Early-Onset Colorectal Cancer: Epidemiology, Surgical Outcomes, Survival and Quality of Life after Surgery

Dr Celine Garrett

Central Clinical School

The University of Sydney

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

(Medicine and Health)

2023

Table of Contents

Statement of originality

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

Dr Celine Garrett, 15th October 2023

Acknowledgements

Firstly, I would like to thank my supervisors, Associate Professor Daniel Steffens, Professor Michael Solomon and Associate Professor Cherry Koh for their guidance and support. Their expertise, encouragement and advice have been greatly appreciated in this process. I would also like to extend my thanks, especially to Associate Professor Cherry Koh who has been a mentor and motivator to me throughout this process, always brainstorming ways to maximise my research output and further my surgical career.

Secondly, I would like to thank the staff at the Surgical Outcomes Research Centre (SOuRCe): Madhu Prasad, who was extremely helpful in coordinating my research meetings with my supervisors; Kiera Taylor and Henna Solanki (the PESQI and PREMIER database managers) who, on multiple occasions, extracted data for me without complaint; and to Sascha Karunaratne and Ruby Cole who helped me tailor my REDCap database to the 36-Item Short Form Survey version 2.0 (SF-36v2) and inputted my SF-36v2 scores into Optum software.

Lastly, I would like to thank my partner George, my parents, and my friends for their endless love and patience throughout this process.

Abstract

Early-onset colorectal cancer (EOCRC) is the diagnosis of colorectal cancer <50 years and is increasing in incidence worldwide, with Australia at the forefront. Existing research is based on American cohorts and minimal studies investigate the postoperative outcomes, survival and health-related quality of life (HRQoL) of EOCRC patients. The aim of this thesis was to summarise the current literature and to report on the postoperative outcomes, survival and the HRQoL of an Australian cohort of EOCRC patients.

A retrospective audit showed that most patients presented with left-sided and stage IV disease. Pelvic exenteration (PE) or cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) were performed in nearly one-third of the cohort, closely followed by low anterior resections. The rate of stoma formation and postoperative minor complications was high. However, the absolute five-year survival rate was 85.5%. A cross-sectional study utilising the SF-36v2 survey found that the physical and mental aspects of HRQoL were within the average range of the general Australian population. Although insignificant, the mental component summary (MCS) scores were below the mean MCS scores of the general Australian population ≤2 and >2 years after surgery. Having stage I disease and an emergency index operation conferred poorer physical component summary (PCS) scores ≤2 years from surgery.

These findings can inform multidisciplinary team discussions, expedite referrals to quaternary services for select patients who require PE or CRS and HIPEC, guide preoperative surgical consultations and highlight the need for postoperative follow-up with psychologists and psychiatrists. Future research should compare EOCRC and later-onset colorectal cancer

outcomes (including functional outcomes) and tumour biology to further our understanding of disease behaviour, investigate the cost-effectiveness of reducing the colorectal cancer screening initiation age and determine alternative minimally invasive diagnostic biomarkers.

Research outputs from this thesis

Publications

1. **Garrett C**, Steffens D, Solomon M, Koh C. Early-onset colorectal cancer: why it should be high on our list of differentials [Internet]. *ANZ Journal of Surgery*. 2022 Apr 21.

Presentations

1. **Garrett C**, Steffens D, Koh C. Characterising Early Onset Colorectal Cancer at a Tertiary Referral Centre in Sydney, Australia (A Descriptive Study). (ePoster) *Tripartite Colorectal Meeting 2022*, Online, February 22-24 2022. (ePoster)
2. **Garrett C**, Steffens D, Solomon M, Koh C. The Current Landscape of Early-onset Colorectal Cancer. (ePoster) *American Society of Colon & Rectal Surgeons Annual Scientific Meeting 2023*, Seattle, USA, June 3-6 2023 (ePoster)
3. **Garrett C**, Steffens D, Solomon M, Koh C. The Postoperative Outcomes and Survival of Early-onset Colorectal Cancer Patients. (ePoster) *American Society of Colon & Rectal Surgeons Annual Scientific Meeting 2023*, Seattle, USA, June 3-6 2023 (ePoster)
4. **Garrett C,** Steffens D, Solomon M, Koh C. The Health-related Quality of Life of Early-onset Colorectal Cancer Patients. (ePoster) *American Society of Colon & Rectal Surgeons Annual Scientific Meeting 2023*, Seattle, USA, June 3-6 2023 (ePoster)

Upcoming presentations or publications under review

1. **Garrett C**, Steffens D, Solomon M, Koh C. Surgical and survival outcomes of early-onset colorectal cancer patients: a single-centre Australian study. (publication under review by *ANZ Journal of Surgery*)
2. **Garrett C,** Koh C, Solomon M, Steffens D. The health-related quality of life of early-onset colorectal cancer patients: an Australian cross-sectional study. (publication under review by *Diseases of the Colon & Rectum*).
3. **Garrett C,** Steffens D, Solomon M, Koh C. The Health-related Quality of Life of Early-onset Colorectal Cancer Patients. *2023 Cancer Research Network HDR Student Symposium 2023,* The University of Sydney, Sydney, Australia, November 16 2023 (Oral Presentation)

Authorship attribution statement

Chapter 2 of this thesis is published as "Early-onset colorectal cancer: why it should be high on our list of differentials".

The contribution of the candidate is as follows:

- Study concept and design
- Data collection and analysis
- Data interpretation
- Manuscript preparation and drafting
- Final approval of the manuscript

The contribution of co-authors are as follows:

Associate Professor Daniel Steffens: study concept and design, critical review of manuscript, final approval of manuscript, supervision

Professor Michael Solomon: study concept and design, critical review of manuscript, final approval of manuscript, supervision

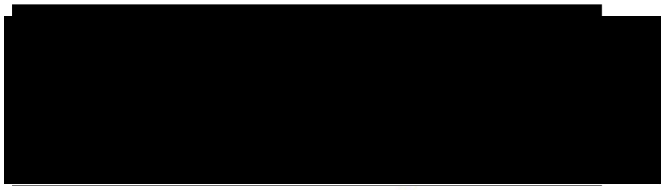
Associate Professor Cherry Koh: study concept and design, critical review of manuscript, final approval of manuscript, supervision

Candidate's signature

Dr Celine Garrett, 15th October 2023

Declaration by co-authors

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



Associate Professor Daniel Steffens, 15th October 2023

Professor Michael Solomon, 15th October 2023

Associate Professor Cherry Koh, 15th October 2023

Chapter 3 of this thesis is submitted for publication as “Surgical and survival outcomes of early-onset colorectal cancer patients: a single-centre Australian study”.

The contribution of the candidate is as follows:

- Study concept and design
- Data collection and analysis
- Data interpretation
- Manuscript preparation and drafting
- Final approval of the manuscript

The contribution of co-authors are as follows:

Associate Professor Daniel Steffens: study concept and design, critical review of manuscript, final approval of manuscript, supervision

Professor Michael Solomon: study concept and design, critical review of manuscript, final approval of manuscript, supervision

Associate Professor Cherry Koh: study concept and design, critical review of manuscript, final approval of manuscript, supervision

Candidate’s signature

Dr Celine Garrett, 15th October 2023

Declaration by co-authors

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

Associate Professor Daniel Steffens, 15th October 2023

Professor Michael Solomon, 15th October 2023

Associate Professor Cherry Koh, 15th October 2023

Chapter 4 of this thesis is submitted for publication as “The health-related quality of life of early-onset colorectal cancer patients: an Australian cross-sectional study”.

The contribution of the candidate is as follows:

- Study concept and design
- Data collection and analysis
- Data interpretation
- Manuscript preparation and drafting
- Final approval of the manuscript

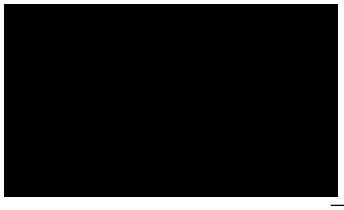
The contribution of co-authors are as follows:

Associate Professor Daniel Steffens: study concept and design, critical review of manuscript, final approval of manuscript, supervision

Professor Michael Solomon: study concept and design, critical review of manuscript, final approval of manuscript, supervision

Associate Professor Cherry Koh: study concept and design, critical review of manuscript, final approval of manuscript, supervision

Candidate’s signature

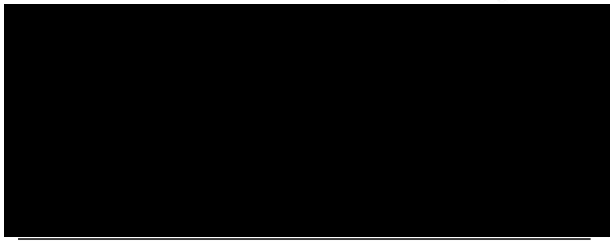


Dr Celine Garrett, 15th October 2023

Declaration by co-authors

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

Associate Professor Daniel Steffens, 15th October 2023



Professor Michael Solomon, 15th October 2023

Associate Professor Cherry Koh, 15th October 2023

Chapter 1: Introduction

1.1 Overview of colorectal cancer (CRC) in Australia

CRC was the third most diagnosed cancer in Australia in 2018. Whilst data from 2022 is still being tabulated, the Australian Institute of Health and Welfare (1) estimates that it will be the fourth most diagnosed cancer in 2022. Despite this, it is predicted to remain the second most common cause of death from cancer in Australia in 2022, contributing to 11% of all cancer-related deaths. Currently, Australians have a 5.2% risk of being diagnosed with CRC by the age of 85 with a relatively even distribution across all stages at the time of diagnosis. Interestingly, stage IV disease was the least prevalent at the time of diagnosis. Australian CRC survival data has demonstrated that increasing stage confers poorer 5-year relative survival rates. Specifically, 5-year survival for stages I, II, III and IV CRC are 98.6%, 88.6%, 71.3% and 13.4%, respectively (2). Recently, there has been growing concern regarding the increase in CRC diagnoses in the younger population.

1.2 What is early-onset colorectal cancer (EOCRC)

There is some heterogeneity in EOCRC definition in the current literature with authors using cut-offs ranging from 40-50 years (3, 4). However, most research, including a recent consensus recommendation from the Delphi Initiative for EOCRC (DIRECt) (5), defines EOCRC as the diagnosis of CRC prior to the age of 50 years as this has typically coincided with the commencement age of CRC screening programs for "average-risk" individuals and is consistent with the third aspect of the Amsterdam criteria for Lynch syndrome (6). For this thesis, a CRC diagnosis before the age of 50 is termed EOCRC.

1.3 The incidence of EOCRC

A 2021 Australian study conducted across four tertiary referral centres demonstrated that 287 of 2,315 patients diagnosed with CRC were aged under 50 (7). This 11% incidence of EOCRC is concerning when the results of a separate 2021 international study are considered which demonstrated a rise in EOCRC diagnosis by 2.8% per annum in Australia versus a 2.2% reduction per annum in later-onset CRC (LOCRC) diagnosis (CRC diagnosis aged 50 or above) (8). These Australian figures are almost double the pooled global annual percentage change in incidence (1.33%, 95% CI 0.97-1.68, $p < 0.001$). Alarmingly, in the same systematic review, the authors noted that it was Australia, the United States (US) and Canada that contributed the most to the worldwide increased risk of EOCRC (8, 9). The inverse relationship between EOCRC and LOCRC incidence has been attributed to rigorous screening and surveillance protocols for CRC and more advanced treatment options.

There are two schools of thought behind the rise in EOCRC incidence (10). The first theory is that of the "birth cohort effect"; whereby, people born in recent decades have an increased EOCRC incidence in comparison to those born in earlier decades. This implicates the role of selective environmental exposures in EOCRC development. For example, Siegal et al. (11) demonstrated that early-onset rectal cancer rates increased from the 1970-1980s in an age-dependent fashion. This has been corroborated in an Australian study but with a younger birth cohort (those born in the 1990s) (12). The second theory is that CRC incidence has increased for all ages. However, the preventative effects of screening colonoscopy in those over 50 have resulted in a disparate increase in EOCRC incidence only (as these patients are not yet routinely screened). For example, EOCRC is most common in those aged 40-49. Thus, at the time of

screening initiation a “catch-up effect” is seen in 50-51-year-olds as there is a transient increase in CRC cancer diagnosis which reflects those EOCRCs that could have been detected earlier with earlier screening (13).

1.4 Changes to CRC screening protocols

In 2018, the American Cancer Society updated their Colorectal Cancer Screening for Average-Risk Adults to reduce the age of screening initiation to 45 (14). This was corroborated by updated 2021 and 2022 guidelines from the American College of Gastroenterology, US Preventive Services Task Force and US Multisociety Task Force (15-17). Despite concerns that lowering the screening initiation age may dilute adenoma detection rates due to self-selection of low-risk, health-conscious 45-49-year-olds, lesion detection rates were comparable to first-time screening in 50-54-year-olds. Notably, whilst first-time screening colonoscopy volume tripled in the 45-49-year-old group, the overall proportion remained low at 11.6% indicating that most first-time screening colonoscopies were still performed on 50-54-year-old patients (18). By comparison, the Australian National Bowel Cancer Screening Program (NBCSP) remains unchanged (target screening group aged 50-74) with Lew et al. (19) demonstrating a less favourable benefits-to-harms ratio using a microsimulation model based on the NBCSP if the screening age were to be reduced to 45. Despite this, the NBCSP recommends (as a consensus-based recommendation) that 2-yearly immunochemical faecal occult blood tests be offered to those aged 45-49 who request screening (20).

1.5 Aims of this thesis

The aim of this thesis was to establish an Australian EOCRC cohort that also included a subset of patients referred for pelvic exenteration (PE) or cytoreductive surgery (CRS) and

hyperthermic intraperitoneal chemotherapy (HIPEC). Specifically, Chapter 2 presents a literature review of EOCRC (published in the ANZ Journal of Surgery) summarising the current evidence on the risk factors, clinical presentation, and pathological and molecular profile of EOCRC. Here, we also identify key gaps in the current understanding of EOCRC relating to the survival, surgical treatment patterns and outcomes and the health-related quality of life (HRQoL) of EOCRC patients and this has directed our subsequent studies. Chapter 3 outlines a retrospective analysis of an Australian cohort of 111 EOCRC patients describing their postoperative outcomes and survival (under review in the ANZ Journal of Surgery). Chapter 4 explores the HRQoL of 50 EOCRC patients through a cross-sectional analysis utilising the SF-36v2, identifying predictors of their HRQoL and evaluating their HRQoL relative to Australian population norms (under review by Diseases of the Colon & Rectum). Finally, Chapter 5 discusses the implications of these findings and concludes this thesis.

1.6 References

1. Cancer Australia. Bowel cancer (Colorectal cancer) in Australia statistics. [Internet]. Canberra: Cancer Australia, Australian Government, 2022 [cited 2023 Sep 13]. Available from: https://www.canceraustralia.gov.au/cancer-types/bowel-cancer/statistics
2. National Cancer Control Indicators. Relative survival by stage at diagnosis (colorectal cancer). [Internet] Canberra: Cancer Australia, Australian Government, 2019 [cited 2023 Sep 13]. Available from: https://ncci.canceraustralia.gov.au/outcomes/relative-survival-rate/relative-survival-stage-diagnosis-colorectal-cancer

3. Frostberg E, Rahr HB. Clinical characteristics and a rising incidence of early-onset colorectal cancer in a nationwide cohort of 521 patients aged 18-40 years. Cancer Epidemiol. 2020;66:101704.

