Colorectal cancer in rural regional Australia

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Introduction

Colorectal cancer (CRC) is the second commonest malignancy after lung cancer, contributing to a significant health burden in Australia. The survival outcome of CRC patients within Australia is reported to vary with population density and between health services, with some literature showing poorer prognosis in rural regional and remote patients.

Chapter one of this thesis aims to outline some key issues in CRC inclusive of epidemiology, diagnosis, staging and management of CRC. At the end of this chapter, we have provided some information regarding the challenges faced by health services in rural regional Australia and a brief description of Barwon Health (The Geelong University Hospital), a regional centre in Victoria, where this thesis is mainly based on.

Chapter two aims to present a systematic review of how geographical disparity influences CRC epidemiology, diagnosis, treatment, survival and patients' quality of life. There are many potential factors that contribute to a poorer prognosis in rural regional CRC patients though the literature is limited and inconsistent.

The third chapter of this thesis aims to assess the long-term outcomes of CRC at Barwon Health, which serves the South West Victoria, a region with a population of some 500,000. The University Hospital Geelong is a major public hospital, variably classified as major or metropolitan by the Victorian Department of Health and Human Services (DHHS). The chapter aimed to determine whether changes in the management of CRC translated into

improved survival after surgery. The literature to date has suggested that patients living in rural and regional Australia (grouped together) have worse colorectal cancer survival rates than those of metropolitan Australia. This thesis was based on a prospectively maintained registry kept over a period of thirteen years from 2002 to 2014, that had accumulated 1079 patients who had undergone surgery at the University Hospital Geelong for CRC (744 colon cancers and 335 rectal cancers).

It is of great importance that cancer management becomes increasingly individualised, since certain patient subgroups are more vulnerable for the adverse effects of medical treatment. Over time, those with earlier tumour stages in the Barwon database, demonstrated a better survival. Therefore, we feel that more advancement could be gained by changing the focus to patients with the poorest outcomes. Chapters four and five focus on a subgroup of patients with the poorest outcomes, namely those diagnosed with metastatic disease at presentation, and those considered to be at risk of developing metastatic disease.

In chapter four, I aim to determine the anastomotic leak rate for CRC resections in patients with metastases (compared to those without), and to determine the impact of anastomotic leaks on survival. The Barwon database included 843 patients who had undergone resection and primary anastomosis for their primary tumour (661 colon cancers, 182 rectal cancers) in this study.

Despite improvements in chemotherapy regimens and aggressive resection of metastatic CRC, the 5-year mortality in patients with metastatic disease is extremely low at approximately 15%. Hence, if metachronous metastasis is identified and treated early,

survival could potentially be improved. The fifth chapter aims to perform a regional study to identify patients with colorectal cancer at higher risk of developing metastatic disease. The ability to predict these risk factors could improve surveillance strategies. The secondary aim is to assess if the identified risk factors are similar to those of the NSW population. There were 503 patients (345 colon and 158 rectal) with non-metastatic (stage I-III) CRC who had resections and were followed up for at least five years in this chapter.

Declaration of Authorship

This is to certify that:

(i) this thesis comprises only my original work towards the Masters of Surgery degree except where indicated in the Preface,

(ii) due acknowledgement has been made in the text to all other material used, and

(iii) this thesis is fewer than 50,000 words in length, exclusive of tables, figures, bibliographies and appendices.

Dr. Suat Chin Ng Date 26/02/2020

Preface

This work was completed with multiple collaboration

The Barwon Health Colorectal Database

The Barwon Health Colorectal Database was established by David Watters, Professor of Surgery at Barwon Health and Deakin University. A list of 1,079 patients whose had colorectal cancer surgery during 2002-2014 were identified. This database contains up to 90 data sets. The database was maintained by 6 surgical fellows from 2002 till end of 2008 and prospectively maintained by a clinical project officer thereafter. The data sets for all the patients incorporated into my study were verified by myself from assessing notes from both paper medical records and electronic medical records (BOSSnet). Further to this, I also performed all statistical treatments pertaining to this dissertation. All interpretations of the results were my own, though guidance and drafting were sought from my supervisors; Professor David Watters and Associate Professor Douglas Stupart. Guidance were also sought from Professor Glenn Guest, Professor Alexander Heriot and Doctor Eileen Moore.

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I would sincerely like to thank my supervisors for their support and guidance, and for sharing their wisdom:

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My family

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My friends

Joseph Kong and Wei Ming Ong for their support

In memory of

My uncle Bernie Ng (1951-2004) for his belief in me.

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Colorectal cancer

1.1 Introduction

Colorectal cancer (CRC) is a major public health problem.[1,2] It is one of the most commonly diagnosed cancers and has contributed enormously to Australia's economic burden. Along with the advances in research, the life expectancies of CRC patients have improved. Over half those newly diagnosed with CRC today, can expect ten or more years disease-free survival. However, there are still opportunities to improve our understanding of how to manage colorectal cancer and patient outcomes.

The first chapter provides some background information about CRC, covering epidemiology, aetiology, staging, treatment, prognosis and surveillance. Concluding this chapter, the focus move to CRC in the rural regional setting. Specifically, I will highlight the similarities and differences in epidemiology and the factors influencing management in rural and regional Australia.

1.2 Incidence of colorectal cancer

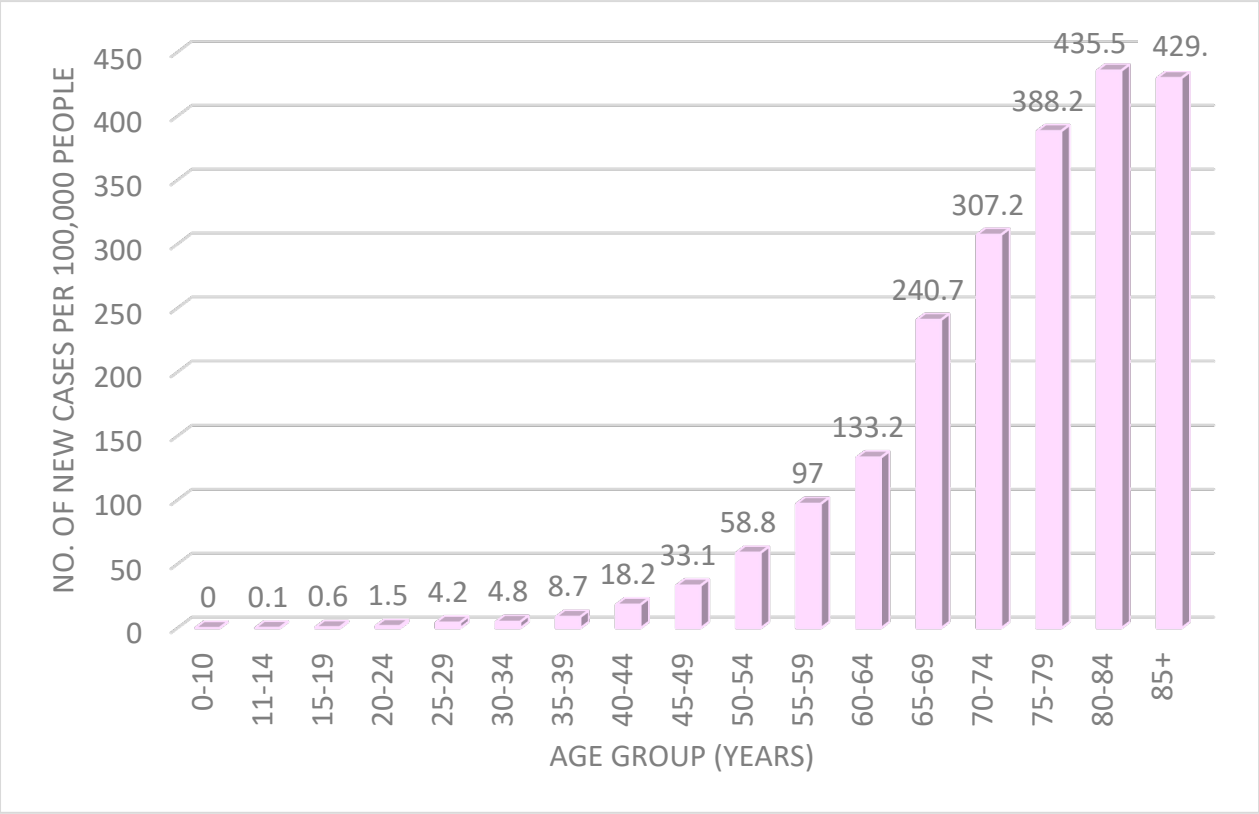
Worldwide,[1-4] the incidence of CRC is increasing, and is now the second most commonly diagnosed cancer in females and the third in males. In 2015, the Australian Institute for Health and Welfare (AIHW) reported the national age-standardized incidence rate for CRC to be 57 cases per 100,000 persons (67 for males and 49 for females).[1,2] The incidence is higher in men,[2] and increases with age. In terms of cancer mortality, CRC is the second commonest cause of cancer death, and in 2015 was responsible for 10% of all cancer deaths in Australia.[2]

The current CRC trends in Australia are those of increasing incidence, declining age-adjusted death rates, and better survival. This correlates with an aging population and suggests our health care is performing well in terms of early detection and effective treatment of cancer.[1,2]

Approximately 10 percent of CRC occurs in patients with either a positive family history or a recognized hereditary condition.[5] The most common causes of inherited CRC are Lynch syndrome and familial adenomatous polyposis (FAP) syndrome. Both syndromes account for approximately 3 percent, and less than 1 percent of all newly diagnosed CRC respectively.[6] In Lynch syndrome, the cancer appears to evolve from an adenoma. The adenoma tends to be larger, flatter, more proximal and often associated with higher grade dysplasia as compared to the sporadic adenomas. The adenoma-carcinoma sequence progresses rapidly. Patients with Lynch syndrome experience a higher risk of synchronous and metachronous CRC. In FAP, the patients typically have more than 100 adenomatous polyps; these predispose to the development of CRC in their second or third decade of life, if left untreated.[7]

Other than hereditary predispositions, inflammatory bowel disease such as Crohn's disease and ulcerative colitis also increase an individual's overall risk of developing CRC over time.[6] The relative risk of CRC in these patients has been estimated to be 4 to 20-fold increasing with the duration of the inflammatory condition.[8]

Figure 1.1 Incidence of colorectal cancer by age group, 2015



AIHW.gov.au

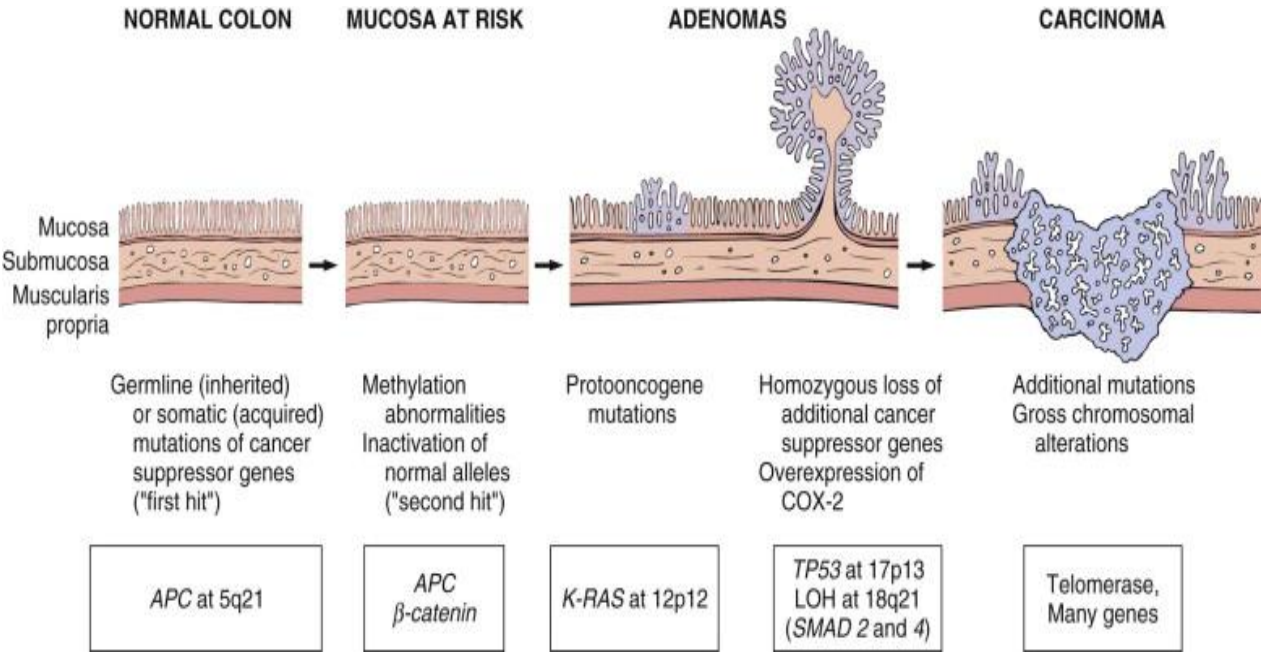
1.3 Burden of colorectal cancer in Australia

