. This low 30-day major morbidity (16.4%) and inpatient mortality rates (0.46%) demonstrate this to be safe and feasible, supporting the argument that specialist centres with centralised care pathways are key to improving patient outcomes. The series in this chapter adds to the increasing evidence that good outcomes can be achieved for pelvic exenterative surgery in locally advanced and recurrent pelvic malignancies. A coordinated approach in specialist centres for beyond TME surgery demonstrates this is a safe and feasible procedure, offering low major complication rates.

In the chapter three, the patterns of general complications are describe and it documents good overall outcomes for urological procedures performed as part of the management of locally advanced and recurrent pelvic malignancies. Urinary tract reconstruction after both cystectomy and partial ureter resection is associated with more specific complications in the context of locally advanced colorectal cancer surgery compared with primary urothelial cancer surgery(10,

11). Prior pelvic radiotherapy and extent of surgical resection are two factors suggested for this increased urological morbidity. It is highlighted in this chapter that major complications, particularly intestinal anastomotic leak and intra-abdominal collection, are more common in patients undergoing a urological procedure within pelvic exenterative surgery which also impacts on 5-year overall survival. Overall, 35.0% (n=226 patients) of all patients required a urological procedure as part of the pelvic exenteration, which is a similar frequency to other large series(12-14). The overall 30-days major complication rate was significantly higher in the urological intervention group (28.3%; n=64) compared to the non-urological group (12.4%; n=52 patients; p=0.001). Surgical complexity is a main driver of complications, with urological procedures being associated with significantly more complications(15). The increase in intra-abdominal collections within the urological intervention group might reflect the nature of the surgery performed, particularly ileal conduit formation or reconstruction following ureteric resection, representing urine leaks. The increased dead space within the pelvic inlet following a total pelvic exenteration may also further explain this observed outcome (16). The frequency of major intra-abdominal collections were similar to other reported series of 13.7% (17). The data recognises an increased number of intestinal anastomotic leaks in the urological intervention group (3.5% n=8), this likely reflects the increased frequency of anastomoses performed in relation to ileal conduits formation. An association between poorer overall survival and post-surgical complications has been observed in colorectal cancer patients (18). This study also showed that development of a major complication impacted 5-year overall survival in the urological intervention group. This effect might be explained by the systemic consequence of the complication on the patient and/or causing delay or rendering the patient unsuitable for further adjuvant therapies (19).

This chapter continues to reflect the cornerstone of this thesis in which advocates that clinical assessment of patient comorbidities prior to surgical intervention is an integral part of risk-stratification because of the direct correlation between the increasing mean age of cancer patients and the presence of one or more comorbidities. Furthermore, it aids in the individualised consenting process by highlighting that patient comorbidities and specific complications can influence long-term survival, emphasising the importance of an individualised discussion and treatment plan for patients requiring pelvic exenterative surgery. Patients must be counselled accordingly when considering surgical intervention and this study documents the necessity in explaining the pathological, technical complexities and patient factors leading to poorer outcomes and affecting survival to both patient and family members.

Chapter four delved deeper into investigating the impact of co-morbidities and post-operative complications on long term overall survival in patients undergoing pelvic exenteration. It is reported in this chapter that when analysing one-year overall survival, primary rectal adenocarcinoma had the best survival whilst recurrent colon cancer had the worse survival ($p=0.047$). The 5-year OS between primary and recurrent cancers were 64.7% and 53% respectively ($p=0.004$). Patient comorbidities should be an integral part of risk stratification for any surgical procedure. As the population ages, so does the mean age of cancer patients and presence of one or more comorbidities.(20) It has been estimated that cancer patients above the age of 65 or older, approximately 60% will have one or more comorbidity; in which 23% were associated with cardiovascular disease.(21) Cardiovascular disease, notably heart failure has been shown to be a significant predictor of in-patient mortality and have poorer 5-year OS (22, 23). Poor independent prognostic markers for 5-year OS were; increasing ASA score, cardiovascular disease, recurrent cancers, ovarian cancers, pulmonary embolus and acute

respiratory distress syndrome. A positive survival benefit was demonstrated with pre-operative radiotherapy. Several reasons can contribute to poorer survival outcome for patients with known cardiovascular disease; the cardiotoxic and antiangiogenic effects commonly used during systemic and radiation therapies can exacerbate cardiac symptoms, lack of awareness and knowledge about cardiac health and suboptimal access to preventive care maybe the cause for these patients.

Patient comorbidities and specific complications can influence long-term survival following extended radical resections. This study highlights important predictors, enabling clinicians to better inform patients of the potential short and long-term outcomes in the management of locally advanced and recurrent pelvic malignancy.

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