4. Low EE, Demb J, Liu L, Earles A, Bustamante R, Williams CD, et al. Risk Factors for Early-Onset Colorectal Cancer. Gastroenterology. 2020;159(2):492-501.e7.

5. Cavestro GM, Mannucci A, Balaguer F, Hampel H, Kupfer SS, Repici A, et al. Delphi Initiative for Early-Onset Colorectal Cancer (DIRECt) International Management Guidelines. Clin Gastroenterol Hepatol. 2023;21(3):581-603.e33.

6. Laird SP, Toribara NW. Chapter 46 - Colorectal Cancer and Colon Cancer Screening. In: McNally PR, editor. GI/Liver Secrets (Fourth Edition). Philadelphia: Mosby; 2010. p. 323-31.

7. Siu DHW, Ali A, Tjokrowidjaja A, De Silva M, Lee J, Clingan PR, et al. Clinical and molecular profile of young adults with early-onset colorectal cancer: Experience from four Australian tertiary centers. Asia Pac J Clin Oncol. 2022;18(6):660-8.

8. Siegel RL, Torre LA, Soerjomataram I, Hayes RB, Bray F, Weber TK, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019;68(12):2179-85.

9. Saad El Din K, Loree JM, Sayre EC, Gill S, Brown CJ, Dau H, et al. Trends in the epidemiology of young-onset colorectal cancer: a worldwide systematic review. BMC Cancer. 2020;20(1):288.

10. Venugopal A, Koi M, Choi C, Kim HR, Speliotes EK, Carethers JM. ALDH1A1 Expression Is Enriched in Early-Onset Colorectal Cancers. Gastroenterology. 2022.

11. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974-2013. J Natl Cancer Inst. 2017;109(8).

12. Feletto E, Yu XQ, Lew JB, St John DJB, Jenkins MA, Macrae FA, et al. Trends in Colon and Rectal Cancer Incidence in Australia from 1982 to 2014: Analysis of Data on Over 375,000 Cases. Cancer Epidemiol Biomarkers Prev. 2019;28(1):83-90.

13. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-93.

14. Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250-81.

15. Davidson KW, Barry MJ, Mangione CM, Cabana M, Caughey AB, Davis EM, et al. Screening for Colorectal Cancer: US Preventive Services Task Force Recommendation Statement. Jama. 2021;325(19):1965-77.

16. Patel SG, May FP, Anderson JC, Burke CA, Dominitz JA, Gross SA, et al. Updates on Age to Start and Stop Colorectal Cancer Screening: Recommendations From the U.S. Multi-Society Task Force on Colorectal Cancer. Gastroenterology. 2022;162(1):285-99.

17. Shaukat A, Kahi CJ, Burke CA, Rabeneck L, Sauer BG, Rex DK. ACG Clinical Guidelines: Colorectal Cancer Screening 2021. Am J Gastroenterol. 2021;116(3):458-79.

18. Ladabaum U, Shepard J, Mannalithara A. Adenoma and Sessile Serrated Lesion Detection Rates at Screening Colonoscopy for Ages 45-49 Years vs Older Ages

Since the Introduction of New Colorectal Cancer Screening Guidelines. Clin Gastroenterol Hepatol. 2022;20(12):2895-904.e4.

19. Lew JB, St John DJB, Macrae FA, Emery JD, Ee HC, Jenkins MA, et al. Benefits, Harms, and Cost-Effectiveness of Potential Age Extensions to the National Bowel Cancer Screening Program in Australia. Cancer Epidemiol Biomarkers Prev. 2018;27(12):1450-61.

20. Cancer Council Australia Colorectal Cancer Guidelines Working Party [Internet]. Sydney: Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer [Internet]. Sydney (AU): Cancer Council Australia; 2017 [cited 2022 June 09]. Available from: https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer

Chapter 2: Early-onset colorectal cancer: why it should be high on our list of differentials

2.1 Introduction

Due to the increasing incidence of EOCRC, there has been a recent paradigm shift in CRC research to investigate EOCRC. So far, studies have established some differences between EOCRC and LOCRC in terms of risk factors, clinical presentation, pathological features and molecular profiles. This review aims to summarise the current EOCRC literature and identify any gaps that warrant further research.

2.2 Established risk factors for EOCRC

2.2.1 Non-modifiable risk factors

Age between 40-50 years, as opposed to < 40 years, is one of the most significant non-modifiable contributing factors to EOCRC development (1). Whilst being a male has been linked to EOCRC, being a female has been reported as a protective factor for colorectal adenomas (1, 2). Inflammatory bowel disease (IBD) is a well-established risk factor for CRC and has also been linked to EOCRC (9). However, in a recent EOCRC study, it was a protective factor, with authors attributing this to intense surveillance protocols (1). A family history of CRC is also a risk factor for EOCRC, however, the proportion of EOCRC patients with a family history of CRC in published EOCRC cohorts ranged from 11.1-25%, which suggests that the majority of EOCRC cases are sporadic (1, 3, 4). Like other risk factors for LOCRC, studies have established cancer syndromes and race (specifically, black, pacific islander or Asian) as risk factors for EOCRC (3, 5). It is currently unclear as to what drives the ethnic disparities

underlying EOCRC, but this may be related to lifestyle factors and socioeconomic status, which has been documented as a risk factor for EOCRC primarily in American-only studies.

2.2.2 Modifiable risk factors

In comparison to non-modifiable risk factors, there is a greater predominance of EOCRC research to investigate modifiable risk factors that represent target areas for prevention with a heavy focus on the timing of the exposure. "The Exposome" identifies exposures during development related to three domains (general external, specific external environment and internal environments) (6).

Exposures resulting in dysbiosis have been explored with weight gain and diet being the two exposures that have been the most heavily investigated. A recent 2021 systematic review and meta-analysis by Li et al. (7) found that overweight and obese younger adults have approximately 32% and 88% higher risk of developing CRC than those with average weight, respectively. Whilst previous literature has demonstrated sex-specific associations between EOCRC and young adulthood obesity (8), this was not substantiated by Li et al. (7). A sedentary lifestyle has also been linked to EOCRC (9). Westernised diet (i.e. increased fat and red meat and decreased fibre), which has also been referred to as a sulphur microbial diet, is an established risk factor for LOCRC and has been demonstrated by Rosato et al. (10), with the addition of increased consumption of alcohol (≥ 14 standards/week), to be linked with EOCRC (6, 10). Two 2021 studies have similarly reproduced these findings; a pooled analysis of 13 population-based comparative studies of EOCRC versus LOCRC which additionally demonstrated that a low-fibre (OR 1.19, 95% CI 1.08-1.31, $p < 0.001$) and low-folate diet (OR 1.16, 95% CI 1.08-1.26, $p < 0.001$) was linked more strongly with early-onset rectal cancer and an analysis of the Nurses' Health Study II data which found an association between those

in the highest quartile of sulphur microbial diet scores and early-onset adenomas with greater malignant potential (villous/tubulovillous histology) (OR 1.65, 95% CI 1.12-2.45, $p = 0.04$) (11, 12). Data from the Nurses' Health Study II has been further analysed by two studies which found that consumption of sugar-sweetened beverages both in adulthood and adolescence conferred a greater risk of EOCRC and colorectal adenomas (13, 14). More specifically, this risk was highest when consumption occurred during adolescence, with a linear relationship between the number of servings per day and a 32% increase in EOCRC risk (13).

Chemical exposures resulting in dysbiosis have also been explored, albeit to a lesser extent. Whilst smoking has been previously associated with LOCRC, current evidence demonstrating its correlation with EOCRC is conflicting (1, 15, 16). Aspirin (OR 0.66, 95% CI 1.68-2.91, $p < 0.05$) and non-steroidal anti-inflammatory drugs (OR 1.43, 95% CI 1.21-1.68, $p < 0.01$) have been found to be protective factors against the development of EOCRC in patients without IBD (2, 11). Certain antibiotics have also been correlated with an increased risk of proximal EOCRC (17). A summary of modifiable and non-modifiable risk factors and protective factors are summarised in Table 1.

Table 1. Non-modifiable and modifiable risk factors and protective factors for EOCRC

Risk factors	Protective factors
Non-modifiable	
Male	Female
Age	IBD
Family history	
Cancer syndromes	
Race (non-Hispanic white, Hispanic, black, Asian)	
Modifiable	
Western diet/sulphur microbial diet	Aspirin
Alcohol	Non-steroidal anti-inflammatory drugs
Sugar-sweetened beverages	
Sedentary lifestyle	
Obesity	
Antibiotics	

2.3 How does EOCRC present?

EOCRC typically involves either the left colon or rectum. Specifically, Siegal et al. (18) in their analysis of the North American Surveillance, Epidemiology, and End Results (SEER) database, found that 41% and 35% of males and females diagnosed with EOCRC, respectively, had rectal cancer. This is significant as previous research has demonstrated a distinct difference in the aetiology, biology, and treatment response between proximal versus distal colonic cancers, with proximal cancers being associated with poorer prognostic features (lymph node involvement, lymphovascular invasion, advanced stage at diagnosis) (19). EOCRC presents with rectal bleeding, abdominal pain, constipation or diarrhoea, unintentional weight loss and iron-deficiency anaemia (20). However, despite these red flag symptoms, studies have shown a significant delay in diagnosis of EOCRC compared to LOCRC. Chen et al. (21) found that it took a median of 128 days to diagnose EOCRC patients whilst it only took 79 days to diagnose LOCRC patients. Scott et al. (22) demonstrated an even greater disparity in delay

from symptom onset to treatment commencement between early-onset and later-onset rectal cancer patients (217 vs 29.5 days, respectively). Previous literature has postulated that this diagnostic and treatment delay is due to a lack of patient awareness, insurance, and the attribution of symptoms to more common benign conditions by physicians and surgeons (23). Despite these hypotheses, no statistically significant relationship between delayed diagnosis and late-stage EOCRC at presentation or adverse five-year survival has been found (21).

2.4 Pathological features and molecular profiles of EOCRC

2.4.1 Pathological features

EOCRCs display more aggressive pathological features in comparison to their LOCRC counterparts. Two large-scale comparative studies of the SEER (1,334 patients aged 20-40 years vs 46,457 patients aged 60-80 years) and the North American National Cancer Database (64,068 patients < 50 years vs 52,4801 patients aged > 50 years) demonstrated poorer differentiation and increased mucinous and signet-ring tumour morphology in their younger cohorts (24, 25). A smaller-scale single-institution study found higher proportions of locally advanced tumours invading adjacent structures (pT4) and lymph node metastases with an overall higher mean lymph node ratio in EOCRC versus LOCRC (26). Moreover, Vuik et al. (27) established that within their EOCRC cohort exclusively, an inverse relationship existed between age and the presence of adverse pathological features; whereby being in a younger age group (20-29 vs 30-39 vs 40-49 years) was associated with an increased presence of signet-ring cells, poorly differentiated tumours, and lymph node involvement.

2.4.2 Molecular features

Studies comparing EOCRC and LOCRC have demonstrated that whilst gene mutation rates remain relatively the same, specific genes that have previously been established as prognostic biomarkers or treatment targets for LOCRC differ in EOCRC. EOCRCs harbour fewer KRAS, BRAFV600E and APC mutations but are more likely to have TP53 and CTNNB1 mutations (28-30). EOCRC tumours are also more likely to undergo epigenetic changes (promoter methylation of the CpG islands) (23). In recent times, consensus molecular subtypes (CMS) have been used to classify CRC based on molecular features. Willauer et al. (30) found that younger patients were more likely to be of the CMS1 subtype characterised by high microsatellite instability and inflammatory/immunogenic markers, which is associated with germline mutations implicated in hereditary syndromes such as Lynch syndrome. Despite this, approximately 80-85% of EOCRCs are sporadic, microsatellite stable tumours (31). Lam et al. (32) demonstrated a link between NR0B2 frameshift variants and increased susceptibility to microsatellite stable, APC-negative EOCRC. Further, recent molecular research has demonstrated a higher tumour mutational burden and distinct innate immune signature of EOCRC, has correlated specific gene mutations (SSA1, C7, CFD, CXCL3, IL1B, MET, TNS1), and aberrant pathways (wild-type WTN and mutated TGF-β pathway) with poorer overall survival (OS) in EOCRC and has identified accelerated ageing in normal mucosa of EOCRC patients as a potential contributor to carcinogenesis (33-36). While molecular studies comprise a substantial amount of the current EOCRC body of literature, most of these studies are limited by a lack of reproducibility, heterogeneous inclusion criteria and methods, and small cohort sizes. To date, the molecular landscape and diagnostic, prognostic, and therapeutic biomarkers of EOCRC are relatively unknown.

2.5 Survival outcomes of EOCRC

At present, EOCRC survival studies are limited with varying EOCRC definitions and different survival measures. As such, the results of these studies are conflicting and are difficult to interpret without more uniform research. For example, two large studies found either superior or equivalent survival outcomes of EOCRC patients compared to their LOCRC counterparts despite a higher rate of advanced stage at diagnosis. More specifically, Saraste et al. (37) in their large Swedish study investigating 34,434 CRC patients found that EOCRC patients had a superior 5-year stage-adjusted disease-free survival (DFS) in comparison to those aged 50-74 and ≥ 75 (stage I: 0.96 vs 0.88 vs 0.69, $p < 0.001$; stage II: 0.90 vs 0.82 vs 0.62, $p < 0.001$ and stage III: 0.77 vs 0.68 vs 0.49, $p < 0.001$). O'Connell et al. (24) in their study of 47,791 SEER database patients demonstrated that whilst younger CRC patients (20-40 vs 60-80 years) had an overall worse 5-year cancer-specific survival (61.5% vs 64.9%, $p = 0.015$), after adjusting for stage, the 5-year stage-specific survival was similar for stage I (93.3% vs 94.9%, $p > 0.05$) and III (58.9% vs 57.2%, $p > 0.05$) disease and better for stage II disease (88.6% vs 82.7%, $p = 0.01$). The improved survival benefit of EOCRC patients following stage adjustment was supported by Cheng et al. (38). Other studies investigating early-onset rectal cancer have found a significant improvement in OS at the 5- and 12-year marks (39, 40). The improved or equivalent survival outcomes of EOCRC patients in these studies has been attributed to their fewer comorbidities and higher receipt of neoadjuvant therapy and surgery. By contrast, a 2021 Australian rectal cancer study found that EOCRC patients had poorer median DFS post-neoadjuvant radiotherapy and surgery (4.67 vs 16.02 months, $p = 0.023$) as well as a poorer progression-free (2.66 vs 9.70 months, $p = 0.006$) and OS (40.46 vs 58.26 months, $p = 0.036$) following relapse. The authors of this study hypothesised that this was due to the more aggressive tumour biology of younger-onset rectal cancer and its potential to create a treatment-resistant environment (41).

2.6 Limitations of current research

Although a substantive platform of EOCRC research exists, there are a few notable limitations. Firstly, most EOCRC studies comprise American-only cohorts, limiting the generalisability of their results. Secondly, aside from research into the risk factors of EOCRC, there is a substantially larger proportion of studies utilising smaller cohort sizes and a retrospective study design. Hence, the impact of selection bias inherently associated with this study design cannot be ignored. Thirdly, a comparison of variables and outcomes with LOCRC was only performed in roughly half of the studies limiting the ability to interpret comparative differences between these groups and thus ascertain whether current management guidelines translate (with the same efficacy) to EOCRC patients. Lastly, current literature primarily investigates the epidemiology, risk factors and molecular profile of EOCRC. However, studies focusing on the surgical outcomes and HRQoL of EOCRC are scarce.