CRC is one of the eight cancers that has been prioritized within the National Health Priority Framework of Australia due to its burden of disease within the country. It accounts for the second highest number of years lost out of the total cancer burden causing premature mortality, and the third highest number of years lost due to the disease-related morbidity.[1,2] AIHW has ranked CRC as the 4th most 'expensive' cancer, accounting for 8.17% of total cancer costs in year 2000-2001, whilst these then quadrupled in the next decade, up to a total health care expenditure estimated at 1 billion dollars in 2011. The total treatment cost per case was estimated at $30,890 to $61,423 (for stage I to stage IV disease respectively).[9]

1.4 Aetiology of colorectal cancer

The aetiology of CRC is complex. The majority of CRC are thought to develop gradually over 10-15 years from benign precursor lesions, whilst a smaller proportion of CRC may occur de novo. The adenoma-carcinoma sequence describes a stepwise mutational activation of oncogenes and inactivation of tumour suppressor genes, ultimately leading to the formation of CRC.[10] The evidence to support the adenoma-carcinoma sequence has come from epidemiological, clinicopathological and molecular genetic studies such as the identification of adenomatous tissue in resected cancers, and the identical anatomic distribution of adenomas and carcinomas. Also, larger adenomas have a tendency to exhibit villous transformation with genetic alteration, higher grade dysplasia and invasive cancer. The transition from normal epithelium to adenoma and carcinoma is associated with at least seven acquired molecular changes (Fig 1.2).[10-12] The adenoma-carcinoma sequence provides a rationale for the current endoscopic practice of removing adenomatous polyps before their transformation to CRC.

Figure 1.2 Adenoma-Carcinoma Sequence



1.5 Stages of colorectal cancer

The staging system for CRC depends on the level of local invasion, the extent of lymph node involvement and the presence of distant metastasis. Historically, a stage A to C classification was first introduced in the 1930s by Cuthbert Dukes, and his system has been widely used for its prognostic value. Dukes' staging did not originally include the D stage of distant metastasis and was later modified by Astler and Coller. Now, although both Dukes and Astler Coller systems are still used by some clinicians, TNM staging system has become the standard for clinicopathological staging (Fig 1.3).[13] Accurate staging helps determine an appropriate management plan and to provide the patient with a prognosis.

Each individual component (T, N, M respectively) of the TNM staging system independently influences survival. The depth of tumour penetration (T stage), more specifically, T4, where the tumour invades into the serosal or local peritoneal surface, is a well-known adverse pathological factor. To date, there is still uncertainty in differentiating between serosal 'involvement' and local peritoneal tumour 'involvement'. The histopathological features that have been used to describe the latter are heterogeneous; with some, more likely to predict intraperitoneal recurrences or persistence than others. Unfortunately, the lack of a standardized guideline on these histopathological interpretations may result in under- or over-staging the tumour.[14]

N stage, the presence or absence of regional lymph node involvement, is another strong predictor of survival outcome following surgical resection of CRC. The number of positive nodes is stratified in the TNM system and identifies patients who may benefit from adjuvant

chemo-radiotherapy. The total number of lymph nodes obtained from a curative surgical resection is also an important indicator of the quality of surgery as it directly influences staging accuracy and prognosis.[15] Most expert groups recommend harvesting at least 12 nodes, though the evidence for this is limited when patients with rectal cancer have had neo-adjuvant chemo-radiotherapy, as these patients commonly end up having a lower number of lymph nodes. An alternative is the lymph node ratio (LNR), which is defined by the ratio of metastatic to examined lymph nodes. A systematic review of this has shown it to be a powerful prognosticator for both the overall and cancer specific survival, though the optimal cut-off values of the LNR category with the best outcome are yet to be defined.[16]

Lastly, the presence of metastatic disease (M0 or M1 stage) is known to depict poorer outcomes. The median survival of patients with M1 disease historically was less than 12 months, but recent reports suggest their median survival may now extend to 29 months.[17] The development of multiple chemotherapy and molecular targeting agents have rendered some previously unresectable metastatic CRC operable. Solitary or focal metastases in the liver or lung can sometimes be successfully resected.

Many clinicopathological features have been cited as indicators for prognosis and survival. Some of the traditionally accepted risk factors include residual tumour, lymphatic invasion, vascular invasion (particularly extramural veins) and poor tumour differentiation. These are independent adverse prognostic determinants. The American College of Pathologists Consensus Statement (1999) reviewed the evidence and have stratified the risk factors according to prognostic significance.[18] For example, the T, N, and M stages mentioned above belong to Category 1; a category assigned to factors that are proven to be of prognostic

importance based on evidence from multiple statistically robust published trials. Residual tumour and lymphovascular invasion are two other factors belonging to this category. The grades in tumour differentiation belong to Category IIA; a category given to factors that have been extensively studied biologically and / or clinically. Although these factors have been repeatedly shown to have prognostic value, they remain to be validated in statistically robust studies.

Figure 1.3 TNM Classification for Staging of Colorectal Cancer

Primary tumor (T)
- TX = primary tumor cannot be assessed
- T0 = no evidence of primary tumor
- Tis = carcinoma in situ
- T1 = tumor invades the submucosa
- T2 = tumor invades the muscularis propria
- T3 = tumor invades through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissues
- T4 = tumor directly invades other organs or structures or perforates the visceral peritoneum

Regional lymph nodes (N)
- NX = regional lymph nodes cannot be assessed
- N0 = no regional lymph node metastasis
- N1 = metastasis in 1–3 pericolic or perirectal lymph nodes
- N2 = metastasis in ≥4 pericolic or perirectal lymph nodes

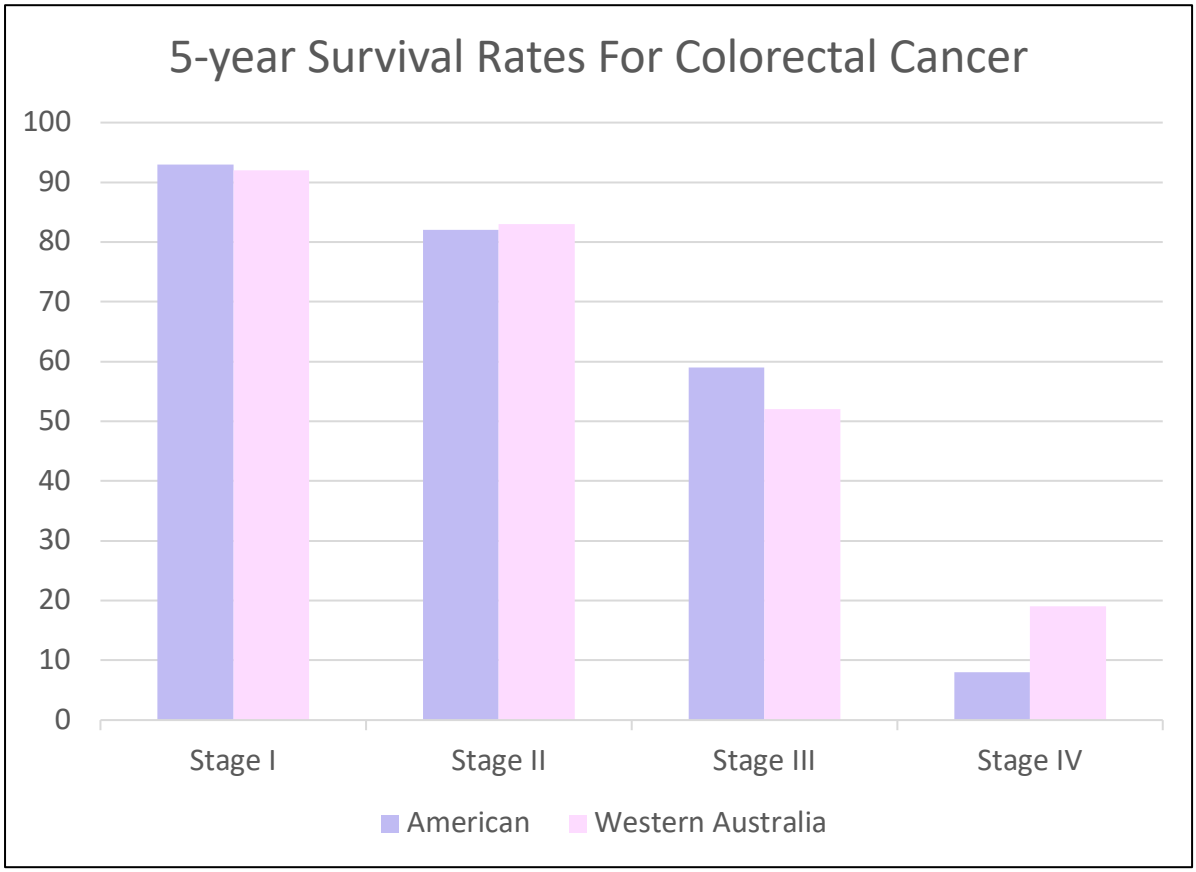
Distant metastasis (M)
- MX = distant metastasis cannot be assessed
- M0 = no distant metastasis
- M1 = distant metastasis

1.6 Prognosis of colon and rectal cancer. Are they different?

Colon and rectal cancer share many clinical features and are often referred to as one entity "colorectal cancer". Many studies have grouped them together and looked at their survival as a whole; a pattern of decreasing survival with more advanced stages of disease. The American SEER 2004 database reports Stage I to IV 5-year CRC survival rates to be 92%, 82%, 59% and 8% respectively. A similar rate of survival was observed in Western Australia.[10]

Are colon and rectal cancer two different tumour entities? Considering the physiology, anatomy, genetic behavior and risk factors, there is certainly heterogeneity amongst both colon and rectal cancers. The American Joint Committee on Cancer (AJCC) reports survival from colon and rectal cancers separately. Colon cancer has a marginally better survival than rectal cancer even without considering the outcomes of neo-adjuvant chemo-radiotherapy.[19-22]

Figure 1.4 Comparison of 5-year Survival Rates for Colorectal Cancer



1.7 Management of colorectal cancer

The treatment varies according to the stage of CRC. Early stages of CRC (i.e. localised, non-metastatic stage I-III disease) are best treated with surgery as it's the only curative treatment available. Preoperative colonoscopy is necessary to help localize the primary lesion and to exclude synchronous lesions; which often dictate the extent or type of surgery. Approximately 95% of Stage I and 70-80% of Stage II colon cancers are curable with surgery alone. Rectal cancer however may require neoadjuvant chemo-radiotherapy to minimize the risk of local and regional recurrence. In a subgroup of patients that could not tolerate chemotherapy, an alternative short course of neoadjuvant radiotherapy was found to be the next best option in reducing local regional recurrence.[23]

The risk of cancer recurrence post curative resection increases with more advanced stages. Thus, adjuvant chemotherapy has become the standard treatment for patients with stage III CRC, but its survival benefit remains unclear in stage II disease.[24, 25] Despite a shortage of robust evidence, many clinicians recommend adjuvant therapy to stage II CRC patients, particularly those with high risk features who are likely to have a higher risk of developing recurrent disease.[26-31]