2.7 Current gaps that require further exploration

Two recent American studies have investigated the comparative short-term surgical outcomes of EOCRC versus LOCRC and early-onset versus later-onset rectal cancer. In both studies, the early-onset groups had significantly reduced 30-day mortality (0.4% vs 1.8%, $p = 0.04$ and 0.3% vs 1.3%, $p = 0.04$, respectively*)* and 30-day postoperative complications (18% vs 22%, $p = 0.02$ and 25% vs 29%, $p = 0.02$, respectively) on univariate analyses, which did not demonstrate statistically significant differences on multivariate analyses. This was thought to be secondary to the confounding effect of the larger tumour sizes and aggressive histopathology of early-onset tumours (42, 43). Unfortunately, these studies were limited by their lack of long-term postoperative data and lack of information regarding surgical margins. Aside from these

two studies, few other large non-American cohort studies investigate the surgical outcomes of EOCRC, and thus further research is warranted.

Utilising the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) questionnaire, Miller et al. (44) compared the HRQoL of EOCRC patients 6-18 months and 19-36 months from diagnosis. They demonstrated low global and domain-specific HRQoL scores overall and a significant positive correlation between time elapsed from diagnosis/relapse and physical (14.31 vs 16.56, $p = 0.001$) and emotional (11.3 vs 12.56, $p = 0.007$) well-being scores. Other current quality-of-life EOCRC research comprises small qualitative interview-style studies that lack reproducibility (45). By comparison, HRQoL in CRC has been widely studied using a variety of measurement tools (FACT-C, the European Organisation for Research and Treatment of Cancer Quality of life (EORTC) and Quality of Life Questionnaire Colorectal Cancer Module (QLQ-CR38/29)) with results demonstrating near equivocal HRQoL following primary treatment to the general population except for those patients receiving palliative care (46). Despite this, scores were heterogeneous between measurement tools. To ascertain if this HRQoL disparity between EOCRC and general CRC is valid, further research comprised of large prospective studies comparing EOCRC and LOCRC utilising a uniform HRQoL assessment tool is imperative.

2.8 Conclusion

This review has demonstrated that EOCRC differs from LOCRC, characterised by subtle dissimilarities in risk factors (particularly regarding timing of exposure) and molecular profiles. Despite the increasing incidence of EOCRC and a plethora of studies that highlight the same, EOCRCs are still diagnosed at more advanced stages with a delay in diagnosis from symptom

onset. Surgeon awareness of this is imperative to timely diagnosis and workup of EOCRC. Moreover, to optimise the current treatment algorithms of EOCRC, larger, prospective research with an emphasis on survival, surgical outcomes and HRQoL needs to be performed.

2.9 References

1. Agazzi S, Lenti MV, Klersy C, Strada E, Pozzi L, Rovedatti L, et al. Incidence and risk factors for preneoplastic and neoplastic lesions of the colon and rectum in patients under 50 referred for colonoscopy. Eur J Intern Med. 2021;87:36-43.
2. Low EE, Demb J, Liu L, Earles A, Bustamante R, Williams CD, et al. Risk Factors for Early-Onset Colorectal Cancer. Gastroenterology. 2020;159(2):492-501.e7.
3. Gausman V, Dornblaser D, Anand S, Hayes RB, O'Connell K, Du M, et al. Risk Factors Associated With Early-Onset Colorectal Cancer. Clin Gastroenterol Hepatol. 2020;18(12):2752-9.e2.
4. Stoffel EM, Murphy CC. Epidemiology and Mechanisms of the Increasing Incidence of Colon and Rectal Cancers in Young Adults. Gastroenterology. 2020;158(2):341-53.
5. Crosbie AB, Roche LM, Johnson LM, Pawlish KS, Paddock LE, Stroup AM. Trends in colorectal cancer incidence among younger adults-Disparities by age, sex, race, ethnicity, and subsite. Cancer Med. 2018;7(8):4077-86.
6. Hofseth LJ, Hebert JR, Chanda A, Chen H, Love BL, Pena MM, et al. Early-onset colorectal cancer: initial clues and current views. Nat Rev Gastroenterol Hepatol. 2020;17(6):352-64.

7. Li H, Boakye D, Chen X, Hoffmeister M, Brenner H. Association of Body Mass Index With Risk of Early-Onset Colorectal Cancer: Systematic Review and Meta-Analysis. Am J Gastroenterol. 2021;116(11):2173-83.

8. Liu PH, Wu K, Ng K, Zauber AG, Nguyen LH, Song M, et al. Association of Obesity With Risk of Early-Onset Colorectal Cancer Among Women. JAMA Oncol. 2019;5(1):37-44.

9. Nguyen LH, Liu PH, Zheng X, Keum N, Zong X, Li X, et al. Sedentary Behaviors, TV Viewing Time, and Risk of Young-Onset Colorectal Cancer. JNCI Cancer Spectr. 2018;2(4):pky073.

10. Rosato V, Bosetti C, Levi F, Polesel J, Zucchetto A, Negri E, et al. Risk factors for young-onset colorectal cancer. Cancer Causes Control. 2013;24(2):335-41.

11. Archambault AN, Lin Y, Jeon J, Harrison TA, Bishop DT, Brenner H, et al. Nongenetic Determinants of Risk for Early-Onset Colorectal Cancer. JNCI Cancer Spectr. 2021;5(3).

12. Nguyen LH, Cao Y, Hur J, Mehta RS, Sikavi DR, Wang Y, et al. The Sulfur Microbial Diet Is Associated With Increased Risk of Early-Onset Colorectal Cancer Precursors. Gastroenterology. 2021;161(5):1423-32.e4.

13. Hur J, Otegbeye E, Joh HK, Nimptsch K, Ng K, Ogino S, et al. Sugar-sweetened beverage intake in adulthood and adolescence and risk of early-onset colorectal cancer among women. Gut. 2021;70(12):2330-6.

14. Joh HK, Lee DH, Hur J, Nimptsch K, Chang Y, Joung H, et al. Simple Sugar and Sugar-Sweetened Beverage Intake During Adolescence and Risk of Colorectal Cancer Precursors. Gastroenterology. 2021;161(1):128-42.e20.

15. Jung YS, Ryu S, Chang Y, Yun KE, Park JH, Kim HJ, et al. Risk factors for colorectal neoplasia in persons aged 30 to 39 years and 40 to 49 years. Gastrointest Endosc. 2015;81(3):637-45.e7.

16. Kim JY, Jung YS, Park JH, Kim HJ, Cho YK, Sohn CI, et al. Different risk factors for advanced colorectal neoplasm in young adults. World J Gastroenterol. 2016;22(13):3611-20.

17. McDowell R, Perrott S, Murchie P, Cardwell C, Hughes C, Samuel L. Oral antibiotic use and early-onset colorectal cancer: findings from a case-control study using a national clinical database. Br J Cancer. 2022;126(6):957-67.

18. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-93.

19. Lim DR, Kuk JK, Kim T, Shin EJ. Comparison of oncological outcomes of right-sided colon cancer versus left-sided colon cancer after curative resection: Which side is better outcome? Medicine (Baltimore). 2017;96(42):e8241.

20. Olivo R, Ratnayake S. Colorectal cancer in young patients: a retrospective cohort study in a single institution. ANZ J Surg. 2019;89(7-8):905-7.

21. Chen FW, Sundaram V, Chew TA, Ladabaum U. Advanced-Stage Colorectal Cancer in Persons Younger Than 50 Years Not Associated With Longer Duration of Symptoms or Time to Diagnosis. Clin Gastroenterol Hepatol. 2017;15(5):728-37.e3.

22. Scott RB, Rangel LE, Osler TM, Hyman NH. Rectal cancer in patients under the age of 50 years: the delayed diagnosis. Am J Surg. 2016;211(6):1014-8.

23. Burnett-Hartman AN, Lee JK, Demb J, Gupta S. An Update on the Epidemiology, Molecular Characterization, Diagnosis, and Screening Strategies for Early-Onset Colorectal Cancer. Gastroenterology. 2021;160(4):1041-9.

24. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? World J Surg. 2004;28(6):558-62.

25. You YN, Moskowitz J, Chang GJ, Mork M, Rodriguez-Bigas M, Bednarski BK, et al. Germline Cancer Risk Profiles of Young-Onset Colorectal Cancer Patients: Findings from a Prospective Universal Germline Testing and Tele-Genetics Program. Dis Colon Rectum. 2022.

26. Mueller M, Schneider MA, Deplazes B, Cabalzar-Wondberg D, Rickenbacher A, Turina M. Colorectal cancer of the young displays distinct features of aggressive tumor biology: A single-center cohort study. World J Gastrointest Surg. 2021;13(2):164-75.

27. Vuik FER, Nieuwenburg SAV, Nagtegaal ID, Kuipers EJ, Spaander MCW. Clinicopathological characteristics of early onset colorectal cancer. Aliment Pharmacol Ther. 2021;54(11-12):1463-71.

28. Lieu CH, Golemis EA, Serebriiskii IG, Newberg J, Hemmerich A, Connelly C, et al. Comprehensive Genomic Landscapes in Early and Later Onset Colorectal Cancer. Clin Cancer Res. 2019;25(19):5852-8.

29. Serebriiskii IG, Connelly C, Frampton G, Newberg J, Cooke M, Miller V, et al. Comprehensive characterization of RAS mutations in colon and rectal cancers in old and young patients. Nat Commun. 2019;10(1):3722.

30. Willauer AN, Liu Y, Pereira AAL, Lam M, Morris JS, Raghav KPS, et al. Clinical and molecular characterization of early-onset colorectal cancer. Cancer. 2019;125(12):2002-10.

31. Saizul Z, Siti-Azrin AH, Zakaria AD, Hassan A, Abdul Rahman WFW, Jalil NAC. BRAF V600E and Mismatch Repair Proteins Expression in Sporadic

Young-onset Colorectal Cancer in Kelantan, Malaysia. Oman Med J. 2021;36(4):e284.

32. Lam KK, Sethi R, Tan G, Tomar S, Lo M, Loi C, et al. The orphan nuclear receptor NR0B2 could be a novel susceptibility locus associated with microsatellite-stable, APC mutation-negative early-onset colorectal carcinomas with metabolic manifestation. Genes Chromosomes Cancer. 2021;60(2):61-72.

33. Gardner IH, Siddharthan R, Watson K, Dewey E, Ruhl R, Khou S, et al. A Distinct Innate Immune Signature of Early Onset Colorectal Cancer. Immunohorizons. 2021;5(6):489-99.

34. Joo JE, Clendenning M, Wong EM, Rosty C, Mahmood K, Georgeson P, et al. DNA Methylation Signatures and the Contribution of Age-Associated Methylomic Drift to Carcinogenesis in Early-Onset Colorectal Cancer. Cancers (Basel). 2021;13(11).

35. Singh MP, Rai S, Singh NK, Srivastava S. Transcriptomic landscape of early age onset of colorectal cancer identifies novel genes and pathways in Indian CRC patients. Scientific Reports. 2021;11(1):11765.

36. Xu T, Zhang Y, Zhang J, Qi C, Liu D, Wang Z, et al. Germline Profiling and Molecular Characterization of Early Onset Metastatic Colorectal Cancer. Front Oncol. 2020;10:568911.

37. Saraste D, Järås J, Martling A. Population-based analysis of outcomes with early-age colorectal cancer. Br J Surg. 2020;107(3):301-9.

38. Cheng E, Blackburn HN, Ng K, Spiegelman D, Irwin ML, Ma X, et al. Analysis of Survival Among Adults With Early-Onset Colorectal Cancer in the National Cancer Database. JAMA Netw Open. 2021;4(6):e2112539.

39. Kolarich A, George TJ, Jr., Hughes SJ, Delitto D, Allegra CJ, Hall WA, et al. Rectal cancer patients younger than 50 years lack a survival benefit from NCCN guideline-directed treatment for stage II and III disease. Cancer. 2018;124(17):3510-9.

40. Zaborowski AM, Murphy B, Creavin B, Rogers AC, Kennelly R, Hanly A, et al. Clinicopathological features and oncological outcomes of patients with young-onset rectal cancer. Br J Surg. 2020;107(5):606-12.

41. Habib R, Burgess NG, Bourke MJ, Wong M, Wilcken N, Toh J, et al. Outcomes of young patients diagnosed with locally advanced rectal cancer. J Gastrointest Oncol. 2021;12(2):592-601.

42. Ewongwo A, Hamidi M, Alattar Z, Ayotunde OP, Tiwari HA, Elquza E, et al. Contributing factors and short-term surgical outcomes of patients with early-onset rectal cancer. Am J Surg. 2020;219(4):578-82.

43. Hanna K, Zeeshan M, Hamidi M, Pandit V, Omesiete P, Cruz A, et al. Colon cancer in the young: contributing factors and short-term surgical outcomes. Int J Colorectal Dis. 2019;34(11):1879-85.

44. Miller KA, Stal J, Gallagher P, Weng Z, Freyer DR, Kaslander JN, et al. Time from Diagnosis and Correlates of Health-Related Quality of Life among Young Adult Colorectal Cancer Survivors. Cancers (Basel). 2021;13(16).

45. Blum-Barnett E, Madrid S, Burnett-Hartman A, Mueller SR, McMullen CK, Dwyer A, et al. Financial burden and quality of life among early-onset colorectal cancer survivors: A qualitative analysis. Health Expect. 2019;22(5):1050-7.

46. Färkkilä N, Sintonen H, Saarto T, Järvinen H, Hänninen J, Taari K, et al. Health-related quality of life in colorectal cancer. Colorectal Dis. 2013;15(5):e215-22.

Chapter 3: Surgical and survival outcomes of early-onset colorectal cancer patients: a single-centre Australian study

3.1 Introduction

As demonstrated in Chapter 2, despite the rise in EOCRC incidence, EOCRC remains a relatively infrequent diagnosis in this age group. Benign anorectal disease also presents similarly and thus EOCRC is a less likely consideration in primary care. Consequently, the proportion of emergency presentations and advanced-stage disease at the time of diagnosis of EOCRC patients is significantly higher (1, 2). Whilst it has been well established that EOCRC patients are more likely to undergo multi-agent chemotherapy and radiotherapy than their LOCRC counterparts, studies investigating their surgical management are scarce (2). Further, over the last few decades, PE, and CRS and HIPEC have become the mainstream treatment options for selected CRC patients with locally invasive pelvic disease and stage IV disease (M1c), respectively. These represent options for the high burden of EOCRC patients with advanced disease. The aim of Chapter 3 is to report on the postoperative and survival outcomes of EOCRC at a single Australia centre, which is also a quaternary referral centre for PE and CRS and HIPEC.

3.2 Methods

This study was conducted in agreement with the Declaration of Helsinki. Ethics approval and Governance Authorisation were obtained from the Sydney Local Health District Human Research Ethics Committee (ethics approval identification X21-0214 and 2021/ETH00976).