For patients with metastatic CRC, the management is often multi-modal, inclusive of chemotherapy, radiotherapy and surgery. Palliative chemotherapy in general is the preferred option for treatment for unresectable disease, as it has been shown to improve survival and quality of life. Palliative radiotherapy is limited to selected metastatic sites such as bone or brain. Biologic agents have assumed a major role in recent years. Their selection and

application are increasingly guided by genetic analysis of the cancer. Infrequently, surgery may play a curative role in patients with limited burden of metastatic disease (i.e. solitary liver or limited lung metastasis).[32-34] The optimal selection of patients for hepatic resection is still evolving as the criteria for resection differs between surgeons, centres and countries.[35-37] Generally, metastatic involvement of more than 70%, or six segments of liver, is deemed inoperable.[38] To date, elective resection of a non-obstructed primary stage IV tumour remains contentious. The risk to benefit ratio of resecting a primary tumour in asymptomatic patients is dubious. For patients with stage IV disease that undergo surgery, there is a 20-30% risk of postoperative morbidity and 1-6% risk of perioperative mortality.[10, 39] Major perioperative complications such as anastomotic leak usually delay and sometimes preclude chemotherapy.[40]

1.8 Surveillance with colonoscopy

All patients with a history of CRC are at risk for developing adenomatous polyps, local recurrences and metachronous cancers. Surveillance colonoscopy aimed at secondary prevention is usually advisable after curative resection of CRC. The National Polyp Study reported a 90 percent CRC incidence reduction in the setting of colonoscopic surveillance for polyps[41] and prompted consensus guidelines recommending surveillance to detect recurrences, further polyps and metachronous cancers.[42]

Whilst most studies have shown that surveillance colonoscopy improves survival, the exact mechanism for the survival benefit remains unclear.[43] The benefits of colonoscopy were thought to have been mainly derived from the detection of metachronous cancer. The inability to detect a survival benefit from early colonoscopic detection of anastomotic recurrences might be due to low incidence.[44] Furthermore, anastomotic recurrence following resection of CRC frequently heralds metastatic disease, ensuing in a high proportion of patients having non-resectable disease at presentation.[44] Even when a recurrence is potentially resectable, the risk of morbidity and mortality associated with reoperation and adjuvant therapy may nullify any potential benefit.

Surveillance is time and resource consuming so requires a good level of evidence. Several studies have advocated for delayed commencement of surveillance colonoscopy due to their lower detection rate of similar lesions during the first three years.[45-46] Some guidelines recommend colonoscopy at one year after curative resection, on the basis that metachronous cancers or advance adenomas occur most frequently during this period.[47] It is

postulated that these second cancers might rather be missed synchronous rather than true metachronous lesions. Nevertheless, there is great value to the individual patient in detecting any missed polyps or tumours.

In view of this evidence, the Australian guidelines[48] have suggested that the first post-operative colonoscopy should be performed at one year, with subsequent colonoscopies undertaken at three to five-year intervals, pending results from previous colonoscopy. Shorter endoscopic testing intervals are indicated in patients with inherited bowel cancer syndromes.

1.9 Colorectal cancer in rural Australia and internationally

Despite having one of the most urbanised populations in the world (89.2%), over a third (approximately 8 million) of Australians live in urban regional, rural or remote locations.[49] There is a rising concern over CRC survival disparity between regional, rural, remote and metropolitan communities in Australia[50] as well as survival rates reported internationally.[51] People living in geographically isolated areas have a significantly higher incidence of CRC, higher proportion of late presentations and higher perioperative morbidity and mortality. Geographical discrepancies in survival are thought to be due to poorer access to general practitioners and/or specialist care. Other contributing factors include differences in ethnicity and demographics (e.g. higher proportion of Aboriginal and Torres Strait Islander, higher proportion of older residents), poorer socioeconomic status, lifestyle (e.g. higher rate of smoking and alcohol usage).[50] Access to multidisciplinary care and decision making has also been limited in rural and regional cancer care.[50]

1.10 Barwon health in context of rural regional health care

Barwon health serves a huge catchment area in South Western Victoria of over 350,000 people, from Werribee to South Australia.[52] Physical access to advanced diagnostic technology and specialist care services within this regional centre is easy for those living in Geelong. However, the barriers to health care previously reported by rural and remote patients applies to the more remote areas of South Western Victoria. The need to travel to access specialised health care poses a great financial and personal burden to those living in remote communities. In the case of rectal cancer, there is evidence that those living in rural/remote areas have a lower uptake and completion rate of radiotherapy.

Despite Barwon Health's ability to provide advanced technology and specialist care, the catchment area, based on the SEIFA index, is associated with a huge range of socioeconomic status, from as low as the 2nd percentile and as high as 95th percentile when ranked across Australia (a percentile of 2 indicates that approximately 2% of Australia's suburbs have socioeconomic statuses that were lower than the described area).[53]

Systematic review of colorectal cancer in rural and regional Australia

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This chapter has been submitted to

World Journal of Colorectal Surgery for publication

2.1 Abstract

Title:

Literature review of colorectal cancer patients in rural regional Australia

Introduction:

Inequality in colorectal cancer survival is a recognized problem in Australia with lower survival rates reported from rural and regional areas. Possible reasons for this disparity include poorer access to treatment, lifestyle and socioeconomic status. An understanding of the factors that influence treatment and survival, should help improve outcomes in those suffering from colorectal cancer.

Purpose:

This review focused on factors influencing the survival outcomes of colorectal cancer patients from rural and regional Australia

Methodology:

A literature search from Medline was performed using keywords “Colorectal Cancer” AND “Australia”. Terms relating to geographic disparities were included. Fifteen clinical questions pertaining to six areas of interest were examined. This included survival outcomes, patient demographic, cancer characteristics, diagnostic, screening, treatment characteristic, psychosocial and finally quality of life. Screening had followed a three-step process: removing duplicates, screening titles, and lastly screening full texts for relevance to one of the fifteen clinical questions. This resulted in a return of 32 studies for final review. During the second phase of selection, the reference list cited by the 32 studies identified above underwent

further screening, resulting in an addition of 26 more items for final review, giving a total of 58 articles.

Results:

There were 50 quantitative, six qualitative and two mixed-methods studies that met the review criteria. In terms of quantitative studies, 21, 22, and 8 studies provided level I / II, level III, and level IV evidence respectively. Seven of eight qualitative studies provided level III evidence. The majority of studies showed poorer colorectal cancer outcomes in rural regional remote patients, especially those from indigenous communities. There was some evidence supporting geographical disparities in the diagnosis and treatment of patients. Very limited evidence was available on the follow up, psychosocial support or quality of life post colorectal cancer treatment, making it difficult for any meaningful conclusions to be drawn on these outcomes.

Conclusion:

There was evidence of geographical disparity in CRC survival. The contributing factors are multi-factorial despite limited, and at times, inconsistent evidence. Regular, and risk-stratified reporting of colorectal cancer outcomes in rural and regional Australia is required. Further studies with more complete data collection are required to determine the significance of these factors. There is a need for qualitative studies that identify themes underpinning patient and clinician choices that influence outcomes.

2.2 Introduction

Australia is a country with vast land areas of relatively low population density. The different districts within the country are classified according to the ASGC Remoteness Areas classification system. [54] ASGC has five categories - “Major Cities”, “Inner Regional”, “Outer Regional”, “Remote” and “Very Remote”. Remote Australia covers about 85% of the Australian land mass, predominantly in Northern and Central Australia. The geographic spread of the country sets a challenge to equity of access to health services.[50] There is also a disparity in survival outcome between the categories of domicile and remoteness. For example, for those with colorectal cancer (CRC) there are lower survival and higher death rates associated with increasing rurality.

The reasons for poorer survival in CRC patients living in rural regional areas are thought to be multi-factorial. Poorer access to services, poorer socioeconomic status, different cultural beliefs, delayed presentation, lower participation rates in the national bowel cancer screening program, and lower health literacy are some of the likely factors.[55] How these factors interact with CRC prognosis are yet to be determined.

2.3 Study design and methodology

A literature review was undertaken using Medline database between 1st January 1998 to 31st December 2018. Studies were included if the paper was peer-reviewed, written in English, and reported data from Australia on CRC patients and relevant to one of 15 questions related to geographical variations on six topics, namely (1) survival outcomes, (2) patient demographics, (3) cancer characteristics, (4) diagnostic and screening, (5) treatment characteristic and (6) psychosocial support and quality of life outcome (Table 2.1). The questions to guide this review were developed by all co-authors of this paper. Two reviewers independently performed the search and identification of relevant studies. Only studies with original data were included. Review articles, letters to the editor, perspectives, books and conference abstracts were excluded.

Table 2.1 Clinical questions

Survival outcomes	Q1 For patients with CRC in rural regional Australia, do they have a poorer survival compared to metropolitan patients?
Patient demographics	Q2. For patients with CRC in rural regional Australia, do they have poorer socioeconomic status compared to metropolitan patients?
Cancer characteristics	Q3. For patients with CRC in rural regional Australia, do they have more advance stages of cancer at diagnosis when compared to metropolitan patients?

Diagnostic and Screening	Q4 For patients who are in the CRC screening target group in rural regional Australia, are they less likely to access screening services compared to metropolitan patients? Q5 For patients investigated with colonoscopy by rural proceduralists, do they have a higher rate of complication?
Treatment characteristic	Q6. For patients with CRC in rural regional Australia, are they more likely to experience delay in treatment compared to metropolitan patients? Q7 For patients with CRC in rural regional Australia, are they less likely to receive guideline recommended treatment (surgical or neoadjuvant or adjuvant therapy) compared to metropolitan patients? Q8. For patients with CRC in rural regional Australia, are they less likely to complete prescribed treatment compared to metropolitan patients?

	Q9 For patients with CRC in rural regional Australia, are they less likely to receive optimal specialist treatment ? Q10. For patients with CRC in rural regional Australia, do they have a higher complication rate compared to metropolitan patients?
Follow up	Q11 For patients with CRC in rural regional Australia, are they less likely to participate in recommended follow up post bowel resection compared to metropolitan patients? Q12. For patients with CRC in rural regional Australia, are they less likely to receive guideline recommended follow up / surveillance?
Psychosocial and quality of life outcome	Q13. For patients with CRC in rural regional Australia, do they have poorer quality of life after treatment compared to metropolitan patients? Q14. For patients with CRC in rural regional Australia, do they have poorer psychosocial support after diagnosis compared to metropolitan patients?

	Q15 For patients with CRC in rural regional Australia, are they contented with their cancer management when compared to metropolitan patients?

The search terms were based on subject headings and key words with separate queries designed for each individual reviewed question. All search strings comprised of the keywords "Colorectal Cancer" and "Australia". Synonyms for CRC were included into the search strings. Terms relating to geographical disparities included "geographic" or "metropolitan" or "urban" or "rural" or "regional" or "remote". Additional terms were added for individual clinical questions; these included terms such as "survival", "mortality", "diagnosis", "screening", "imaging", "clinical management", "chemotherapy", radiotherapy", "follow up", "quality of life", "psychosocial support", and "psychosocial distress".

There were two phases of selection: Phase one: selection of articles followed a 3-step screening process: (1) screening for duplicates, (2) screening of the title and abstract, (3) screening of the full text. After removing duplicates, the titles and abstracts were screened for relevance to one of the review questions. In cases where there was insufficient information in the abstract to determine relevance, the full-text of the article was obtained and checked against the inclusion criteria outlined above. The Medline search strategy yielded 572 records. After removing duplicates, 373 records were screened by title and abstract for relevance to one of the review questions. Of these, 47 full text articles were

potentially relevant and assessed for eligibility. Following assessment, 32 studies were included in the final review.

Phase two: The reference lists of the 32 studies identified from phase one selection were further screened. These references also followed the same 3-step screening process, being checked against the inclusion criteria outlined above, and yielded 26 further studies. The methodological quality of the identified papers was assessed against the NHMRC level of evidence framework. Study quality appraisal was carried out by one author.