A retrospective study was conducted on 111 EOCRC patients treated in the Colorectal Surgical Unit at the Royal Prince Alfred Hospital (RPAH), Sydney, Australia between January 2013 and December 2021 (inclusive). Patients were included if they had: (1) histopathologically diagnosed colorectal adenocarcinoma prior to the age of 50 and (2) underwent surgical resection (regardless of primary or subsequent resection) of their CRC at RPAH. Patients were excluded if no data from their primary operation was available.

Data regarding patients' primary operations were collected from electronic and paper medical records. Patients' demographic and surgical outcomes data were collected. High and low anterior resection were defined as final anastomosis above and below the peritoneal reflection, respectively (3). The Clavien-Dindo Classification was used to grade complication severity (4). Survival data collected included: absolute survival, DFS and OS. Absolute survival was defined as the percentage proportion of patients alive at one, three and five-year time intervals from their primary surgery. DFS was defined as the time from resection to radiological or histopathological confirmation of disease recurrence. OS was defined as the time from resection to death. If recurrence or death did not occur prior to the end date of this study (1st July 2022), the patient's date of last contact was used as the censored date.

Statistical analyses were performed using IBM SPSS Statistics Version 26. A descriptive analysis was performed. DFS and OS were calculated using Kaplan-Meier survival curves. After matching for stage, log-rank tests assessed whether DFS and OS differed significantly based on age, tumour location and surgery type. Data were complete for each variable in this study.

3.3 Results

Of the 156 patients who met the inclusion criteria for this study, 45 were excluded due to no information on their primary operation. Thus, a total of 111 EOCRC patients were included for data analysis (Figure 1).

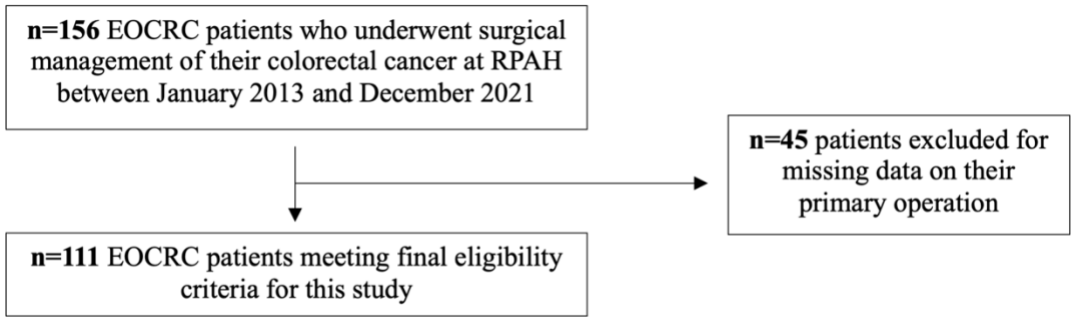


Figure 1. Flowchart demonstrating final study numbers after exclusion criteria applied

3.3.1 Demographic and tumour characteristics

This cohort was comprised of 57.66% women (n = 64/111). The average age at diagnosis was 38.20 ± 6.80 years. Most patients were diagnosed between the ages 40-49 years (46.85%, n = 52/111), followed by 30-39 years (41.44%, n = 46/111) and <30 years (11.71%, n = 13/111). In this study, 68 patients (61.26%) had colon cancer and 43 had rectal cancer (38.74%). Despite this, almost 80% of all tumours were left-sided with a nearly equal distribution between tumours located between the splenic flexure and sigmoid colon (37.84%, n = 42/111) and those located in the rectum (38.74%, n = 43/111). Forty-two (37.84%) patients were diagnosed with stage IV disease at the time of presentation. Thirty-four (30.63%), 20 (18.02%) and 15 (13.51%) patients were diagnosed with stage III, II and I disease respectively. Whilst 16 patients (14.41%) did not receive any chemotherapy or radiotherapy, 26.13% (n = 29/111) underwent neoadjuvant chemoradiotherapy (CRT), 45.95% (n = 51/111) had adjuvant

chemotherapy and 10.81% (n = 12/111) had combined neoadjuvant CRT and adjuvant chemotherapy. Three patients (2.70%) underwent palliative chemotherapy or radiotherapy. Further demographic and tumour characteristics are detailed in Table 1.

Table 1. Patient and tumour characteristics of EOCRC patients

Variables	**Frequency (n=111, %)**
Gender, female	n=64 (57.66%)
Age at diagnosis	
<30 years	n=13 (11.71%)
30-39 years	n=46 (41.44%)
40-49 years	n=52 (46.85%)
Chemotherapy or radiotherapy	
None	n=16 (14.41%)
Neoadjuvant CRT	n=29 (26.13%)
Adjuvant chemotherapy	n=51 (45.95%)
Neoadjuvant CRT and adjuvant chemotherapy	n=12 (10.81%)
Palliative chemotherapy or radiotherapy	n=3 (2.70%)
Tumour location	
Caecum to transverse colon	n=26 (23.42%)
Splenic flexure to sigmoid colon	n=42 (37.84%)
Rectum	n=43 (38.74%)
Mucinous	n=28 (25.23%)
Signet ring	n=14 (12.61%)
Stage at diagnosis	
I	n=15 (13.51%)
II	n=20 (18.02%)
III	n=34 (30.63%)
IV	n=42 (37.84%)

3.3.2 Surgical outcomes

Eighty patients (72.07%) did not undergo either PE or CRS and HIPEC. In this group, low anterior resection (19.82%, n = 22/111) was performed most frequently followed by high anterior resection (17.12%, n = 19/111), right hemicolectomy (14.41%, n = 16/111), abdominoperineal resection (6.31%, n = 7/111), Hartmann's procedure (5.41%, n = 6/111), extended right hemicolectomy (2.70%, n = 3/111), left hemicolectomy (2.70%, n = 3/111), total colectomy (1.80%, n = 2/111) and total proctocolectomy (1.80%, n = 2/111). Thirty-one patients (27.93%) underwent either PE or CRS and HIPEC. PE was performed in 11.71% (n = 13/111) of patients and CRS and HIPEC was performed in 15.32% (n = 17/111) of patients. One patient underwent combined PE and CRS and HIPEC. Half of this study's cohort had a stoma fashioned (50.45%, n = 56/111) and 26.13% (n = 29/111) of all patients had their surgery performed in an emergency setting.

A postoperative intensive care unit (ICU) admission occurred in 40.54% (n =45/111) patients with a mean duration of 5.80 ± 11.60 days. Total parenteral nutrition (TPN) was administered to 30.63% (n = 34/111) patients postoperatively for an average of 16.10 ± 23.20 days. The mean time to pass flatus and stool was 4.80 ± 2.80 and 5.20 ± 3.10 days, respectively. Complications occurred in 54.95% (n = 61/111) patients of which Clavien-Dindo grade II (47.54%, n = 29/61) was the most common followed by grades III (19.67%, n = 12/61) and IV and I (16.39%, n = 10/61 for both). Ten (9.01%) patients were taken back to theatres and there were no deaths within 30 days following surgery. All postoperative outcomes for EOCRC patients are demonstrated in Table 2.

CRS/HIPEC and PE-specific outcomes

Of the 13 patients that had a PE, ten (76.92%) had an R0 resection and three had an R1 resection (23.08%). No patients had an R2 resection. Out of the 17 patients who underwent CRS and HIPEC, mitomycin was used as the HIPEC agent in 12 patients (70.59%) and oxaliplatin in five (29.41%). The mean PCI was 10.00 ± 4.66 and most patients (88.24%, n = 15/17) had a CC-1 score followed by CC-0 (11.76%, n = 2/17,). No patients had a CC score of two or three.

Table 2. Surgical outcomes of EOCRC patients

Variables	**Frequencies (n (%) or mean ± SD**		
Type of Surgery	**All (n=111)**	**Other colorectal resections (n=80)**	**CRS and HIPEC or PE (n=31)**
Emergency surgery	n=29/111 (26.13%)	n=17/80 (21.25%)	n=12/31 (n=38.71%)
Stoma	n=56/111 (50.54%)	n=38/80 (47.50%)	n=18/31 (58.06%)
ICU admission	n=45/111 (40.54%)	n=14/80 (17.50%)	n=31/31 (100.00%)
ICU length of stay (days)	5.80 ± 11.60	4.50 ± 4.20	6.30 ± 13.60
TPN	n=34/111 (30.63%)	n=5/80 (6.25%)	n=29/31 (93.55%)
Time on TPN (days)	16.10 ± 23.20	15.00 ± 13.50	16.30 ± 24.60
Time to pass flatus (days)	4.80 ± 2.80	3.60 ± 1.50	6.10 ± 3.40
Time to first bowel motion (days)	5.20 ± 3.10	4.20 ± 1.80	6.40 ± 3.90
Length of hospital stay (days)	15.90 ± 18.40	11.40 ± 9.60	27.10 ± 28.30
Complications	n=61/111 (54.95%)	n=37/80 (46.25%)	n=24/31 (77.42%)
Clavien-Dindo grades			
I	n=10/61 (16.39%)	n=7/37 (18.92%)	n=3/24 (12.50%)
II	n=29/61 (47.54%)	n=17/37 (45.95%)	n=12/24 (50.00%)
III	n=12/61 (19.67%)	n=6/37 (16.22%)	n=6/24 (25.00%)
IV	n=10/61 (16.39%)	n=7/37 (18.92%)	n=3/24 (12.50%)
Wound complications	n=12/111 (10.81%)	n=8/80 (10.00%)	n=4/31 (12.90%)
Abdominal collection	n=20/111 (18.02%)	n=8/80 (10.00%)	n=12/31 (38.71%)
Return to theatre < 30 days	n=10/111 (9.01%)	n=6/80 (7.50%)	n=4/31 (12.90%)
Death < 30 days	n=0/111 (0.00%)	n=0/80 (0.00%)	n=0/31 (0.00%)

3.3.4 Survival

For survival analysis, the singular patient who underwent PE and CRS and HIPEC was excluded. The median follow-up time was 21.00 months (IQR: 8.00-36.50). Disease recurrence occurred in 38.74% of the patients (n = 43/111) and their median DFS was 13.90 (IQR: 7.20 - 29.30) months. Absolute survival rates at 1-, 3- and 5-year time intervals were 93.69%, 87.39% and 86.48%, respectively. After adjusting for stage, an adverse DFS and OS were demonstrated for PE followed by CRS and HIPEC then other colorectal resections for patients with stage IV disease ($p < 0.001$ and $p = 0.003$, respectively) (Figure 2). DFS was significantly poorer in those aged < 30 followed by 30-39 and 40-49 with stage II disease ($p < 0.001$). However, it is important to note that only one patient < 30 years old had stage II disease. For all other matched stages, age, type of surgery and tumour location had equivocal DFS and OS.

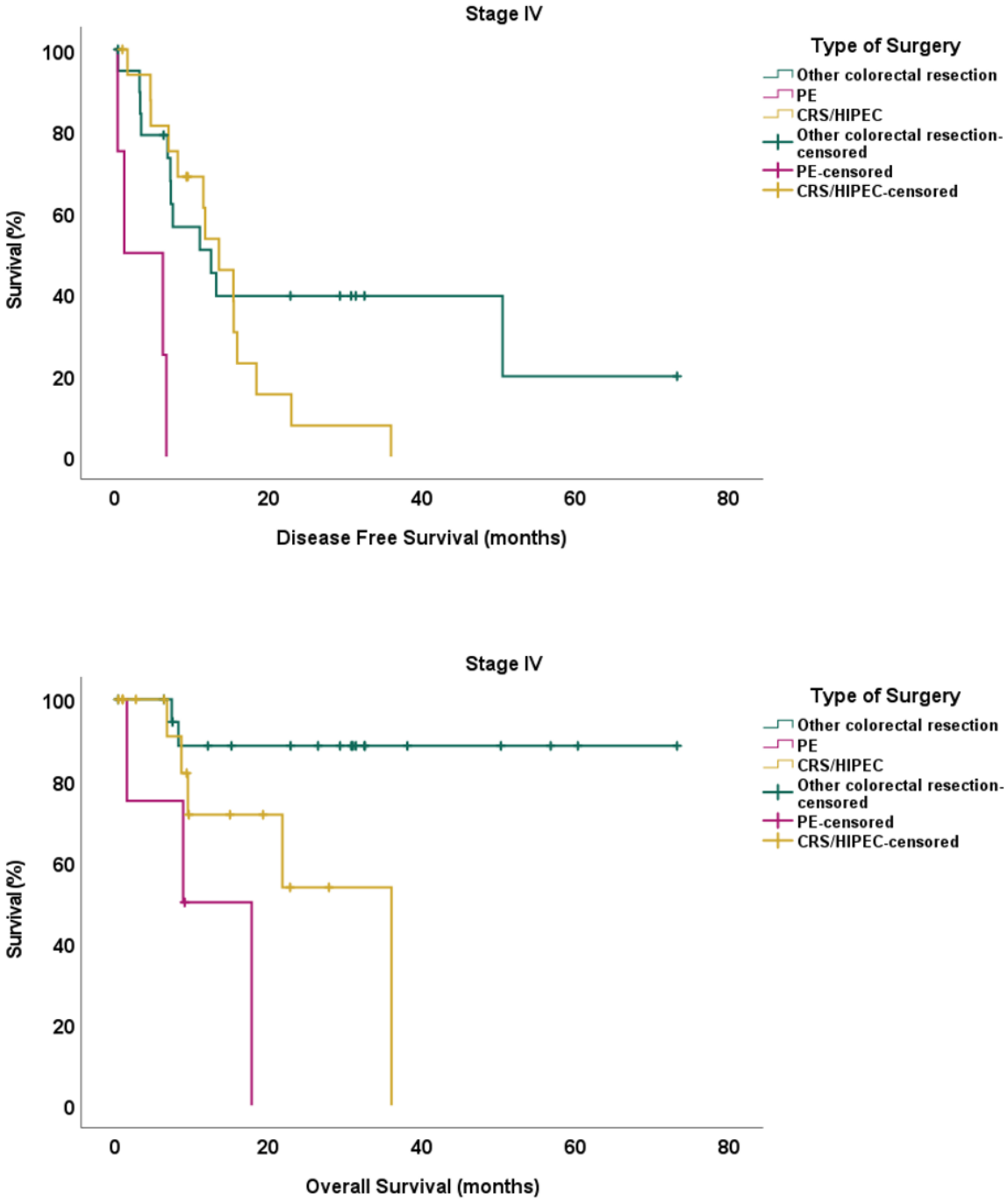


Figure 2. DFS and OS for stage IV EOCRC patients based on type of surgery

3.4 Discussion

This study is the first of its kind to examine the surgical treatment patterns and outcomes of an Australian EOCRC cohort that included a subset of patients who had undergone PE and CRS and HIPEC. Overall, we demonstrated that left-sided and advanced disease at the time of presentation was common. A substantial proportion of our EOCRC patients underwent either PE or CRS and HIPEC and had a stoma fashioned. Although they had complicated postoperative courses, the majority were minor. Whilst PE and CRS and HIPEC were associated with poorer stage-matched DFS and OS in comparison to other colorectal resections, the overall 5-year absolute survival in this cohort was good (86.48%).

In keeping with previous literature, the majority of our EOCRC cohort had stage IV disease at the time of presentation (37.84%) and left-sided disease was more common (76.58%) (1, 5-8). Subsequently, almost one-third of our EOCRC patients underwent either PE, CRS and HIPEC or both for their primary operation. This trend towards more aggressive surgical approaches in EOCRC patients has also been demonstrated in a large Chinese cohort. Gao et al. (9), through their comparison of 6,369 EOCRC and 27,698 LOCRC patients, found that EOCRC patients were more likely to undergo an extended radical resection (12.6% vs 10.2%, $p < 0.001$). Unfortunately, their paper did not define extended radical resections and thus, it is unclear if they were referring to PE and CRS and HIPEC. In our study, for those patients who did not undergo PE or CRS and HIPEC, the most common operation types were variations of left colonic resections.