The two phases of selection yielded 58 original papers for the final systematic review (Table 2.2).

2.4 Results

Table 2.2 Studies included in the systematic review

Publication	Year	Design	Level	Question
Wilkinson et al[56]	2004	Quantitative	II	1
AIHW[57]	2007	Quantitative	II	1
Baade et al[58]	2011(i)	Quantitative	II	1
Cramb et al[59]	2012	Quantitative	II	1
Wichmann et al[60]	2013	Quantitative	III-2	1
Coory et al[61]	2013	Quantitative	III-2	1
Dasgupta et al[62]	2013	Quantitative	III-2	1
Baade et a[63]	2013	Quantitative	III-2	1
AIHW[64]	2014	Quantitative	II	1
Chen et al[65]	2015	Quantitative	II	1
Roder et al[66]	2015	Quantitative	II	1
Beckmann et al[67]	2016	Quantitative	II	1
Beckmann et al[68]	2017	Quantitative	III-3	1
Ireland et al[69]	2017	Quantitative	I	1
Coory et al[70]	2000	Quantitative	III-2	2
Cramb et al[71]	2011	Quantitative	IV	2
Weir et al[72]	2016	Quantitative	III-3	2
Depeyenski et al[73]	2018	Quantitative	III-2	3
Tong et al[74]	2000	Quantitative	IV	4
Weber et al[75]	2008	Quantitative	II	4

Javanparast et al[76]	2010	Quantitative	IV	4
Paddison et al[77]	2010	Qualitative	III	4
Martini et al[78]	2011	Quantitative	IV	4
Ward et al[79]	2011	Quantitative	IV	4
Steffan et al[80]	2014	Quantitative	II	4
Varlow et al[81]	2014	Quantitative	IV	4
AIHW[82]	2015	Quantitative	IV	4
Sun et al[83]	2018	Quantitative	III-3	4
Azzopardi et al[84]	2012	Quantitative	III-3	5
Evans et al[85]	2014	Quantitative	I	5
Yu et al[86]	2005	Quantitative	II	7
Young et al[87]	2007	Quantitative	II	7
Beckmann et al[88]	2014	Quantitative	III-2	7
Gilbar et al[89]	2015	Quantitative	III-2	7
Bloem et al[90]	2016	Quantitative + Qualitative	III-3 / III	7
Morris et al[91]	2007	Quantitative	III-2	8
Goldsbury et al[92]	2012	Quantitative	III-2	9
Pascoe et al[93]	2013	Qualitative	III	9
Drury et al[94]	2010	Qualitative	III	12
Young et al[95]	2018	Quantitative	III-2	12
Dunn et al[96]	2013(i)	Quantitative	II	13
Dunn et al[97]	2013(ii)	Quantitative	II	13

Lashbrook et al[98]	2018	Quantitative	III-2	13
Ieropoli et al[99]	2011	Qualitative	III	14
Bergin et al[100]	2016	Qualitative	II	15
Baade et al[101]	2011(ii)	Quantitative	III-2	1, 3
Birks et al[102]	2001	Quantitative	IV	1, 3, 10
Jong et al[103]	2004	Quantitative	II	1, 4
Hall et al[104]	2005	Quantitative	II	1, 7
Singla et al[105]	2014	Quantitative	II	1, 7, 9
Martin et al[106]	2015	Quantitative	III-3	1, 2
Homewood et al[107]	2005	Quantitative	III-2	2, 3
Emery et al[108]	2013	Quantitative + Qualitative	III-2 / II	4, 6, 7, 9
Veitch et al[109]	2008	Qualitative	III	4, 7, 9, 11, 14
Crawford-Williams et al[110]	2018	Quantitative	I	6, 7
Armstrong et al[111]	2004	Quantitative	III-2	7, 8
Hocking et al[112]	2014	Quantitative	II	7, 9
Armstrong et al[113]	2005	Quantitative	III-2	7, 9
Armstrong et al[114]	2007	Quantitative	III-2	7, 9

After two phases of screening and selection, 58 articles were reviewed. Table 2.2 has listed the studies reviewed by year of publication, type of study, level of evidence and research question(s) addressed. Of the 58 articles, 50 were quantitative, six were qualitative and two were mixed methods. The method of data collection method varied greatly from population

linkage data, to surveys, interviews, etc. Fourteen articles included in more than one review question (Tables 2.1 and 2.2).

Table 2.3 Number of studies graded by type and level of evidence

Level of evidence	Quantitative	Qualitative
Level I	3 (5.7%)	0 (0%)
Level II	18 (34.0%)	2 (25.0%)
Level III • III-1 • III-2 • III-3	24 (45.2%) 0 18 6	6 (75.0%)
Level IV	8 (15.1%)	0 (0%)
Total	53	8

Table 2.3 footnote: The quantitative and qualitative analyses within the two articles (that used mixed method studies) were accounted for separately in the above chart

Almost half of the quantitative studies were graded as good quality with 5.7% classified as level I studies and 45.2% level II studies. Two of the 8 included qualitative and mixed method studies was of good quality with six providing Level III evidence.

2.4.1 Survival outcomes

For survival outcomes (Q1), 14 out of 19 studies showed significantly poorer CRC survival for individuals residing outside of metropolitan areas[56-59, 61-65, 67-68, 78, 101, 103]. However, several studies[56-57, 61, 64, 71, 103] showed varying degrees of poorer outcomes in the non-metropolitan regions; with slightly better survival seen in the inner regional compared with remote or very remote areas.

2.4.2 Patient demographics and cancer characteristics

Few studies have focused on patient factors and its implications on geographic disparities (Q2). Of the five studies, one investigated gender,[71] one investigated socioeconomic status,[106] and three investigated indigenous status.[70, 72, 107]

The only study of gender distribution found no evidence of geographical variation in CRC incidence for either gender; males (p=0.693) or females (p=0.216).[71]

As for socioeconomic status, its impact on geographic disparities is unclear. There was some indication that a rural regional population is associated with a lower socioeconomic status and lower health literacy and these may both affect CRC prognosis.[71] Social factors such as lower levels of income, employment, housing and education can influence the health of individuals and communities.[115] Lower education and lower health literacy may be associated with poorer lifestyle choices such as a higher rates of alcohol abuse and smoking leading to the development of chronic conditions including cardiovascular and pulmonary diseases, diabetes mellitus, cirrhosis and obesity.[115] The presence of these comorbidities increases not

only the risk of life-threatening complications during the different phases of cancer management including surgery, chemotherapy and radiotherapy, but may also affect long term disease free survival rates.

As for Indigenous status, one study in Queensland showed a lower incidence of CRC in the rural remote Indigenous communities.[70] Two studies showed poorer cancer survival in the Indigenous population[72, 107] though the survival difference was only evident after 18 months after diagnosis in one of the studies.[72] Qualitative research has shown that both cultural differences and communication difficulties (i.e. non-English speaking) contributed to this disparity. There was often tardiness and reluctance in seeking medical help because of nihilistic beliefs about CRC and the chance of cure.[116] Hesitancy towards approaching culturally insensitive services and cultural barriers including feelings of fatalism, shame, avoidance and fear associated with CRC. These latter are all impediments to treatment, whilst cancer may be perceived as a form of punishment;[117] as something that cannot be prevented and even 'God's will". Such cancer fatalism often accompanies unrealistic expectations of treatment. Another possible consequence, is that follow up after the initial treatment is often incomplete because of a belief of being cured.

In terms of cancer characteristics, this review found limited evidence (only one study) to support geographical differences in CRC stages (Q3).[107] Early detection of CRC is imperative in ensuring good survival outcomes. One study found that rural regional patients presented with more advanced stages of CRC, although this was mainly observed in the indigenous population.[107] It was difficult to distinguish whether indigenous ethnicity or the rural regional abode was the underlying reason.[107]

2.4.3 Diagnostic and screening

Australia has two main types of oncological systems across the states; some decentralized (e.g. in Victoria), and some centralized (e.g. in South Australia). Both systems have their respective merits and drawbacks, based on how they are administered, resourced, and politically championed. Regardless which type, both aim to provide best practice management and optimal cancer outcomes. When centralized, diagnostic delay is common for rural/remote patients due to a lack of access to advanced diagnostic facilities such as MRI and PET scanners or to colonoscopy facilities.

Thirteen studies have focused on the geographical disparities in diagnosis and screening (Q4). Three studies showed lower uptake of screening by rural regional patients (who lived in areas with more disadvantage) when compared to metropolitan patients (who lived in area of less disadvantage), in keeping with the inverse care law.[76, 78-79] Although great success has been achieved by the National Bowel Cancer Screening Program in reducing deaths from CRC through earlier detection,[118] there was still a relative lack of participation by rural regional patients. Incomplete screening due to a lack of follow up after positive FOBT, resulted in delayed detection of CRC and possibly a higher rate of missed opportunities for preventative measures such as polyp removal. One study identified a proportion of patients who felt that screening should only be done when symptomatic; reflecting a severe lack of understanding of the term screening.[81] Two studies showed differences in the uptake rate of FOBT screening by rural regional communities.[75, 83] A higher uptake was found in inner regional areas when compared with a metropolitan region, but this rate was observed to be much lower in the remote regions.[75, 83] The study that included gender found that participation rates for screening were significantly higher in females than males.[74]

For diagnostic colonoscopies, two studies have assessed the quality of rural regional colonoscopies (Q5) and showed that colonoscopies can be safely and effectively performed in rural regional settings.[84, 85] The cancer and adenoma detection rates were consistent with acceptable standards and had correspondingly low rates of complications. This result was not only achieved by the rural generalist, but also observed amongst rural general practitioner (GP) proceduralists. With appropriate training and the establishment of clear performance parameters, local rural GP proceduralists could potentially address the increasing demands for colonoscopy services.

2.4.4 Treatment characteristics

Regarding CRC treatment (Q6, 7, 8, 9 and 10), five studies investigated geographical disparities in surgery,[104-105, 108, 110-111] nine in chemotherapy,[86-91, 110, 112-113] three in radiotherapy,[86, 110, 113] one in adherence to treatment guidelines[86] one in the completion of prescribed treatment[91] and six investigated the opportunities for specialist treatment.[92-93, 105, 108-109, 112]

Of the five studies that have focused on surgery (Q7), three showed no geographical differences in the rate of provision of surgical intervention for patients with CRC.[104, 105, 108] This remains true with regards to the provision of liver surgery for rural regional patients with liver metastases.[105] However, one study showed that patients in rural regional areas were more likely to experience surgical delay (Q6).[110] Another study reported that rural regional patients were more likely to be operated by general surgeons with lower colorectal caseloads (Q9).[111]

Nine studies focused on chemotherapy.[86-91, 110, 112-113] Five studies showed that adjuvant chemotherapy was less likely to be offered to rural regional patients with node-positive colon cancers.[68, 86-87, 110, 113] For those who did receive chemotherapy, treatment was often delayed. Although oral agents are generally easier to administer, in contrast to the conventional intravenous chemotherapy agents, there was no obvious preference to prescribe oral capecitabine.[90] Two studies showed equivalent rates of chemotherapy between metropolitan and rural regional patients.[89, 112] Only one study assessed the geographical differences in the completion of prescribed treatment (Q8) and found rural patients had approximately half the rate of chemotherapy completion compared to metropolitan patients. The reasons for this discrepancy were not reported.

Two studies, both based in NSW, focused on radiotherapy. [86, 114] One showed no difference in the utilization of radiotherapy between metropolitan and rural regional communities.[114] However, there was a marked variation between different health services in what treatment was offered to high-risk rectal cancers. The other study suggested that poorer access to radiotherapy centres is the reason for poorer CRC prognosis in rural regional patients.[86] In a centralized cancer service, such as that seen in NSW, rural patients usually need to travel to larger regional or metropolitan for cancer treatment. The time and cost needed for travelling can be substantial despite subsidized travel for patients and carers. The subsidies offered are often small. Poor transport services in some remote areas may also impede access. The need for regular long-distance travel for treatment becomes a practical consideration especially when considering adjuvant treatment. Specialists less likely to follow up patients from remote areas. There is also reduced clinical trial participation amongst the rural regional population, which deprives them of the attention paid to trial participants. Each of these

potential obstacles may limit provision or uptake of optimal cancer therapy, subsequently affecting cancer survival rates.