Only three other studies have investigated the short-term surgical outcomes of EOCRC patients. Two large-scale studies utilised the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) dataset to compare early- and late-onset colon and

rectal cancer and found that younger patients had lower complication rates (18% vs. 22%, p = 0.02 and 25% vs. 29%, p = 0.02) (10, 11). By comparison, Avellaneda et al. (1), in their Argentinian cohort of 34 EOCRC and 175 LOCRC patients, demonstrated a higher reoperation rate (18.75% vs. 7.43%, p = 0.04) and complication rate in their younger patients (43.75% vs. 28%, p = 0.07) of which 64.29% were graded III and IV Clavien-Dindo complications. Interestingly, EOCRC patients in our study had a higher complication rate (54.95%) but lower rates of major complications (36.06%) and return to theatres (9.01%). This high complication rate is contributed to, at large, by the cohort undergoing either PE or CRS and HIPEC with 77.42% experiencing complications. The fact RPAH is a quaternary referral service for PE and CRS and HIPEC may explain the fewer major complications and takebacks to theatres. Unfortunately, data on postoperative complication type, return to normal gut function and nutrition, ICU admission and length-of-stay were not reported in these EOCRC surgical outcomes studies.

Whilst the wound complication rate in this EOCRC cohort is equivalent to those reported for LOCRC (10.81% vs 12.6%), the rate of abdominal collections (18.02% vs 9.9%) and time to first flatus (4.80 vs 2.3-3.8) and bowel motion (5.20 vs 3.4-4.9) were increased (12, 13). These results are again contributed to by the cohort undergoing PE and CRS and HIPEC where 38.71% of patients had abdominal collections and the mean time to pass first flatus and stool was 6.10 and 6.40 days, respectively. Postoperative abdominal collections have been associated with prior radiation and are a common complication following CRS and HIPEC with heat injury, the shrinking effect of HIPEC on infiltrating tumour nodules located on the intestinal wall and the suctioning of the outflow catheter as proposed mechanisms (12, 14). Postoperative ileus has been linked with stoma formation and in this study, nearly 60% of PE and CRS and HIPEC patients had a stoma fashioned (15). Although this rate is high, it is secondary to

patients who required faecal diversion following pelvic anastomoses post-HIPEC and patients who underwent PE (16). Surprisingly, the rate of stoma formation in patients undergoing other colorectal resections was close to 50% which can be explained by the high proportion of patients in this group who underwent an emergency operation (21.25%). Other studies have also demonstrated comparatively higher rates of emergency resections in their EOCRC versus LOCRC cohorts (11.3-15.63% vs 6.86-7.8%) (10, 11). The large percentage of patients requiring ICU admission and TPN is secondary to the standardised postoperative management of patients undergoing PE and CRS and HIPEC at RPAH.

PE followed by CRS and HIPEC then other colorectal resections had significantly poorer DFS and OS in EOCRC patients with stage IV disease only. This result is not surprising and is explained by the relatively smaller disease burden of non-PE and CRS and HIPEC patients and the enhanced cytotoxicity from direct exposure to heated chemotherapy in the CRS and HIPEC group which has been shown to confer a survival benefit (17, 18). Interestingly, despite this finding and the fact that nearly one-third of our cohort underwent either PE or CRS and HIPEC, the absolute five-year survival rate was 85.5%. This highlights that in appropriately selected EOCRC patients who have been referred to a quaternary hospital specialising in PE and CRS and HIPEC, these can be performed with acceptable survival with the trade-off of high rates of stoma formation and minor postoperative complications. To assess the impact of this on the quality of life of EOCRC patients, our centre has conducted a cross-sectional analysis utilising the SF-36v2. The results of this analysis will be detailed in Chapter 4.

3.4.1 Limitations

Firstly, this study utilised data from a single quaternary referral centre for CRC patients in Australia and thus, referral bias, particularly for advanced cancers may have skewed the results

of this study, limiting its generalisability. Secondly, due to the retrospective nature of this study, there is an inherent risk of selection bias. Thirdly, although EOCRC incidence is increasing, the number of EOCRC patients relative to LOCRC patients is still small. This limited the study size of our cohort and decreased the statistical power of our study. Fourthly, due to the high proportion of patients referred to RPAH, a significant amount of EOCRC patients' molecular and oncological data were not captured in the electronic databases interrogated for this study. Lastly, no comparison to LOCRC patients was made in this study, limiting the ability to determine if any significant differences in surgical outcomes and survival exist between EOCRC and LOCRC patients.

3.5 Conclusion

This study is the first of its kind to describe the surgical and survival outcomes of EOCRC patients treated at an Australian centre which is also a quaternary referral centre for PE and CRS and HIPEC. The majority of EOCRC patients had left-sided and stage IV disease at the time of presentation. PE and CRS and HIPEC were performed in nearly one-third of the cohort and the rate of stoma formation was high. Postoperative complications were common; however, the majority were minor. The absolute five-year survival rate was 85.5% and PE and CRS and HIPEC conferred poorer DFS and OS in comparison to other colorectal resections in stage IV patients. Future research evaluating the impact of this on the functional outcomes and quality of life of EOCRC is necessitated.

3.6 References

1. Luis Avellaneda N, Lasa J, Veracierto F, Hernandez A, Santillan M, Olivera Sendra P, et al. Early-Onset Colorectal Cancer in Younger Patients with a More

Advanced Stage and Worse Postoperative Results: A Retrospective Review. Turkish Journal of Colorectal Disease. 2021;31(3).

2. O'Sullivan DE, Cheung WY, Boyne DJ, Jarada TN, Tang PA, Gill S, et al. Treatment patterns and survival outcomes of early-onset colorectal cancer patients in Alberta, Canada: a population-based study. Cancer Treatment and Research Communications. 2022;32:100585.
3. Ganapathi SK, Subbiah R, Rudramurthy S, Kakkilaya H, Ramakrishnan P, Chinnusamy P. Laparoscopic anterior resection: Analysis of technique over 1000 cases. J Minim Access Surg. 2021;17(3):356-62.
4. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo Classification of Surgical Complications: Five-Year Experience. Annals of Surgery. 2009;250(2).
5. Park KS, Hong YK, Choi YJ, Kang JG. Clinicopathologic characteristics of early-onset colorectal cancer. Ann Coloproctol. 2022.
6. Habib R, Burgess NG, Bourke MJ, Wong M, Wilcken N, Toh J, et al. Outcomes of young patients diagnosed with locally advanced rectal cancer. J Gastrointest Oncol. 2021;12(2):592-601.
7. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A, et al. Colorectal cancer statistics, 2017. CA Cancer J Clin. 2017;67(3):177-93.
8. Siu DHW, Ali A, Tjokrowidjaja A, De Silva M, Lee J, Clingan PR, et al. Clinical and molecular profile of young adults with early-onset colorectal cancer: Experience from four Australian tertiary centers. Asia Pac J Clin Oncol. 2022.
9. Gao XH, Li J, Liu LJ, Zheng NX, Zheng K, Mei Z, et al. Trends, clinicopathological features, surgical treatment patterns and prognoses of early-onset versus late-onset colorectal cancer: A retrospective cohort study on 34067

patients managed from 2000 to 2021 in a Chinese tertiary center. Int J Surg. 2022;104:106780.

10. Ewongwo A, Hamidi M, Alattar Z, Ayotunde OP, Tiwari HA, Elquza E, et al. Contributing factors and short-term surgical outcomes of patients with early-onset rectal cancer. Am J Surg. 2020;219(4):578-82.

11. Hanna K, Zeeshan M, Hamidi M, Pandit V, Omesiete P, Cruz A, et al. Colon cancer in the young: contributing factors and short-term surgical outcomes. Int J Colorectal Dis. 2019;34(11):1879-85.

12. Ho VP, Stein SL, Trencheva K, Barie PS, Milsom JW, Lee SW, et al. Differing risk factors for incisional and organ/space surgical site infections following abdominal colorectal surgery. Dis Colon Rectum. 2011;54(7):818-25.

13. Chen K, Zhang Z, Zuo Y, Ren S. Comparison of the clinical outcomes of laparoscopic-assisted versus open surgery for colorectal cancer. Oncol Lett. 2014;7(4):1213-8.

14. Baratti D, Kusamura S, Laterza B, Balestra MR, Deraco M. Early and long-term postoperative management following cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. World J Gastrointest Oncol. 2010;2(1):36-43.

15. Chapuis PH, Bokey L, Keshava A, Rickard MJ, Stewart P, Young CJ, et al. Risk factors for prolonged ileus after resection of colorectal cancer: an observational study of 2400 consecutive patients. Ann Surg. 2013;257(5):909-15.

16. Whealon MD, Gahagan JV, Sujatha-Bhaskar S, O'Leary MP, Selleck M, Dumitra S, et al. Is Fecal Diversion Needed in Pelvic Anastomoses During Hyperthermic Intraperitoneal Chemotherapy (HIPEC)? Ann Surg Oncol. 2017;24(8):2122-8.

17. González-Moreno S, González-Bayón LA, Ortega-Pérez G. Hyperthermic intraperitoneal chemotherapy: rationale and technique. World journal of gastrointestinal oncology. 2010;2(2):68.

18. Klaver CE, Musters GD, Bemelman WA, Punt CJ, Verwaal VJ, Dijkgraaf MG, et al. Adjuvant hyperthermic intraperitoneal chemotherapy (HIPEC) in patients with colon cancer at high risk of peritoneal carcinomatosis; the COLOPEC randomized multicentre trial. BMC Cancer. 2015;15:428.

Chapter 4: The health-related quality of life of early-onset colorectal cancer patients: an Australian cross-sectional study

4.1 Introduction

EOCRC patients are a unique cohort that is theoretically more likely to place significant value on returning to or improving upon their preoperative HRQoL following surgery due to their need to return to paid work, their studies, or their familial roles. In Chapter 3, we showed that a high proportion of EOCRC patients presented with advanced disease, underwent either PE or CRS and HIPEC, had their surgery performed in an emergency setting with high rates of stoma formation and experienced significant rates of minor postoperative complications (1-5). Whilst these findings have been corroborated by other EOCRC studies, minimal qualitative and quantitative research exists that evaluates the impact of this on the postoperative HRQoL of EOCRC patients. Generally, these studies have demonstrated lower HRQoL of EOCRC patients relative to LOCRC patients with significantly poorer physical, psychosocial, and financial well-being (6-10). However, a recent systematic review of these studies found significant heterogeneity in quantitative HRQoL scoring tools and a lack of comparison to population norms (11). Current HRQoL EOCRC research is also limited by a lack of evaluation of patients undergoing PE or CRS and HIPEC.

Therefore, this study is the first of its kind to quantitatively evaluate the postoperative HRQoL of an Australian cohort of EOCRC patients referred to a highly specialised centre utilising norm-based summary scores from SF-36v2. A secondary aim of this study will be to identify the determinants of EOCRC patients' HRQoL.

4.2 Methods

This study was conducted in agreement with the Declaration of Helsinki. Ethics approval and Governance Authorisation were obtained from the Sydney Local Health District Human Research Ethics Committee (ethics approval identification X21-0214 and 2021/ETH00976).

4.2.1 Study Design, Setting and Participants

A cross-sectional study was performed on EOCRC patients who were treated in the Colorectal Surgical Unit at the RPAH, Sydney, Australia. This study's methodology adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines on reporting cross-sectional studies (12). Patients were included if they had: histopathologically diagnosed colorectal adenocarcinoma prior to the age of 50 and were surgically treated for their CRC between January 2013 and December 2021 (inclusive) at RPAH (regardless of primary or subsequent resection). Patients were excluded if no data from their primary operation was available, they did not consent to participate or had passed away. Further, for ethical purposes, patients who were in the terminal phase were also excluded.

4.2.2 Variables, Data Sources and Measurement

The SF-36v2 is a tool that quantitatively evaluates HRQoL. It is comprised of 36 questions that target eight domains of health (physical functioning, role physical, bodily pain, general health, vitality, social functioning, role emotional and mental health). Overall physical and mental HRQoL can be derived from these scores as reflected by the physical component summary (PCS) and mental component summary (MCS) scores. Further, norm-based scores were used to represent the data for EOCRC patients in this study and these were compared to the norm-based scores of the general Australian population. Scores that fell within plus or minus three of the population mean of 50 were normal. Therefore, scores below 47 or above 53 reflected

poorer or better than average health status. The SF-36v2 is a well-validated HRQoL assessment of general and scientific populations that compares the relative burden of disease and differentiates the health benefits of a variety of different treatments (13). It has also been validated as a metric of postoperative recovery in colorectal patients (14).

For patients who underwent PE or CRS and HIPEC, SF-36v2 surveys are performed routinely pre- and postoperatively at 6-monthly intervals up to three years, then at 12-monthly intervals up to five years as part of the PESQI and PREMIER databases at RPAH. The PESQI and PREMIER databases are prospectively maintained databases on PE and CRS and HIPEC patients at RPAH (15, 16). For these patients in our cohort, the most recent SF-36v2 (relative to this study's data collection end date) was used. For patients who underwent other colorectal resections, SF-36v2 surveys were posted to patients in November 2022. Follow-up phone calls were made to patients who had not returned the survey one and two months following the initial postage. The end date for data collection was March 2023.

Data was collected from a combination of the PESQI and PREMIER databases and patients' electronic and paper medical records. Data collected included patient demographics, the time interval from initial surgery and surgical outcomes data such as surgery type, duration of surgery (hours), emergency operation, ostomy formation, ICU admission, TPN requirement, hospital length of stay (days) and in-hospital complications. Data collection was complete for all variables.

4.2.3 Bias, Quantitative Variables and Statistical Methods

The cross-sectional design of this study was chosen to reduce the confounding effect of time and disease progression on HRQoL scores. Specifically, our cohort was divided into those ≤ 2

years from their index surgery and those who were > 2 years. A cut-off of two years was chosen as studies have demonstrated that over 50% of CRC patients recur within this time frame (17). Optum software was used to transform SF-36v2 question answers into norm-based PCS and MCS scores. Statistical analyses were performed using IBM SPSS Statistics Version 26. Utilising the Shapiro-Wilk test, data was determined to be non-parametric. Continuous data were presented as medians (interquartile range (IQR)) and categorical data were presented as frequencies (%). The Mann-Whitney U test and Kruskal-Wallis one-way analysis of variance were used to assess if a significant relationship existed between variables and PCS and MCS scores.

4.3 Results

4.3.1 Participants

A total of 156 patients met the inclusion criteria for this study. After accounting for those who did not have complete data on their primary operation or were terminal or dead, 93 patients remained. Of the 21 (n = 21/93, 22.6%) patients who had undergone PE or CRS and HIPEC, 16 (n = 16/93, 17.2%) consented to have their SF-36v2 surveys stored in PESQI and PREMIER databases. Of the 72 (n = 72/93, 77.4%) patients who underwent other colorectal resections, 34 (n = 34/93, 36.6%) consented and returned their SF-36v2 surveys. In total, 50 (n = 50/93, 53.8%) patients were included for analysis in this study (Figure 1).