With a decentralized cancer service (e.g. in Victoria), regional services are more common, but the supply does not yet meet the demand. This is evident by the long waiting list of specialist outpatient clinics (surgical, radiation oncology and medical oncology) in the public sectors. Access to timely treatment becomes challenging. Insufficient high-quality oncological and surgical care in rural regional Australia remains a constant challenge and requires ongoing commitment to address the underlying causes by state/territory and federal governments. Eight studies in this review investigated access to specialist treatment (Q9).[92-93, 105, 108-109, 112-114] Five studies reported that patients living in rural areas were less likely to receive optimal specialist treatment[92, 108-109, 113-114] whilst two showed no difference.[105, 112] Two studies showed a tendency for delayed referral from rural GP to colorectal specialists without directly comparing geographical locations.[93, 108] There was one study in which rural patients reported receiving sub-optimal care with limited information exchange between their specialists and GPs.[93]

A single study investigated complications (Q10) but reported no differences in surgical related mortality, anastomotic leak nor wound infection rates.[102]

2.4.5 Follow up

There is limited evidence regarding the geographical disparities of participation in recommended follow-up in Australia (Q11). One study reported rural patients were willing to participate in follow-up but encountered difficulties with travel for outpatient/ambulatory treatment.[109] Another study showed highly variable follow-up rates across the State of NSW, with less than half of the patients receiving surveillance colonoscopy or CEA assay a year after their diagnosis as per the guidelines (Q12).[87] Only 110 of 483 (23%) patients received a written follow-up plan, with lower rates for rural patients. A qualitative study identified lack of coordination for rural based patients as a cause of failure to follow the surveillance guidelines.[94] Further studies are needed, region by region to determine the local causes and potential solutions.

2.4.6 Quality of life and psychosocial outcome

A small number of Australian studies have investigated the psychosocial outcome and support of patients with CRC. One study found the geographical disparities affecting quality of life and experience of distress post CRC treatment (Q13) were also influenced by gender.[97] Men had more global distress post CRC treatment than women and the effect of oncological treatment on sexual function was thought to have potentially played a role here. Women on the other hand were more likely to experience anxiety.[97] Lower optimism, negative cognitive appraisal and younger age were associated with poorer life satisfaction. Remoteness of residence was associated with poorer outcomes in a survey of CRC-specific quality of life.[96] Another study reported rural based survivors had higher rate of sleep disturbance than their metropolitan counterparts.[98]

Some of these findings may be due to geographic disparities in the availability of psychosocial support (Q14). Men are less likely than women to seek or engage with any cancer support services.[97] Although rural/regional patients were willing to attend peer support group sessions they were often deterred by travel time and distance, family commitments or other medical appointments.[99]

Rural patients tend to experience more complex decision making, as they need to balance a range of social factors affecting their access to oncological care (Q15).[100] However, the majority of rural patients valued their freedom to share decision making and so reported satisfaction with treatment even when limited options were offered by their treating specialist.

2.5 Discussion

This review was limited by the small number of Australian studies and the use of inconsistent methodology across studies. The variation in population samples made direct comparisons between studies difficult. Above all, research identifying geographical disparities in cancer outcomes was hindered by the lack of accurate patient and treatment data at a population level.

Historically, there has been a lack of research on the disparities affecting cancer treatment in the rural/regional health system, its cost effectiveness and long-term sustainability.[118] However, in recent years, funding of $694 million has been invested in the development of regional cancer centres[118]. Despite this, significant inequalities still exist.

The review found that rural/regional CRC patients generally experience worse outcomes. This was also true for indigenous Australians. However, the prognosis for different rural regional populations varied, which means there is a great need for further studies within each region.

The disparity in survival makes it hard for those tasked with planning and delivering colorectal cancer care. The relevant local and regional issues need to be identified to ensure efficient and cost-effective care. A one-size-fits-all approach would be impossible and overly simplistic when managing CRC across the country. There is a need for cancer data from each region such as the audit produced by the Queensland Colorectal Cancer Sub-committee and the Queensland Cancer Control Analysis Team (QCCAT).[119] The Bi-national CRC audit for another, is working towards creating a large record that contains Australia and New Zealand

data, allowing for research and quality improvement.[120] It aims to enhance our knowledge in the treatment of CRC. However, to date, there is still a lack of rural or regional representation despite the ongoing efforts that have been put into encourage participation. It is also a voluntary audit and therefore unlikely to recruit all cases.[120]

Better, more comprehensive, outcome and survival data will help us understand the quality of care in and disease-free survival from CRC in rural regional centres. We also need further studies to determine which factors may contribute to the disparities experienced by those living in rural/regional areas. Thus, we will be able to further improve the management and outcomes of CRC care for those populations.

2.6 Conclusion

Rural/regional CRC patients, including indigenous Australians, generally experienced worse CRC outcomes. However, the prognosis for different rural regional populations varied, which highlights the need for further studies within each region. The trends in the reviewed studies addressing issues of geographical disparity relating to patient demographics, cancer characteristics and treatment profile were mixed. Reports addressing the influence of geography on CRC follow up and psychosocial outcome post diagnosis of CRC are limited. The reviewed studies emphasize the need for better and more consistent data collection and reporting. It is likely that many rural/regional patients with CRC have less access to some modalities of care which affects their management and outcomes. We need better, more comprehensive registries that include all patients, domiciles matched to longer term survival. This review also highlights an opportunity to use of data linkage to accumulate some of the relevant data.

Trends in survival after colorectal cancer surgery in an Australian regional hospital

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3.1 Abstract

Introduction:

Colorectal cancer (CRC) is the second commonest cancer in Australia. Improvements in patient outcome after resections for CRC have been reported on Australian metropolitan hospital, but significant outcome variability exist between health systems and institutions.

Objective:

This study sought to determine whether changes in the management of colorectal cancer (CRC) have translated into improved survival after surgery in an Australian regional hospital.

Methods:

All patients that underwent surgery for resection of CRC at the University Hospital, Geelong between January 2002 and December 2014 were studied retrospectively. Demographic information, comorbidities, types of surgery performed, and tumour staging were recorded. Patients were followed up for life whenever possible. Categorical data were recorded using Chi-squared test for trend as appropriate. Survival analysis was performed using Kaplan-Meier method.

Results:

There were 1079 patients who underwent CRC resections surgery for CRC over the thirteen-year study period (744 colon cancers and 335 rectal cancers). The number or operations per year increased over time (p=0.037). The median age was 72 years (range 23-98) and this did not change over time (p=0.67). There were no temporal changes in tumour stage distribution

(p=0.21) or in the proportion of emergency cases (p=0.75), but the proportion of patients with severe comorbidities had increased (p=0.015). The peri-operative mortality rate was 4.5%. Median survival after surgery by stage was 123 months, 141 months, 76 months and 17 months for Stage I to IV tumours respectively. Over the study period, there were improvements in both peri-operative mortality (p=0.028) and long- term survival (p=0.0025).

Conclusion:

Both short and long- term survival after surgery for colorectal cancer improved in this Australian regional institution.

3.2 Introduction

Colorectal cancer (CRC) is the second commonest cancer in Australian men (after prostate cancer), and women (after breast cancer).[121] The incidence of CRC in Australia has increased over time, but the overall mortality from this disease has decreased.[121] Improvements in the care of patients with CRC, as well as earlier diagnosis (following the introduction of bowel cancer screening) have contributed to improved survival for CRC patients.[122] In addition, peri-operative mortality rates have been declining in Australia for surgical procedures overall.[123-124]

Numerous interventions have been shown to improve both short and long- term outcomes of CRC patients. These include advances in adjuvant and palliative chemotherapy and radiotherapy, as well as improvements in surgical technique and peri-operative care.[125-131]

Dent et al. have reported improvements in both long- and short-term outcomes after resections of CRC over a very long time-period in a large Australian metropolitan teaching hospital.[132-133] However, it is well-recognised that there is significant variability in patient outcomes between health systems and institutions.[134-136]

The purpose of this study was to determine if changes in the care of CRC patients have translated into improved short- and long-term survival after surgery in a regional hospital in Victoria, Australia.

University Hospital, Geelong (UGH) is a large Victorian regional hospital that covers the full spectrum of services from emergency to mental health, primary care, community services, aged care, subacute care and rehabilitation.[52] All types of imaging technology and subspecialty care are offered in this hospital, including major specialties such as oncology, cardiology and cardiothoracic surgery with the exception of neurosurgery and transplantation. This centre provides care to a geographically dispersed population of 350,000 to 500,000 people including urban, rural and remote populations.[52]

3.3 Study Design and methodology

3.3.1 Ethical approval

The AIHW Ethics Committee reviewed and approved this project under the reference number EC2013/1/1.

3.3.2 Methods

This is a retrospective study of a prospectively maintained colorectal database at Barwon Health. Eligible patients were recruited from the database; they had resection of their primary colorectal cancer (histopathology confirmed as adenocarcinoma) from 1st of January 2002 until 31st of December 2014. The sites of cancer ranged from ileocaecal valve through to but not including anal canal. Data extracted from the database comprised of: demographic details (hospital ID, surname and first name of patient, date of birth, gender, postcode and age at admission), comorbidities (smoking, lists of conditions, Charlson's comorbidities score[136] and Elixhauser comorbidity index), operative details (date of surgery, admission date, discharge date, name of surgery, name of surgeon, open or laparoscopic or open conversion to laparoscopic surgery and elective or emergency surgery), postoperative medical and surgical immediate complication (death, anastomotic leak, return to theatre during index admission, unplanned ICU admission and unplanned readmission) and histopathology details (tumour site, TNM status, tumour size, distal margin clearance, if cancer was resected and the presence of residual macroscopic disease).

For patients eligible for the study, supplementary data was obtained from accessing records of BOSSNET (an electronic medical record based at Barwon Health). During this process, all

the original (i.e. pre-existing) data from the colorectal database were internally validated by myself to ensure accuracy of recording by the clinical information project officer. The supplementary data further added to the analysis included extra histopathology details (MSI testing, presence of other polyps, kikuchi status if present, grade of cancer, lymphovascular invasion, perineural invasion, radial margin clearance), clinical findings relating to tumour (presence of obstruction, synchronous cancers, perforation, site of metastasis and intent of treatment during index admission), multidisciplinary outcomes (medical radio-oncological therapies), long term surgical specific complications and follow up details (carcinoembryonic antigen (CEA), imaging and colonoscopy findings, dates of local recurrence, metastasis and metachronous disease).

Patients had lifelong clinical follow up wherever possible. When patients were lost to clinical follow up, attempts were made to contact the patient or his/ her family or general practitioner in order to find the patient or to confirm if and when s/he had died. I attempted to contact all patients whose survival status was uncertain. Follow up was up to at least 31 December 2015.

Survival analysis was done using the Kaplan- Meier method to allow for variable follow up, and comparisons made using the Cox proportional- hazards method. Categorical data were compared using the chi- squared test or chi- squared test for trend as appropriate. A P- value of ≤ 0.05 was considered significant. Statistical analysis was done using Medcalc® (Mariakerke, Belgium) software.

3.4 Results

3.4.1 Demographics of cohort

A total of 1079 patients underwent colorectal adenocarcinoma resection during the study period. A median of 80 (range 68 to 103) patients underwent surgery each year, with an increasing number of being patients operated on annually over the study period (see Figure 1; correlation coefficient r=0.58, p=0.037). Five patients were lost to follow up.

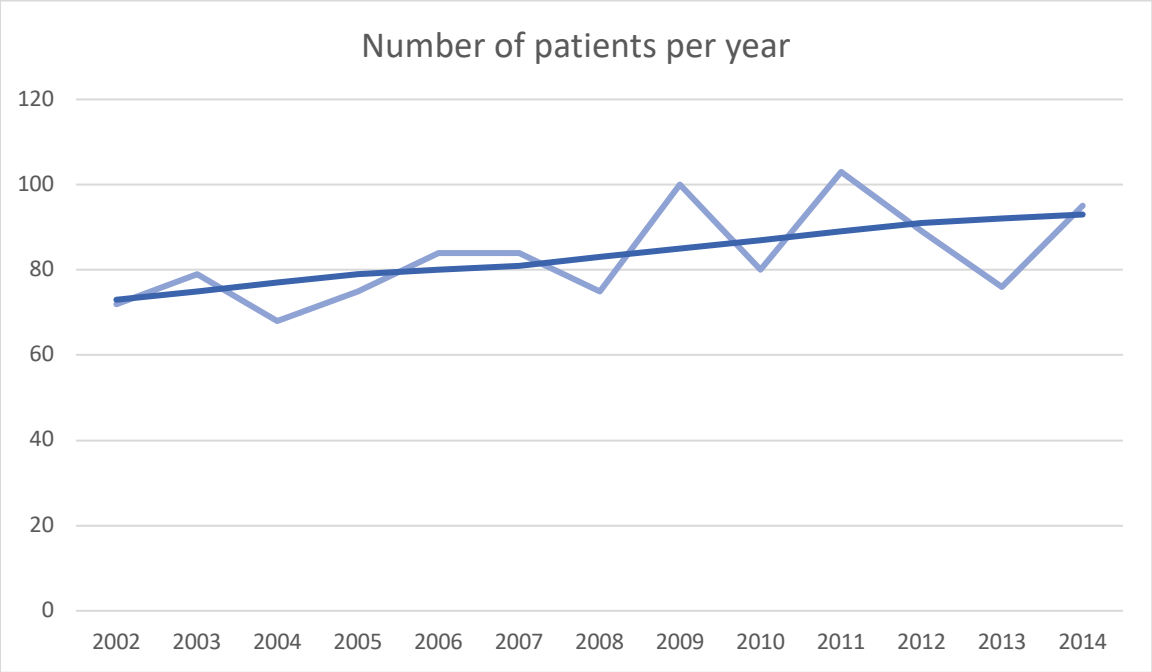

Figure 3.1: Number of patients undergoing surgery annually over the study period (r= 0.58; p=0.037)

Of the 1079 patients, 744 had surgery for colon cancer, and 335 for rectal cancer. There was a total of 617 men and 462 women (see Figure 3.2). The median age at surgery was 72 years (range 23 to 98), and the patients' age distribution has not changed over the study period (correlation coefficient r=0.013, P=0.67) (see Figure 3.3). Overall, 235/1079 (22%) patients underwent surgery in an emergency setting (see Table 3.1). The proportion of emergency operations varied over time, with a minimum of 11% in 2006, and a maximum of 31% in 2002, but with no significant temporal trend (P=0.75; Chi- squared test for trend).

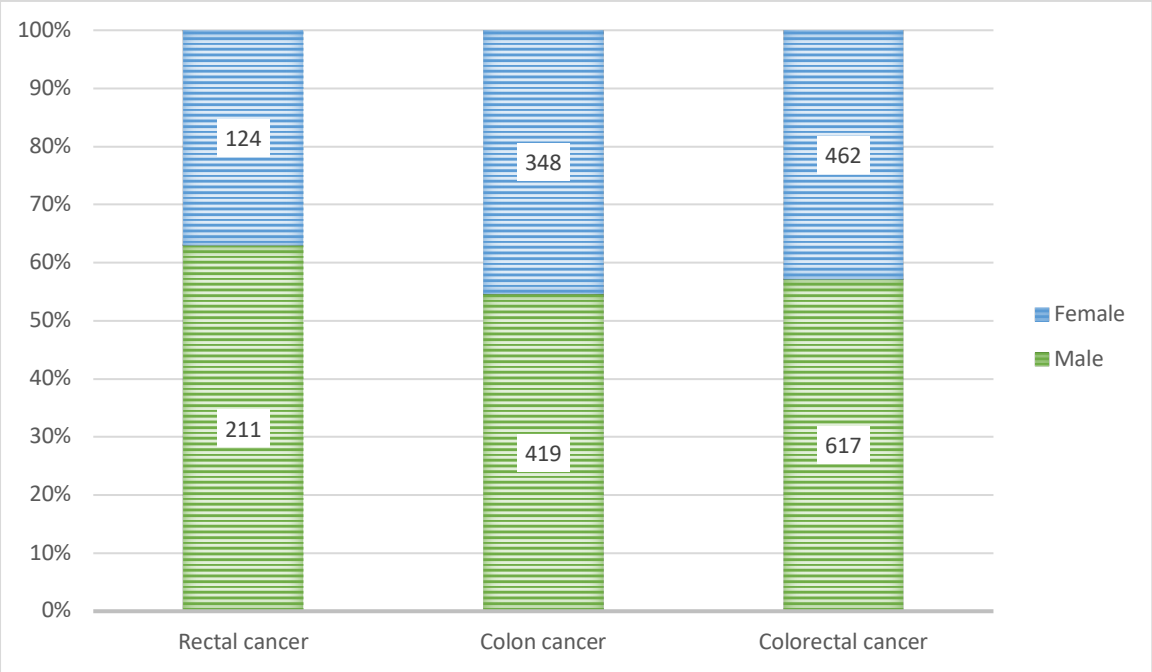

Figure 3.2 Gender distribution of colorectal cancer patients

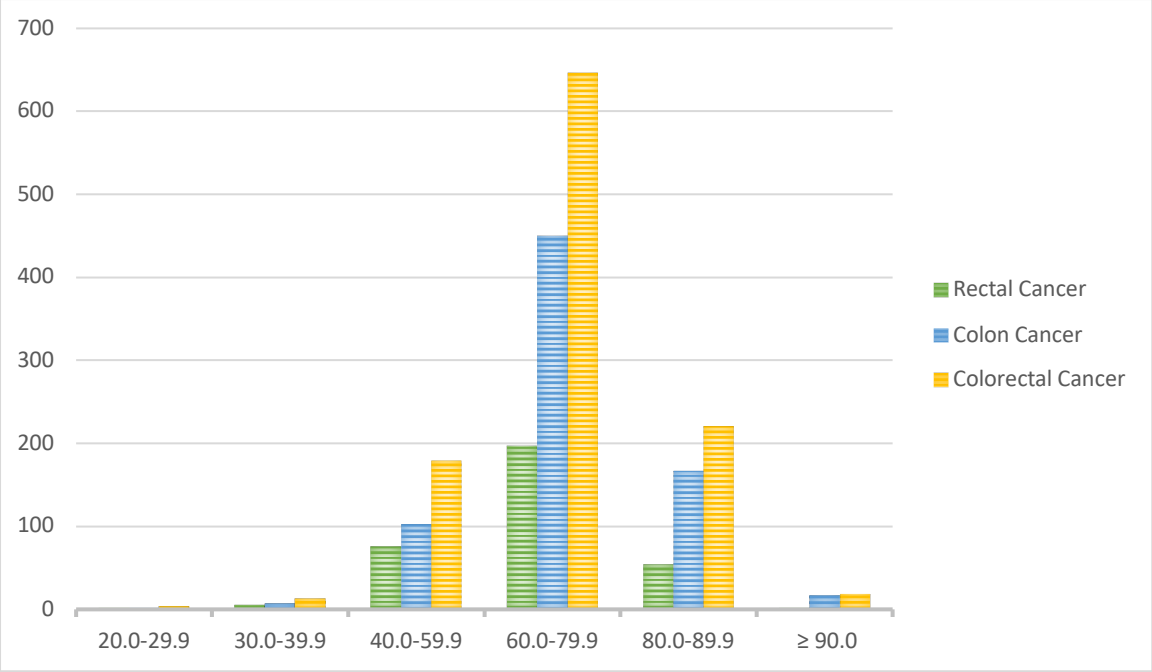

Figure 3.3 Age categories of colorectal cancer patients

Table 3.1 Emergency and elective colorectal cancer surgeries

Surgery	Colon	Rectum	Total
Emergency	202 (27.2%)	33 (9.9%)	235 (21.8%)
Elective	542 (72.8%)	302 (90.1%)	844 (78.2%)
Total	744	335	1079

Patient comorbidities, classified according to the Charlson Comorbidity Index (CCI)[137] were grouped as mild (CCI scores of 1-2), moderate (CCI scores of 3-4) or severe (CCI scores ≥ 5). Overall, 408 (38%) patients had no comorbidities, 415 (39%) had mild, 192 (18%) had moderate, and 64 (6%) had severe comorbidities (see Table 3.2). The percentage of patients with particular comorbidities were as shown in Table 3.3. The proportion of patients with severe comorbidities increased over the study period from 1/72 (1.4%) in 2002 to 9/95 (9.5%) in 2014 (p=0.015; Chi- squared test for trend).

Table 3.2 Charlson's comorbidity index for colorectal cancer patients

Charlson's Comorbidity Index	Number of patients (percentage of the cohort)
0	408 (37.7%)
1	239 (22.1%)
2	176 (16.4%)
3	111 (10.3%)
4	81 (7.5%)
≥5	64 (6.0%)

Table 3.3 Percentage of colorectal cancer patients with serious comorbidities

	Rectal cancer (%) N=335	Colon cancer (%) N=744	% of whole cohort with disease
Cardiac disease	92 (27.4%)	230 (30.9%)	29.8
Lung disease	68 (20.3%)	158 (21.2%)	20.9
Diabetes	59 (17.6%)	142 (19.1%)	18.6
Cerebrovascular disease	25 (7.5%)	104 (14.0%)	12.0
Renal disease	33 (9.9%)	75 (10.1%)	10.0
Vascular disease	24 (7.2%)	57 (7.7%)	7.5
Liver disease	16 (4.8%)	34 (4.6%)	4.6
Hematological cancer	7 (2.1%)	11 (1.5%)	1.7

The types of bowel surgeries performed are shown in tables 3.4 and 3.5. There were 838 (77.7%) patients who had a bowel resection with an anastomosis. Of these, 158 (18.9%) patients also received a diverting loop ileostomy. The lower the rectal cancer, the higher the rate of defunctioning stoma. The remaining 241 patients (22.3%) in the cohort had no anastomosis performed. The commonest non-anastomotic procedure was abdominoperineal resection, followed by Hartmann's procedure.

Table 3.4 Types of operation with anastomosis

Types of operation with anastomosis	Patients, n	Diverting loop (%)
Right hemicolectomy	312	0
Extended right hemicolectomy	52	1 (1.9%)
Right ileocolic resection	2	0
Transverse colectomy	2	0
Left hemicolectomy	28	0
Sigmoid resection	21	1 (4.8%)
Anterior High	175	16 (9.1%)
Anterior low	98	63 (64.2%)
Anterior Ultralow	76	75 (98.7%)
Subtotal colectomy	67	2 (3.0%)
Total colectomy	5	1 (20%)
Total	838	158 (18.9%)

Table 3.5 Types of operation without anastomosis

Types of operation without anastomosis	Patients, n
Right hemicolectomy + end ileostomy	11
Extended right hemicolectomy + end ileostomy	2
Left hemicolectomy + end ileostomy	2
Hartmann's	74
Hartmann's low	18
Hartmann's Ultralow	18
Subtotal colectomy + end ileostomy	8
Total colectomy + end ileostomy	9
Proctocolectomy + end ileostomy	5
Proctectomy + end ileostomy	2
APR	92
Total	241

A total of 21 surgeons performed these operations. The case- load mix of the surgeons is summarized in Table 3.6. Just over half (55%) of the operations were performed by three surgeons who did more than 10 colorectal cancer resections per year. Surgeons with higher caseloads treated a larger proportion of patients with rectal cancer; 131 (71%) patients with low rectal cancer had their operations (ultralow, abdominoperineal resection and completion proctectomy; n=184) performed by high volume surgeons.