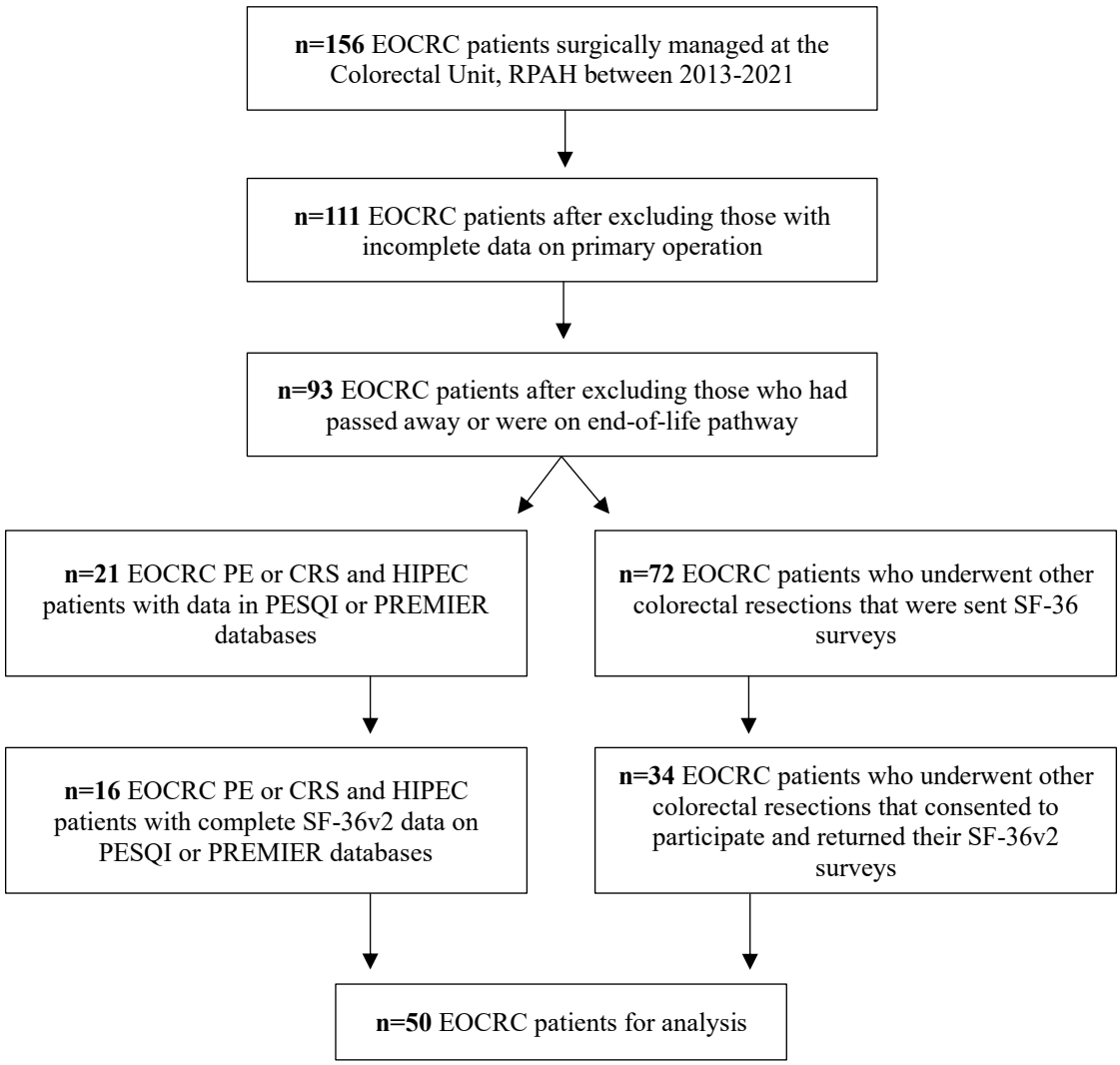


Figure 1. Flowchart demonstrating final study numbers after exclusion criteria were applied

4.3.2 Demographic and surgical outcomes

Overall, the median age of patients was 40.0 (36.8-45.0) years. Most patients had stage IV disease at the time of diagnosis (n = 16, 32.0%), followed by stages II (n = 13, 26.0%), III (n = 11, 22.0%) then I (n = 10, 20.0%). Left-sided disease occurred in 39 patients (78.0%), whilst right-sided disease occurred in 10 (20.0%). Of the 16 patients that underwent PE or CRS and HIPEC, six (12.0%) underwent PE and ten (20.9%) underwent CRS and HIPEC. Other

colorectal resections were performed in 34 patients (68.0%). Emergency surgery was performed in 12 patients (24.0%), a stoma was fashioned in nearly half of the cohort (n = 20, 40.0%) and 19 patients (38.0%) experienced postoperative complications. Whilst 19 patients (38.0%) were ≤ 2 years from their index colorectal surgery, 31 patients (62.0%) were > 2 years. Table 1 demonstrates demographic and surgical variables based on the time interval from surgery using the cut-off of two years. In the ≤ 2 vs > 2-years groups, there were smaller proportions of rectal tumours (15.8% vs 54.8%) and no PEs performed (0% vs 19.4%). Otherwise, all other variables remained similar. The median follow-up time for patients was 24.0 months (range, 1.0-95.0 months).

4.3.3 PCS and MCS scores relative to the Australian population

For patients ≤ 2 years from the initial surgery, the median PCS and MCS scores were 53.3 (IQR: 36.4-58.9) and 47.3 (IQR: 37.5-55.7), respectively. For those > 2 years from index procedure, the median PCS and MCS scores were 50.6 (IQR: 43.3-57.7) and 50.2 (IQR: 39.04-56.2), respectively. EOCRC patients ≤ 2 years from index surgery had PCS scores that were higher than the norm-based range (47-53) and the Australian population PCS score. The PCS score for EOCRC patients > 2 years from index surgery was within the norm-based range and was similar to the Australian population PCS score. EOCRC patients ≤ 2 and > 2 years from index surgery had MCS scores that were within the norm-based range but were slightly lower than the Australian population MCS score (Table 2).

Table 1. Demographic and surgical variables of patients ≤ 2 and > 2 years from index surgery

	Frequency n (%)		
Variables	**Overall (n=50)**	**≤ 2 years (n=19)**	**> 2 years (n=31)**
Sex (male)	n=13 (26.0)	n=6 (31.6)	n=7 (22.6)
Tumour location			
Caecum to transverse colon	n=11 (22.0)	n=8 (42.1)	n=3 (9.7)
Splenic flexure to sigmoid colon	n=19 (38.0)	n=8 (42.1)	n=11 (35.5)
Rectum	n=20 (40.0)	n=3 (15.8)	n=17 (54.8)
Tumour stage			
I	n=10 (20.0)	n=3 (15.8)	n=7 (22.6)
II	n=13 (26.0)	n=5 (26.3)	n=8 (25.8)
III	n=11 (22.0)	n=4 (21.1)	n=7 (22.6)
IV	n=16 (32.0)	n=7 (36.8)	n=9 (29.0)
Chemotherapy or radiotherapy	n=41 (82.0)	n=15 (78.9)	n=26 (83.9)
Type of surgery			
PE or CRS and HIPEC			
PE	n=6 (12.0)	n=0 (0.0)	n=6 (19.4)
CRS and HIPEC	n=10 (20.0)	n=6 (31.6)	n=4 (12.9)
Other colorectal resection	n=34 (68.0)	n=13 (68.4)	n=21 (67.7)
Emergency operation	n=12 (24.0)	n=6 (31.6)	n=6 (19.4)
Length of surgery			
≤ 4 hours	n=27 (54.0)	n=12 (63.2)	n=15 (48.4)
> 4 hours	n=23 (46.0)	n=7 (36.8)	n=16 (51.6)
Length of hospital stay (days)			
≤ 5 days	n=18 (36.0)	n=5 (26.3)	n=13 (41.9)
> 5 days	n=32 (64.0)	n=14 (73.7)	n=18 (58.1)
Stoma formation	n=20 (40.0)	n=6 (31.6)	n=14 (45.2)
ICU admission	n=17 (34.0)	n=6 (31.6)	n=11 (35.5)
TPN	n=16 (32.0)	n=6 (31.6)	n=10 (32.3)
Complications	n=19 (38.0)	n=6 (31.6)	n=13 (41.9)

Table 2. PCS and MCS scores for patients ≤ 2 and > 2 years from index surgery compared with Australian population norms

Subscale	Overall[a]	≤ 2 years[a]	> 2 years[a]	Australian population[b]
Physical component summary	52.0 (42.6-58.7)	53.3 (36.4-58.9)	50.6 (43.3-57.7)	50.3 (9.7)
Mental component summary	48.8 (39.0-55.8)	47.3 (37.5-55.7)	50.2 (39.0-56.2)	52.9 (10.2)

[a]values are median (IQR) due to the non-normal distribution of this study's data

[b]values are mean (SD) as presented by Austin et al. (18)

4.3.4 Variables that impacted PCS and MCS scores between groups

Tables 3 and 4 demonstrate the association between variables and PCS and MCS scores in EOCRC patients ≤ 2 and > 2 years from index surgery, respectively. Stage was significantly associated with PCS scores in patients ≤ 2 years but not > 2 years from surgery (p = 0.02). Specifically, having stage I disease at the time of presentation detrimentally impacted PCS scores in comparison to those with stage II disease (31.9 vs 58.9, p = 0.04). All other comparisons between stages were insignificant. Having had their primary operation within an emergency setting was associated with poorer PCS scores in patients ≤ 2 years from surgery (36.1 vs 56.3, p = 0.007*)* but superior MCS scores in those > 2 years from surgery (56.6 vs 44.2, p = 0.02). No other variables significantly impacted PCS or MCS scores in EOCRC patients ≤ 2 and > 2 years from index surgery.

Table 3. Association between variables and PCS and MCS scores in EOCRC patients ≤ 2 years from index surgery

	PCS		MCS	
Variables	**Median (IQR)**	**P-value**	**Median (IQR)**	**P-value**
Gender		0.52		0.90
Male	54.0 (44.20-60.5)		49.2 (39.6-56.0)	
Female	53.3 (34.2-59.1)		47.3 (36.1-55.9)	
Tumour location		0.39		0.34
Caecum to transverse colon	54.0 (32.9-60.9)		52.0 (41.9-56.5)	
Splenic flexure to sigmoid colon	45.7 (36.6-55.2)		41.1 (33.8-55.3)	
Rectum	58.8[a]		47.3[a]	
Stage		**0.02**		0.20
I	31.9[a]		33.5[a]	
II	58.9 (57.0-62.3)		47.3 (35.9-56.5)	
III	55.5 (48.2-60.9)		45.5 (41.5-51.8)	
IV	37.1 (35.8-55.2)		55.1 (40.4-57.0)	
Type of surgery		0.07		0.34
PE or CRS and HIPEC				
PE	-		-	
CRS and HIPEC	36.7 (34.4-54.0)		54.5 (39.7-56.8)	
Other colorectal resection	55.2 (45.7-59.5)		46.3 (35.9-54.7)	
Emergency operation		**0.007**		0.90
Yes	36.1 (31.5-46.6)		52.2 (38.7-55.5)	
No	56.3 (49.3-59.5)		46.3 (37.3-56.4)	
Stoma		0.96		0.73
Yes	55.8 (36.9-59.0)		43.9 (36.8-54.7)	
No	51.6 (31.0-59.6)		50.5 (37.1-55.7)	
Length of surgery		0.10		0.77
≤ 4 hours	57.0 (45.0-59.5)		46.8 (37.9-55.2)	
> 4 hours	37.1[a]		53.9[a]	
ICU admission		0.07		0.37
Yes	36.7 (34.4-54.0)		54.5 (39.7-56.8)	
No	55.2 (45.7-59.5)		46.3 (35.9-54.7)	
Postoperative TPN		0.07		0.37
Yes	36.7 (34.4-54.0)		54.5 (39.7-56.8)	
No	55.2 (45.7-59.5)		46.3 (35.9-54.7)	
Complications		0.15		0.75
Yes	36.7 (34.4-54.8)		47.2 (39.7-55.5)	
No	55.2 (45.1-59.4)		46.8 (35.3-55.2)	
Length of hospital stay		0.44		0.07
≤ 5 days	58.8 (39.3-62.3)		40.5 (34.9-46.0)	
> 5 days	52.5 (36.3-57.0)		53.7 (39.7-56.8)	

[a]Sample size too small for IQR

Table 4. Association between variables and PCS and MCS scores in EOCRC patients > 2 years from index surgery

	PCS		MCS	
Variables	**Median (IQR)**	**P-value**	**Median (IQR)**	**P-value**
Gender		0.13		0.34
Male	45.5 (41.1-53.1)		43.0 (36.9-51.7)	
Female	51.8 (43.5-58.7)		51.6 (40.0-56.3)	
Tumour location		0.35		0.49
Caecum to transverse colon	47.9[a]		43.0[a]	
Splenic flexure to sigmoid colon	55.1 (43.3-59.6)		55.0 (46.4-56.4)	
Rectum	50.6 (42.1-56.4)		44.2 (39.0-54.9)	
Stage		0.12		0.34
I	58.7 (50.6-59.6)		56.2 (43.0-56.5)	
II	43.5 (41.2-57.3)		45.3 (37.5-49.8)	
III	53.0 (44.5-55.1)		52.5 (39.1-55.6)	
IV	47.0 (41.1-52.8)		43.0 (35.8-56.7)	
Type of surgery		0.10		0.19
PE or CRS and HIPEC				
PE	43.2 (39.4-47.5)		39.0 (31.6-53.1)	
CRS and HIPEC	45.1 (34.5-58.6)		56.7 (38.7-59.6)	
Other colorectal resection	53.1 (46.2-58.2)		50.2 (43.0-55.9)	
Emergency operation		0.61		**0.02**
Yes	53.6 (47.2-56.5)		56.6 (51.0-58.4)	
No	47.9 (43.2-58.2)		44.2 (38.0-55.4)	
Stoma		0.55		0.59
Yes	52.7 (41.3-57.0)		50.5 (39.1-57.6)	
No	52.2 (45.0-58.1)		46.6 (41.5-55.8)	
Length of surgery		0.12		0.77
≤ 4 hours	53.1 (47.0-60.5)		46.8 (39.1-55.6)	
> 4 hours	44.6 (41.2-57.5)		50.5 (38.9-57.4)	
ICU admission		0.28		0.61
Yes	43.4 (44.4-57.0)		46.4 (33.0-57.7)	
No	53.1 (41.1-58.7)		50.2 (43.0-56.0)	
Postoperative TPN		0.15		0.83
Yes	43.2 (39.1-58.7)		53.2 (32.8-58.3)	
No	54.2 (44.6-58.6)		46.4 (43.0-54.1)	
Complications		0.23		1.00
Yes	45.5 (41.1-56.4)		50.2 (35.0-57.1)	
No	54.1 (43.4-58.4)		45.5 (40.1-54.8)	
Length of hospital stay		0.49		0.74
≤ 5 days	50.6 (44.4-58.4)		46.8 (38.0-56.0)	
> 5 days	50.8 (41.3-56.9)		50.5 (39.1-56.8)	

[a]Sample size too small for IQR

4.4 Discussion

This is the first Australian study to evaluate the HRQoL of EOCRC patients including a subset of patients who underwent PE and CRS and HIPEC and to utilise norm-based scores to enable a comparison with the Australian population.