Table 3.6 Distribution of patients and surgeons by surgeons' caseload

Surgeons Caseload	Patients n (%)	Surgeons n (%)
<10 cases per annum	481 (45%)	18 (86%)
>10 cases per annum	598 (55%)	3 (14%)
Total	1079	21

Overall, the number of tumours classified by stage were as follows: Stage I: 164 (15%); Stage II: 353 (33%); Stage III: 375 (35%); Stage IV: 187 (17%) (see Table 3.7). The stage distribution of cancers did not vary significantly during the study period (p= 0.21; Chi- squared test).

Table 3.7 TNM stages of colorectal cancer patients

TNM Stage	Tumour Site		Total
	Colon	Rectum	
I	101 (13.6%)	63 (18.8%)	164 (15.2%)
II	256 (34.4%)	97 (29.0%)	353 (32.7%)
III	244 (32.8%)	131 (39.1%)	375 (34.8%)
IV	143 (19.2%)	44 (13.1%)	187 (17.3%)
Total	744 (100.0%)	335 (100.0%)	1079 (100.0%)

3.4.2 Trends in adjuvant therapy

Overall, 232/375 (62%) patients with Stage III cancers, and 57/353 (16%) patients with Stage II cancers received adjuvant chemotherapy. There was no significant change over time in either group (p=0.19 for Stage III, P=0.61 for Stage II; Chi- squared test for trend). Palliative chemotherapy was given to 122/187 (65%) patients with Stage IV cancers, and this rate did not change significantly over time (p=0.59; Chi- squared test for trend). Among patients with rectal cancers, 89/335 (27%) have received neo- adjuvant chemoradiotherapy. This rate has increased significantly over time (p=0.039; Chi- squared test for trend).

3.4.3 Short-term outcomes

Peri-operative mortality (defined as death before discharge or within thirty days of surgery) occurred in 49/1079 (4.5%) patients during the study period. Peri-operative mortality was higher for emergency cases (21/235 (8.9%)) than elective cases (28/844 (3.3%); p=0.0009). At the beginning of the study period, there was a high peri-operative mortality rate of 8% in 2002 and 14% in 2003. Peri-operative mortality had decreased over the study period, maintaining below 5% since year 2007 (see Figure 3.4; p=0.028; Chi- squared test for trend).

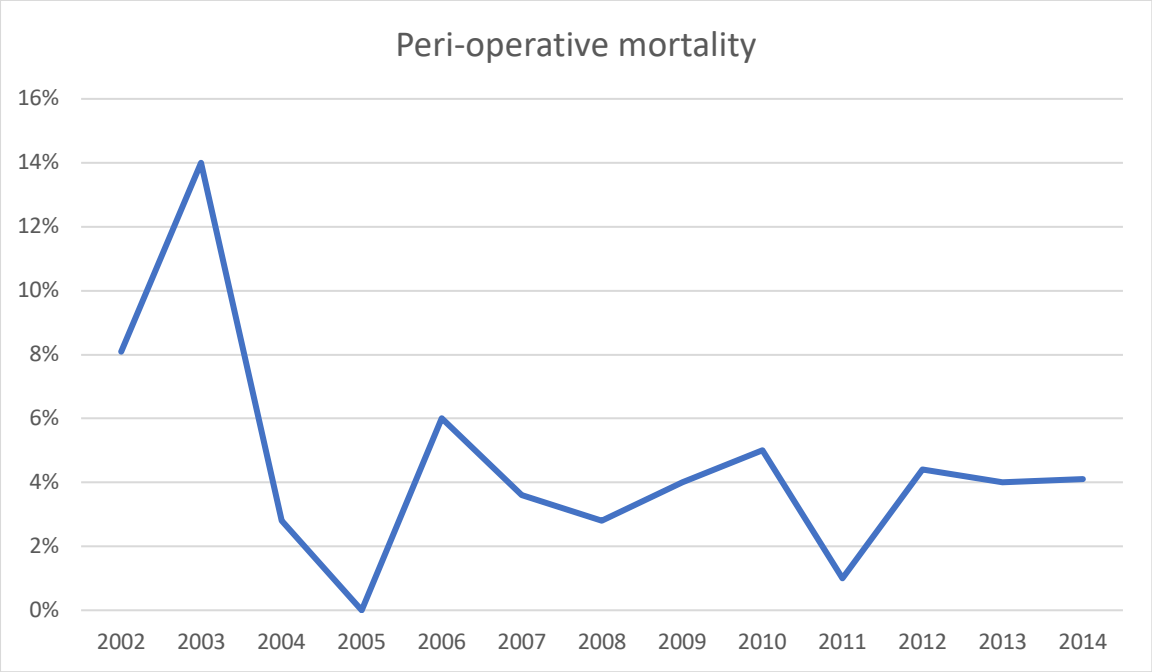

Figure 3.4 Peri- operative mortality rate per year over the study period. Note the steep decline in mortality that occurred between 2003 and 2004, and the consistently lower mortality rate thereafter.

Acute complications, defined as complications that occurred within 3 months of surgery, were categorized according to the Clavien-Dindo classification.[138] In the colon cancer group, 619 (83.2%) patients had curative operations while 125 (16.8%) patients had surgery with palliative intent. Overall, 322 (43.3%) had no complications, 264 (35.5%) had mild (Clavien-Dindo I and II) complications, and 117 (15.7%) had severe but non-fatal complications (Clavien-Dindo III and IV) that required either radiological, endoscopic, surgical or intensive care management (see Table 3.8). In the rectal cancer group, 293 (87.5%) patients had curative operations while the remaining 42 (12.5%) patients had operations with palliative intent. There were 133 (36.7%) patients that had no complications, 362 (40.9%) that had mild and 72 (19.9%) that had severe complications (see Table 3.9). Overall, complications occurred more commonly in emergency than elective operations (see Table 3.10).

Of the 1079 patients, 837 underwent a resection and primary anastomosis. Anastomotic leaks occurred in 54/837 (6.5%) of patients, and there was no significant variation in this rate over time (P=0.31; Chi- squared test).

Table 3.8 Complication post-colon cancer surgery categorized by Clavien-Dindo

Clavien-Dindo	Colon Cancer N = 744	
	Curative (N = 619)	Palliative (N = 125)
0	274	48
I	83	15
II	137	29
III	42	7
IV	59	9
V	24	17

Table 3.9 Complication post-rectal cancer surgery categorized by Clavien-Dindo

Clavien-Dindo	Rectal cancer N = 335	
	Curative (N = 293)	Palliative (N= 42)
0	103	14
I	48	7
II	79	7
III	32	10
IV	25	3
V	6	1

Table 3.10 Post-operative complications between emergency and elective surgeries

Postoperative complication	Emergency	Elective	P value
Yes	161 (68.5%)	479 (56.8%)	0.001
Surgical site infection	29 (12.3%)	88 (10.4%)	0.41
Anastomotic leak	12 (6.6%)	43 (6.6%)	1.00
Postoperative ileus	17 (7.2%)	58 (6.9%)	0.88
Mild complication (Clavien-Dindo I, II)	95 (40.4%)	310 (36.7%)	0.32
Severe complication (Clavien-Dindo III, IV)	45 (19.1%)	141 (16.7%)	0.38
Mortality (Clavien-Dindo V)	21 (8.9%)	28 (3.3%)	0.0006

3.4.4 Long- term survival

Kaplan-Meier estimates of long-term survival after surgery, grouped by tumour stage are illustrated in Figure 3.5. Median survival after surgery was 123 months for patients with Stage I, 141 months for Stage II, 76 months for Stage III, and 17 months for Stage IV cancers. The Kaplan-Meier estimate of overall median survival was 87 months, and there was a significant improvement in survival over the study period (p=0.0052; Cox proportional- hazards method (see Figure 3.6). Over the study period, long-term survival has improved over time for patients with Stage I (p=0.018) and Stage IV cancers (p=0.0025) but have remained constant for those with Stage II (p=0.81) and Stage III cancers (p=0.60; Cox proportional- hazards method). These improvements in long-term survival for Stage I and Stage IV were still apparent if patients that died peri-operatively were excluded from the analysis (p=0.38 and p=0.011 respectively). Two-year survival after surgery grouped by tumour stage is illustrated in Figure 3.7. Although there appeared to be a trend towards increasing two-year survival for patients with Stage IV tumours over the study period, this was not statistically significant (p=0.094; Chi- squared test for trend). Nor was there any significant change in two-year survival for Stage I (p=0.17), Stage II (p=0.84), Stage III (p=0.72) cancers or overall (p=0.19; Chi- squared test for trend).

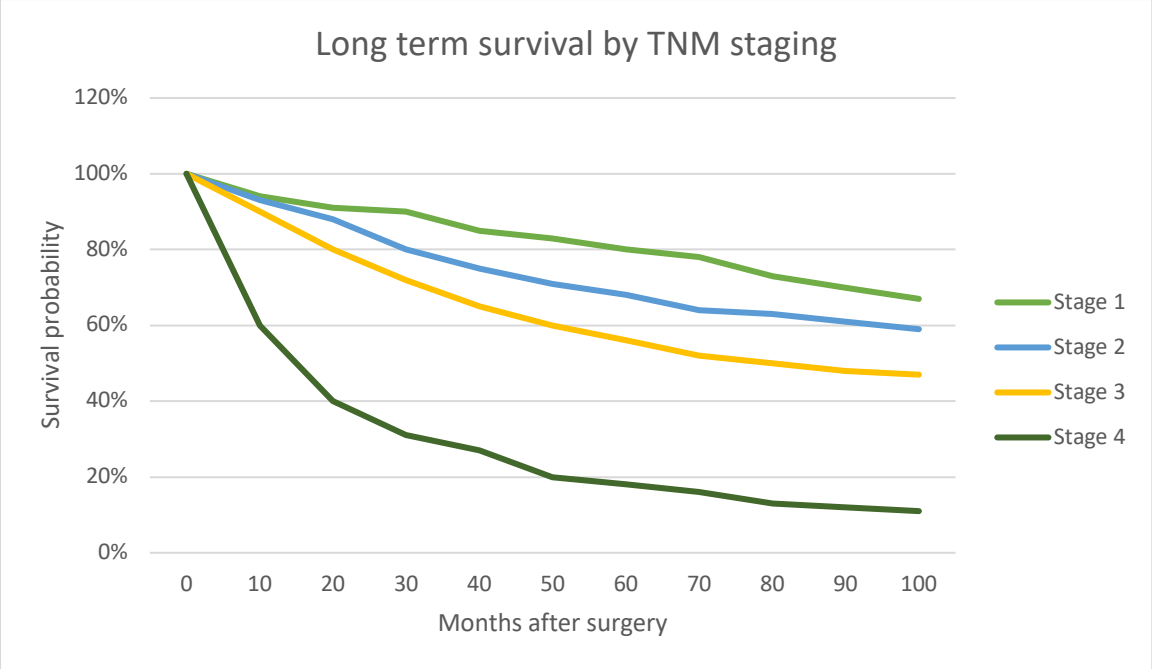

Figure 3.5 Kaplan- Meier estimates of long- term survival over time grouped by TNM stage at time of initial surgery.