For all time intervals from surgery, EOCRC patients' PCS and MCS scores remained within the norm-based range. Thus, we found that EOCRC patients' HRQoL was comparable to that of the Australian population. In previous studies, average-onset CRC patients' QoL has been found to be equivalent to German and Finnish population norms (19, 20). However, surgical outcomes studies have demonstrated that EOCRC patients are more likely to undergo extended radical resections with higher rates of complications (2, 21). The impact of this on the QoL of EOCRC patients remains a grey area in the current literature and, to our knowledge, only one other study has compared the HRQoL of younger CRC patients to the general population. Arndt et al. (22) found that CRC patients aged 60 years or under had lower mean scores across all health domains relative to German population controls one year following surgery. The difference in their findings is likely explained by their inclusion of patients who were within a shorter postoperative time frame. Thus, the findings of our study demonstrate the resilience of EOCRC patients and suggest that the "longer-term" HRQoL of EOCRC patients is not hindered by an aggressive surgical approach and that postoperative morbidity does not necessarily translate into poorer physical or mental functioning.

When compared to the Australian population PCS score, EOCRC patients' PCS scores trended slightly higher in the ≤ 2-year group (53.3 vs 50.3) but were similar in the > 2-year group (50.6 vs 50.3). EOCRC patients often present with advanced disease, and this was true for our study where 32.0% of patients had stage IV disease at the time of diagnosis (2, 23). EOCRC patients

also experience delays in diagnosis with their symptoms being attributed to more benign common conditions (24-26). Thus, the transiently superior PCS score of EOCRC patients in comparison to the Australian population could reflect the perceived improvement of their physical functioning relative to their extensive preoperative disease burden and symptom duration.

EOCRC patients in both groups had lower MCS scores in comparison to the Australian population's MCS score. This is not surprising as EOCRC patients have reported significant impacts on the financial and emotional aspects of their QoL in previous qualitative research. Specifically, EOCRC patients have expressed concerns regarding their financial income, work performance, and career trajectory and have reported a lack of social support networks, prolonged time away from family and significant relationship strains (27). Further, this finding could be explained by Calman's (28) "gap" hypothesis; whereby EOCRC patients report poorer QoL due to the "gap" between their previous expectations and aspirations as a healthy individual and their new lived reality.

In the ≤ 2-year group, having stage II disease was associated with better PCS scores than EOCRC patients with stage I disease at the time of presentation. All other comparisons between stages for the ≤ 2-year and > 2-year groups were insignificant. Ramsey et al. (29) conducted a longitudinal prospective HRQoL analysis using the FACT-C survey on 173 CRC patients over five years. They found that for stage I disease, whilst average HRQoL scores were initially low, they began to increase steadily around the two-year mark. For stage II and III disease, average HRQoL scores declined over the first two years but then increased. For stage IV disease, HRQoL scores declined and then plateaued at the two-year mark. Although the cross-sectional nature of our study prohibited an assessment of temporal changes in HRQoL, our findings are

similar to Ramsey et al. (29). The impact of stage on the HRQoL of EOCRC patients is likely dynamic and most prominent in the first two years following treatment as EOCRC patients re-conceptualise their QoL (30).

Having had an emergency index operation was significantly associated with poorer PCS scores in patients in the ≤ 2-year group. Emergency resections in the setting of CRC are performed when bowel obstruction, perforation or significant bleeding occurs (31). Although there is a scarcity of literature evaluating the correlation between emergency colorectal resections and postoperative QoL, Seeto et al. (32) demonstrated that emergency colorectal resections were associated with increased minor, but not major, complications and end stoma formation rates. Interestingly, complications and ostomy formation did not impact PCS or MCS scores in either ≤ 2 or > 2-year groups in our study. This suggests that other factors may contribute to the temporary correlation between emergency surgery and poorer physical functioning such as exacerbation of pre-existing conditions and lack of prehabilitation, particularly for those undergoing either PE or CRS and HIPEC (32, 33). MCS scores were better in patients in the > 2-year group who had an emergent, rather than elective, index surgery. This was an unexpected finding that may reflect small sample bias and thus warrants further investigation with larger cohorts.

Our findings should be interpreted with some caution as this study had a small cohort limiting its statistical power. This is likely derived from multiple factors including the non-digital method of survey delivery, the length of the SF-36v2 survey itself and the fact that younger patients are more likely to be time-poor. This study was also limited by its cross-sectional study design making it subject to participation and response bias and prohibiting an assessment of a temporal association between EOCRC and HRQoL. The SF-36v2 survey was utilised due to

its ability to calculate normative scores and the fact SF-36v2 surveys were already collected as part of the prospectively maintained PESQI and PREMIER databases. However, the SF-36v2 survey does not include CRC-specific questions that focus on functional outcomes such as bowel and urinary continence and sexual dysfunction. In the < 2-year group, PE patients either did not meet inclusion criteria or did not consent to have their HRQoL data collected. Therefore, no PE patients were included in this group which limited the analysis of surgery type and HRQoL. Lastly, no comparison to LOCRC was made.

4.5 Conclusion

Despite the encouraging results of this study, it is important to note that because of its limitations, strong conclusions could not be made. This study suggested that the HRQoL of EOCRC patients was equivocal to the Australian population. Having an earlier stage at diagnosis and emergency index operation was associated with poorer levels of physical functioning in patients ≤ 2 years from surgery. No other demographic or surgical variables significantly impacted physical or mental functioning in EOCRC patients ≤ 2 years or > 2 years from surgery. These findings require validation in future large-scale prospective studies that compare the temporal HRQoL and functional outcomes of EOCRC patients to LOCRC patients.

4.6 References

1. Franklyn J, Lomax J, Labib PLZ, Baker A, Balasubramanya S, Natale J, et al. Young-onset colorectal cancer: Insights from an English population-based study. Colorectal Dis. 2022.

2. Gao XH, Li J, Liu LJ, Zheng NX, Zheng K, Mei Z, et al. Trends, clinicopathological features, surgical treatment patterns and prognoses of early-onset versus late-onset colorectal cancer: A retrospective cohort study on 34067 patients managed from 2000 to 2021 in a Chinese tertiary center. Int J Surg. 2022;104:106780.
3. Georgiou A, Khakoo S, Edwards P, Minchom A, Kouvelakis K, Kalaitzaki E, et al. Outcomes of Patients with Early Onset Colorectal Cancer Treated in a UK Specialist Cancer Center. Cancers (Basel). 2019;11(10).
4. Kneuertz PJ, Chang GJ, Hu CY, Rodriguez-Bigas MA, Eng C, Vilar E, et al. Overtreatment of young adults with colon cancer: more intense treatments with unmatched survival gains. JAMA Surg. 2015;150(5):402-9.
5. O'Sullivan DE, Cheung WY, Boyne DJ, Jarada TN, Tang PA, Gill S, et al. Treatment patterns and survival outcomes of early-onset colorectal cancer patients in Alberta, Canada: a population-based study. Cancer Treatment and Research Communications. 2022;32:100585.
6. Aminisani N, Nikbakht H, Asghari Jafarabadi M, Shamshirgaran SM. Depression, anxiety, and health related quality of life among colorectal cancer survivors. J Gastrointest Oncol. 2017;8(1):81-8.
7. Boehmer U, Ozonoff A, Winter M, Berklein F, Potter J, Hartshorn KL, et al. Health-related quality of life among colorectal cancer survivors of diverse sexual orientations. Cancer. 2021;127(20):3847-55.
8. Kobayashi R, Ishizaki M. Relationship Between Health Literacy and Social Support and the Quality of Life in Patients With Cancer: Questionnaire Study. J Particip Med. 2020;12(1):e17163.

9. Perl G, Nordheimer S, Lando S, Benedict C, Brenner B, Perry S, et al. Young patients and gastrointestinal (GI) tract malignancies - are we addressing the unmet needs? BMC Cancer. 2016;16:630.

10. Potosky AL, Graves KD, Lin L, Pan W, Fall-Dickson JM, Ahn J, et al. The prevalence and risk of symptom and function clusters in colorectal cancer survivors. J Cancer Surviv. 2022;16(6):1449-60.

11. Waddell O, McLauchlan J, McCombie A, Glyn T, Frizelle F. Quality of life in early-onset colorectal cancer patients: systematic review. BJS Open. 2023;7(3).

12. von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. Epidemiology. 2007;18(6):800-4.

13. Ware JE, Kosinski M, Gandek B. SF-36® Health Survey: Manual and Interpretation Guide. Lincoln RI: QualityMetric Incorporated; 1993, 2000.

14. Antonescu I, Carli F, Mayo NE, Feldman LS. Validation of the SF-36 as a measure of postoperative recovery after colorectal surgery. Surg Endosc. 2014;28(11):3168-78.

15. Steffens D, Koh C, Ansari N, Solomon MJ, Brown K, McBride K, et al. Quality of Life After Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy: Early Results from a Prospective Cohort Study of 115 Patients. Ann Surg Oncol. 2020;27(10):3986-94.

16. Steffens D, Solomon MJ, Young JM, Koh C, Venchiarutti RL, Lee P, et al. Cohort study of long-term survival and quality of life following pelvic exenteration. BJS Open. 2018;2(5):328-35.

17. Reece MM, Chapuis PH, Keshava A, Stewart P, Suen M, Rickard M. When does curatively treated colorectal cancer recur? An Australian perspective. ANZ J Surg. 2018;88(11):1163-7.

18. Austin KK, Young JM, Solomon MJ. Quality of life of survivors after pelvic exenteration for rectal cancer. Dis Colon Rectum. 2010;53(8):1121-6.

19. Färkkilä N, Sintonen H, Saarto T, Järvinen H, Hänninen J, Taari K, et al. Health-related quality of life in colorectal cancer. Colorectal Dis. 2013;15(5):e215-22.

20. Ratjen I, Schafmayer C, Enderle J, di Giuseppe R, Waniek S, Koch M, et al. Health-related quality of life in long-term survivors of colorectal cancer and its association with all-cause mortality: a German cohort study. BMC Cancer. 2018;18(1):1156.

21. Avellaneda NL, Lasa J, Veracierto F, Hernandez A, Santillán M, Sendra PO, et al. Early-Onset Colorectal Cancer in Younger Patients with a More Advanced Stage and Worse Postoperative Results: A Retrospective Review. Turkish journal of colorectal disease. 2021;31(3):174-81.

22. Arndt V, Merx H, Stegmaier C, Ziegler H, Brenner H. Quality of life in patients with colorectal cancer 1 year after diagnosis compared with the general population: a population-based study. J Clin Oncol. 2004;22(23):4829-36.

23. Siu DHW, Ali A, Tjokrowidjaja A, De Silva M, Lee J, Clingan PR, et al. Clinical and molecular profile of young adults with early-onset colorectal cancer: Experience from four Australian tertiary centers. Asia Pac J Clin Oncol. 2022;18(6):660-8.

24. Chen K, Zhang Z, Zuo Y, Ren S. Comparison of the clinical outcomes of laparoscopic-assisted versus open surgery for colorectal cancer. Oncol Lett. 2014;7(4):1213-8.

25. Lamprell K, Pulido DF, Arnolda G, Easpaig BNG, Tran Y, Owais SS, et al. People with early-onset colorectal cancer describe primary care barriers to timely diagnosis: a mixed-methods study of web-based patient reports in the United Kingdom, Australia and New Zealand. BMC Prim Care. 2023;24(1):12.

26. Scott RB, Rangel LE, Osler TM, Hyman NH. Rectal cancer in patients under the age of 50 years: the delayed diagnosis. Am J Surg. 2016;211(6):1014-8.

27. Blum-Barnett E, Madrid S, Burnett-Hartman A, Mueller SR, McMullen CK, Dwyer A, et al. Financial burden and quality of life among early-onset colorectal cancer survivors: A qualitative analysis. Health Expect. 2019;22(5):1050-7.

28. Calman KC. Quality of life in cancer patients--an hypothesis. J Med Ethics. 1984;10(3):124-7.

29. Ramsey SD, Andersen MR, Etzioni R, Moinpour C, Peacock S, Potosky A, et al. Quality of life in survivors of colorectal carcinoma. Cancer. 2000;88(6):1294-303.

30. Sprangers MA, Schwartz CE. Integrating response shift into health-related quality of life research: a theoretical model. Soc Sci Med. 1999;48(11):1507-15.

31. Pisano M, Zorcolo L, Merli C, Cimbanassi S, Poiasina E, Ceresoli M, et al. 2017 WSES guidelines on colon and rectal cancer emergencies: obstruction and perforation. World J Emerg Surg. 2018;13:36.

32. Seeto AH, Nabi H, Burstow MJ, Lancashire RP, Grundy J, Gillespie C, et al. Perioperative outcomes of emergency and elective colorectal surgery: a bi-institutional study. ANZ J Surg. 2023;93(4):926-31.

33. Molenaar CJ, van Rooijen SJ, Fokkenrood HJ, Roumen RM, Janssen L, Slooter GD. Prehabilitation versus no prehabilitation to improve functional capacity, reduce postoperative complications and improve quality of life in colorectal cancer surgery. Cochrane Database Syst Rev. 2022;5(5):Cd013259.

Chapter 5: Discussion and Conclusion

5.1 Overview of principle findings

EOCRC incidence has been increasing worldwide, particularly in Westernised countries such as Australia (1). Recently, CRC research has shifted its focus to establishing how EOCRC differs from LOCRC. In Chapter 2 we summarised these unique differences. Of particular importance, EOCRC patients experience delays in their diagnosis and EOCRC tumours harbour more aggressive histopathological features such as invasion of adjacent structures, perineural and lymphovascular invasion and mucinous component and signet ring morphology. Subsequently, advanced disease is common at the time of diagnosis of EOCRC patients. Despite this, there is a paucity of studies, let alone Australian studies, investigating the surgical outcomes of EOCRC patients and their HRQoL. Therefore, in addition to summarising the current EOCRC literature, this thesis aimed to describe the postoperative outcomes, survival and HRQoL of an Australian cohort of EOCRC patients including a subset who underwent PE or CRS and HIPEC.

Chapter 3 described the surgical outcomes and survival of our Australian EOCRC cohort. We demonstrated that stage IV and left-sided disease were common at the time of presentation. Thus, nearly one-third of the cohort underwent either PE or CRS and HIPEC, with low anterior resection being the next most performed colorectal resection. Rates of stoma formation and minor (Clavien-Dindo grade II) postoperative complications were high. Despite this, the absolute five-year survival rate for the EOCRC cohort was acceptable at 85.5%.

Understanding the impact of these invasive oncological resections associated with high rates of stoma formation and postoperative morbidity on the HRQoL of EOCRC patients is paramount, especially in the setting of acceptable five-year survival rates. Thus, Chapter 4 evaluated the quantitative HRQoL of our Australian EOCRC cohort utilising normative PCS and MCS scores from the SF-36v2 survey and identified predictors of HRQoL. Chapter 4 showed that the physical and mental functioning of EOCRC patients were within the average range of the general Australian population. However, MCS scores were slightly lower than the mean normative MCS scores for the Australian population at both ≤ 2 and > 2-year time intervals. Stage I disease and emergency index operation were associated with poorer levels of physical functioning in the first two postoperative years.

5.2 Contribution of this thesis to current knowledge and practice

In Chapter 1, we demonstrated that the burden of EOCRC follows a geographical pattern (2). As a result, screening guidelines in the US changed in 2018 to reduce the screening initiation age to 45 (3). In Chapter 2, it became evident that the development of EOCRC is contributed to, at large, by environmental exposures resulting in disruption to the gut microbiome (4). Therefore, the findings of most EOCRC studies which predominantly evaluate US young-onset cohorts have limited translatability to an Australian clinical context.

To address this, this thesis established an Australian cohort of EOCRC patients and to our knowledge, only one other Australian EOCRC cohort exists. Siu et al.'s (5) EOCRC cohort, whilst larger than ours with 217 patients spanning across four tertiary referral centres in NSW, only investigates the clinicopathological characteristics of their EOCRC patients. Therefore, our EOCRC cohort is unique in that its dataset is focused on postoperative outcomes, survival

and HRQoL and includes patients undergoing the most invasive types of colorectal oncological resections (PE and CRS and HIPEC). This is imperative as in Chapter 2 we demonstrated that EOCRC patients present with advanced disease with aggressive histopathological features. Thus, stage IV patients undergoing invasive oncological resections should be included in EOCRC datasets to obtain a complete surgical snapshot of EOCRC, minimising exclusion bias, and providing a foundation to direct future, more targeted, Australian research.

Multidisciplinary team (MDT) meetings have been incorporated as part of the "standard-of-care" management of CRC in Australia. It is recommended that all new CRC patients and mandatory that all high-risk and complex CRC cases be discussed at an MDT meeting (6). Whilst the composition of the MDT differs from centre to centre, they are typically comprised of a colorectal surgeon, medical oncologist, radiation oncologist, pathologist, and radiologist. At MDT meetings, patient histories and comorbidities as well as the pre-MDT work-up are presented followed by clinical staging by the pathologist and radiologist. Thereafter, an agreement is reached on optimal treatment (7).

In Chapter 3, it became evident that despite a high proportion of patients with stage IV disease who underwent invasive oncological resections such as PE or CRS and HIPEC, the absolute five-year survival rate for EOCRC was acceptable. This will help guide preoperative decision-making and MDT discussions, particularly regarding expediting onward referral to a quaternary service for PE or CRS and HIPEC in appropriately selected EOCRC patients. Further, Chapter 3 also demonstrated that EOCRC patients are more likely to have left-sided disease, undergo stoma formation and have their index surgery performed in an emergency setting (for example, for bowel perforation). Therefore, we advocate that all EOCRC patients should be considered as high-risk, and thus referred to an MDT for discussion.

In Chapter 4 we demonstrated that despite a high rate of stoma formation and postoperative minor complications, EOCRC patients' physical and mental HRQoL was within the average range of the general Australian population. This finding is significant, as every CRC patient undergoes extensive discussion with their surgeon preoperatively regarding the nature of their surgery, the expected postoperative course, and its associated risks. Understandably, in addition to being focused on the treatment of their CRC itself, EOCRC patients often ask when they can return to work and what their QoL will be both in the short- and long-term setting postoperatively. Therefore, the results of Chapter 4 can guide clinicians in their reassurance and counselling of EOCRC patients in the preoperative setting.

Although insignificant, MCS scores ≤ 2 and > 2 years from index surgery were lower than the mean MCS scores of the general Australian population. EOCRC patients thus represent a cohort that may benefit from preoperative psychological consultations to strengthen their mental well-being prior to surgery and tailored postoperative outpatient clinics that enable ongoing access to social workers to obtain guidance regarding services and financial support, psychologists and psychiatrists to develop positive coping mechanisms and to physiotherapists (particularly in EOCRC patients who underwent an emergency operation or have early-stage disease) to optimise their physical rehabilitation.

5.3 Implications for future research

This thesis exclusively evaluated an EOCRC cohort. In Chapter 3 we established that EOCRC patients undergo more invasive surgeries, emergency surgeries, stoma formations and postoperative minor complications with acceptable absolute five-year survival rates. However,

it is unclear if these surgical and survival outcomes are unique to EOCRC patients only. Certainly, there have been conflicting results in the current literature (8-13). Therefore, future Australian EOCRC studies should include a comparison to LOCRC to ascertain if any discrepancies in their postoperative morbidity and mortality exist.

Whilst Chapter 4 demonstrated that the physical and mental functioning of EOCRC patients was within the average range of the general Australian population, the SF-36v2 survey did not address CRC-specific functional outcomes. In our EOCRC cohort in Chapter 3, the majority of tumours were in the rectum with anterior resections being the most performed operation in those who did not undergo PE or CRS and HIPEC. Low-anterior resection syndrome (LARS) is a constellation of symptoms including faecal and gas incontinence, urgency, frequent bowel motions, clustering of stools and difficulty emptying (14, 15). Whether it is a high or low anterior resection that is performed, some degree of LARS is common and can impair patients' long-term level of function. Moreover, injury to the hypogastric nerves (either with high ligation of the inferior mesenteric artery, at the sacral promontory or in the anterolateral and posterolateral rectal dissections) may lead to bladder and sexual dysfunction (16). Therefore, future prospective comparative studies investigating the functional outcomes of EOCRC and LOCRC patients are imperative.

In order to adequately capture at-risk patients, particularly in view of the steep rise in incidence of EOCRC, the US has reduced the CRC screening initiation age to 45, whilst in Australia the NBCSP commences at the age of 50. Given the high rates of invasive oncological surgeries, associated with increased postoperative morbidity and high rates of stoma formation (of which some will require return to theatre for reversal post adjuvant therapy) in our EOCRC cohort, it would be prudent to perform a cost-effectiveness analysis investigating the cost-effectiveness

ratio of reducing the NBCSP screening initiation age to 45 or even 40. Although this has already been done by Lew et al. (17), who found that commencing screening at 45 would be cost-effective but would also increase colonoscopy demand, their study was limited by their use of 2001 Australian population data and their assumption that adherence to screening would be similar for patients in their 40s and 50s.

If cost-effectiveness studies reveal that lowering the CRC screening initiation age is cost-ineffective or has a less favourable benefit-to-harms ratio, future research should focus on discovering robust minimally invasive diagnostic biomarkers. For example, Loomans-Kropp et al. (18) found that the Epi proColon® V2.0, a commercially available mSEPT9 cell-free DNA detection kit for patients > 50 years in the US, had good statistical performance characteristics to predict EOCRC in comparison to all healthy controls. Nakamura et al. (19) established a combination signature of four circulating microRNA (miRNA) (miR-193aa-5p, miR-210, miR-513a-5p and miR-628-3p) via genome-wide transcriptomic profiling as a diagnostic biomarker for EOCRC in their training cohort with good performance characteristics which were reproduced in two independent validation cohorts. If these non-invasive diagnostic biomarkers are validated in Australian EOCRC cohorts, they may represent cost-effective alternatives to the faecal occult blood test and colonoscopy to screen the Australian 40-50-year-old population.

5.4 References

1. Siegel RL, Torre LA, Soerjomataram I, Hayes RB, Bray F, Weber TK, et al. Global patterns and trends in colorectal cancer incidence in young adults. Gut. 2019;68(12):2179-85.

2. Saad El Din K, Loree JM, Sayre EC, Gill S, Brown CJ, Dau H, et al. Trends in the epidemiology of young-onset colorectal cancer: a worldwide systematic review. BMC Cancer. 2020;20(1):288.
3. Wolf AMD, Fontham ETH, Church TR, Flowers CR, Guerra CE, LaMonte SJ, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin. 2018;68(4):250-81.
4. Hofseth LJ, Hebert JR, Chanda A, Chen H, Love BL, Pena MM, et al. Early-onset colorectal cancer: initial clues and current views. Nat Rev Gastroenterol Hepatol. 2020;17(6):352-64.
5. Siu DHW, Ali A, Tjokrowidjaja A, De Silva M, Lee J, Clingan PR, et al. Clinical and molecular profile of young adults with early-onset colorectal cancer: Experience from four Australian tertiary centers. Asia Pac J Clin Oncol. 2022;18(6):660-8.
6. Cancer Council Australia Colorectal Cancer Guidelines Working Party [Internet]. Sydney: Cancer Council Australia. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer: multidisciplinary meetings [Internet]. Sydney (AU): Cancer Council Australia; 2017 [cited 2023 Sept 23]. Available from: https://https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer/Multidisciplinary_meeting
7. Fehervari M, Hamrang-Yousefi S, Fadel MG, Mills SC, Warren OJ, Tekkis PP, et al. A systematic review of colorectal multidisciplinary team meetings: an international comparison. BJS Open. 2021;5(3).

8. O'Connell JB, Maggard MA, Liu JH, Etzioni DA, Livingston EH, Ko CY. Do young colon cancer patients have worse outcomes? World J Surg. 2004;28(6):558-62.

9. Saraste D, Järås J, Martling A. Population-based analysis of outcomes with early-age colorectal cancer. Br J Surg. 2020;107(3):301-9.

10. Habib R, Burgess NG, Bourke MJ, Wong M, Wilcken N, Toh J, et al. Outcomes of young patients diagnosed with locally advanced rectal cancer. J Gastrointest Oncol. 2021;12(2):592-601.

11. Avellaneda NL, Lasa J, Veracierto F, Hernandez A, Santillán M, Sendra PO, et al. Early-Onset Colorectal Cancer in Younger Patients with a More Advanced Stage and Worse Postoperative Results: A Retrospective Review. Turkish journal of colorectal disease. 2021;31(3):174-81.

12. Ewongwo A, Hamidi M, Alattar Z, Ayotunde OP, Tiwari HA, Elquza E, et al. Contributing factors and short-term surgical outcomes of patients with early-onset rectal cancer. Am J Surg. 2020;219(4):578-82.

13. Hanna K, Zeeshan M, Hamidi M, Pandit V, Omesiete P, Cruz A, et al. Colon cancer in the young: contributing factors and short-term surgical outcomes. Int J Colorectal Dis. 2019;34(11):1879-85.

14. Ridolfi TJ, Berger N, Ludwig KA. Low Anterior Resection Syndrome: Current Management and Future Directions. Clin Colon Rectal Surg. 2016;29(3):239-45.

15. Sarcher T, Dupont B, Alves A, Menahem B. Anterior resection syndrome: What should we tell practitioners and patients in 2018? Journal of Visceral Surgery. 2018;155(5):383-91.

16. Giglia MD, Stein SL. Overlooked Long-Term Complications of Colorectal Surgery. Clin Colon Rectal Surg. 2019;32(3):204-11.

17. Lew JB, St John DJB, Macrae FA, Emery JD, Ee HC, Jenkins MA, et al. Benefits, Harms, and Cost-Effectiveness of Potential Age Extensions to the National Bowel Cancer Screening Program in Australia. Cancer Epidemiol Biomarkers Prev. 2018;27(12):1450-61.

18. Loomans-Kropp HA, Song Y, Gala M, Parikh AR, Van Seventer EE, Alvarez R, et al. Methylated Septin9 (mSEPT9): A promising blood-based biomarker for the detection and screening of early-onset colorectal cancer. Cancer Res Commun. 2022;2(2):90-8.

19. Nakamura K, Hernández G, Sharma GG, Wada Y, Banwait JK, González N, et al. A Liquid Biopsy Signature for the Detection of Patients with Early-Onset Colorectal Cancer. Gastroenterology. 2022.

Chapter 6: Appendices

Dear Associate Professor Daniel Steffens,

Thank you for submitting the following Site Specific Assessment (SSA) for governance review;
X21-0214 - 2021/STE02480: Early Onset Colorectal Cancer: epidemiology, survival, quality of life after surgery and surgical outcomes.

The Application has been reviewed by the Chief Executive's Delegate who has determined the application has been **AUTHORISED** to begin at this site - :
Royal Prince Alfred Hospital

The following documentation is included in this authorisation and other HREC approved documents are NOTED for use:

- **Waiver of Consent granted by the HREC for the retrospective data collection**
- **Protocol (Version 2, 4 August 2021)**
- **Participant Information Sheet (Version 2, 4 August 2021)**
- **Participant Consent Form (Version 1, 15 May 2021)**
- **Letter of Invitation (Version 1, 4 August 2021)**

Site authorisation will cease on the date of HREA expiry **4/08/2026**.

The following conditions apply to this research study. These are additional to those conditions imposed by the human research ethics committee (HREC) that granted ethical approval:
1. No data can be transferred from the SLHD to any organisation within Australia or overseas without an appropriate agreement in place.
2. A copy of the annual report and any other reports to the approving HREC, accompanied by a copy of the HREC's acknowledgement letter, must be provided to me via REGIS for review.
3. If you wish to access patient records from the Medical Records Department their head of department's signature must be provided via REGIS.
4. If any non-SLHD employee wishes to be added to the project, the appropriate documentation must be submitted to the RGO via REGIS for authorisation.
5. Proposed amendments to the research protocol or conduct of the research which are submitted to the lead HREC for review, must be submitted to me via REGIS.
6. Proposed amendments to the research protocol or conduct of the research, which may affect the ongoing site acceptability of the study, must be submitted to me via REGIS.
7. The Investigators follow the relevant jurisdictional public health guidelines in relation to COVID-19 site requirements.

I wish you every success in your research.

Yours sincerely,

Maree LARKIN
Research Governance Officer
Research Ethics & Governance Office
Royal Prince Alfred Hospital,
Missenden Road CAMPERDOWN NSW 2050
Tel 02 9515 7899 I maree.larkin@health.nsw.gov.au
http://www.slhd.nsw.gov.au/rpa/research/default.html

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

TELEPHONE: (02) 9515 6766
EMAIL: SLHD-RPAEthics@health.nsw.gov.au
REFERENCE: X21-0214 & 2021/ETH00976

NSW GOVERNMENT Health
Sydney Local Health District

5 August 2021

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

Dear Professor Koh,

Re: Protocol no. X21-0214 & 2021/ETH00976 - "Early Onset Colorectal Cancer: epidemiology, survival, quality of life after surgery and surgical outcomes

The Executive of the Ethics Review Committee, at its meeting of 5 August 2021 considered your correspondence of 5 August 2021. In accordance with the decision made by the Ethics Review Committee, at its meeting of 14 July 2021, ethical approval is granted.

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

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

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

This approval includes the following:

- HREA (Version 2, dated 26 July 2021)

- Protocol (Version 2, 4 August 2021) * see additional condition below

- Participant Information Sheet (Version 2, 4 August 2021)

- Participant Consent Form (Version 1, 15 May 2021)

- Letter of Invitation (Version 1, 4 August 2021)

- Telephone Script for follow up (Version 1, 4 August 2021)
- SF-36 Questionnaire (Version 1, 23 May 2021)
- Data Collection Form (Version 2, 4 August 2021)
- Master Code Sheet (Version 1, 15 May 2021)
- SLHD Privacy Compliance Form (Version 2, 4 August 2021)
- Research Data Management Plan (Version 2, 4 August 2021)

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

You are asked to note the following:

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

- Royal Prince Alfred Hospital

- This approval is valid for **five years**, and the Committee requires that you furnish it with annual reports on the study's progress beginning in **August 2022.** This will be through the submission of a milestone in REGIS.

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

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

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

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

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

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

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

Regards,

Estelle Ali
Ethics Support Officer

for:

Merela Ghazal
Acting Executive Officer
Ethics Review Committee (RPAH Zone)

HERC\EXCOR\21-08