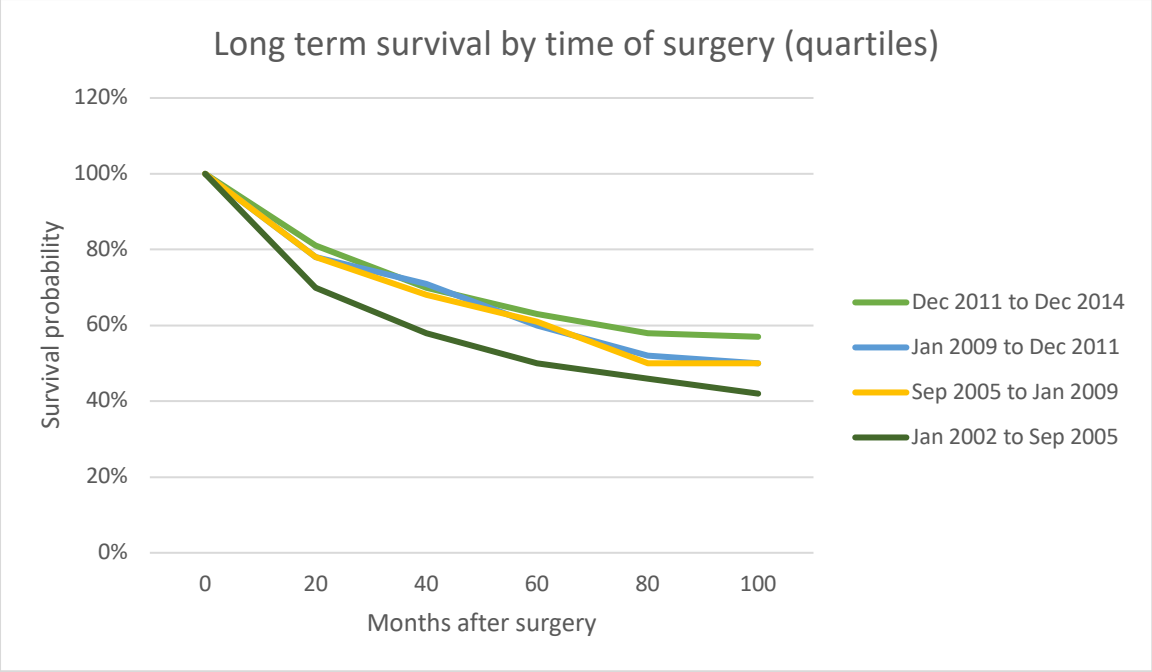

Figure 3.6 Long- term survival after surgery grouped by time of operation. The patients have been grouped into equal quartiles by date of surgery. The choice of quartiles is arbitrary to allow for easier reading of the graph. Long- term survival has improved over time (p=0.0052).

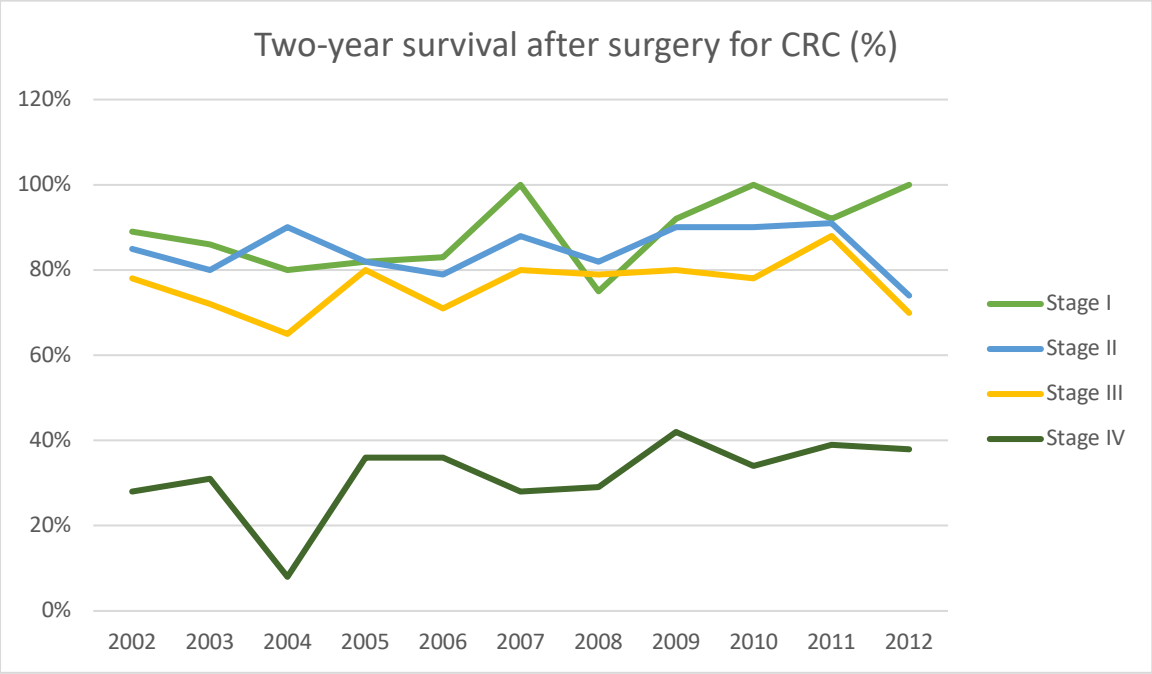

Figure 3.7 Two-year survival after surgery grouped by TNM stage.

3.5 Discussion

Over the study period, we found significant improvements in short and long- term survival for patients undergoing surgery for CRC at this regional institution. Peri-operative mortality has halved between 2002 and 2014, and long-term survival has improved overall. The survival rate has improved most significantly in patients with Stage IV CRC. The two-year survival after surgery is approximately 40%, comparable to the rates found in a large South Australian study on rural regional patients.[112] This improvement in survival has occurred despite an increasing proportion of comorbid patients undergoing surgery, and despite there being no change in tumour stage at diagnosis over the study period at UHG.

A number of changes have been instituted in the Department of Surgery at University Hospital, Geelong (UHG) that may have contributed to the improvement in peri- operative survival rates over the study period. In 2004, a formalised process of involuntary audit and feedback to individual surgeons was introduced in response to the high peri- operative mortality that occurred in 2003. Since that time, the peri- operative mortality rate has remained between zero and six percent annually. This intervention in this institution has been described previously[139-140] and has been shown to be beneficial elsewhere in Australia.[123] There has also been a significant shift towards surgical sub-specialisation in the department with more sub-speciality trained colorectal surgeons recruited. Over 90% of elective surgery for CRC is now performed by the colorectal surgical unit. There has also been a significant increase in the overall volume of CRC surgery. Intensive Care Unit (ICU) capacity has increased, and the indications for admission to ICU post-operatively have become more liberal. The introduction of dedicated emergency theatres at UHG previously been shown to improve the delivery of emergency surgery services generally.[141]

Approximately 60% of patients with Stage III CRC were given adjuvant chemotherapy, which is in keeping with Australian and international norms.[142-144] The significant improvement in long-term survival associated with adjuvant chemotherapy in this group of patients is well established,[145-146] and it has been routinely offered (in the absence of prohibitively advanced age or comorbidities) throughout the study period. Similarly, the proportion of patients with metastatic disease that received palliative chemotherapy has not changed over time. The benefit of adjuvant chemotherapy in the setting of Stage II cancers remains controversial and is seldom offered at the UHG.

The rates of administration of adjuvant and palliative chemotherapy have remained constant despite the introduction of colorectal multidisciplinary team (MDT) meetings in 2006 (as previously described).[147] The choice of chemotherapy agents has, however, expanded over the study period. Specifically, bevacizumab became available in 2009, and cetuximab and panitumumab have been available since 2011. These agents have been shown to improve survival in selected patients with metastatic CRC.[148-150] The changes in systemic therapy for patients with metastatic disease provide the most likely explanation for the overall improvement in long-term survival (beyond the peri-operative phase) in this institution over the study period.

It is difficult to draw clear causal conclusions from this study, as multiple changes have been made in this practice over the study period, and this is a retrospective audit with all of the limitations inherent in that methodology. It is encouraging, however, that the reported improvements in short and long-term oncological outcomes have been replicated within the institution.

3.6 Conclusion

This study has looked into the demographics, morbidity and mortality outcomes following colorectal cancer surgery in a regional centre in Victoria. The quality of surgical care in this centre, illustrated by its mortality rate, leak rate and survival analysis were all comparable to the Australian benchmarks. Both short and long-term survival after surgery for CRC have improved in the institution. With the evolution seen in all aspects of CRC treatment, a more comprehensive collection and analysis of multi-centre data is required to enable further assessment of the long-term trends in rural regional Australia for ongoing quality assurance.

Anastomotic leaks in Stage IV colorectal cancer

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ANZ J Surg. 2018 Sep;88(9):E649-E653

4.1 Abstract

Aim:

The purpose of this study was to determine the anastomotic leak rate for colorectal cancer resections in patients with metastases (compared to those without), and to determine the impact of anastomotic leaks on survival.

Method:

This is a retrospective analysis of all patients who underwent resection and primary anastomosis for colorectal adenocarcinoma at a single institution between January 2002 and December 2014.

Results:

A total of 843 patients underwent a resection and primary anastomosis for colorectal adenocarcinoma (661 colon, 182 rectal). Of these, 135 (16%) had metastases and 708 (84%) did not. Anastomotic leaks occurred in 17/ 135 (13%) patients with metastases, and in 37/798 (5.2%) without metastases (p=0.003). Peri- operative mortality occurred in 13/135 (9.6%) of patients with metastases, compared with 19/708 (2.7%) for patients without metastases (p=0.0003). Anastomotic leak was associated with a reduction in overall survival (median survival 121 months without anastomotic leak vs. 66 months in patients who had an anastomotic leak (p=0.02). Patients who died peri- operatively were excluded from this analysis. However, the long- term mortality was similar (125 months vs. 101 months; p=0.70).

Conclusion:

Metastatic disease was associated with an increased risk of anastomotic leak and a higher peri- operative mortality rate after colorectal resections for cancer. Patients with anastomotic leaks had a higher peri- operative mortality rate, but long- term survival was unaffected beyond the peri- operative phase.

4.2 Introduction

Approximately 20 to 25% of patients with colorectal cancer have metastases at the time of their initial presentation, and the majority of these are not amenable to resection with curative intent.[151]

There is ongoing controversy regarding the optimal management of the primary tumour in patients with colorectal cancer and distant metastases. In those patients with incurable metastatic disease in whom the primary tumour is minimally symptomatic or asymptomatic, resection of the primary carries significant risks for mortality or morbidity, and it is uncertain whether resecting the primary tumour confers any survival benefit.[152-153] In patients who have metastatic disease which is potentially amenable to curative resection, there is also ongoing debate as to the optimal approach in terms of the timing and order of resection of the primary tumour and of the metastatic disease.[154] Of particular relevance to this debate is the concern that anastomotic leaks may lead to an unacceptable delay in commencing chemotherapy, with the potential to deleteriously affect long- term survival.

Optimal decision-making regarding resection of the primary tumour, as well as whether a primary anastomosis should be performed, for the patient with colorectal cancer and metastatic disease (whether potentially curative or for the purpose of palliation) requires knowledge of the risks and potential consequences of anastomotic leakage.
The purpose of this study was to determine the anastomotic leak rate for colorectal cancer resections in patients with known metastatic disease (compared to those without

metastases), and to determine the impact of anastomotic leaks on survival in this group of patients.

4.3 Study design and methodology

This is a retrospective analysis of a prospectively maintained database of all colorectal operations performed at University Hospital, Geelong (a regional teaching hospital in Victoria, Australia). All patients who underwent a resection and primary anastomosis for colorectal adenocarcinoma from 1 January 2002 until 31 December 2014 were included and followed up until 31 December 2015.

Patient demographics and tumour characteristics were recorded. Comorbidities were scored using the Elixhauser comorbidity score. Resections were grouped as right colon (as far distal as the distal transverse colon), left colon (splenic flexure to rectum), subtotal colectomy or rectum.

Anastomotic leaks were diagnosed clinically (by digital examination in the case of low anastomoses), radiologically or at re- operation. Contrast studies were not routinely done following surgery- imaging was only performed if clinically indicated. Whenever it was uncertain from the 2015 clinical records whether a patient was still alive, direct contact was made with the patient, his family or his general practitioner to confirm survival status. Peri-operative mortality was defined as any death within thirty days of surgery or prior to discharge from hospital.

Categorical data were compared using the two- sided Fisher's exact test or Pearson's chi-square test as appropriate. Ordinal data were compared using the Student's T-test (for parametric data) or the Mann- Whitney test (for non- parametric data). Long- term survival

was calculated using the Kaplan- Meier technique and compared using the logrank method. A p-value of <0.05 was regarded as significant. Multivariate analysis was done using a binary logistic regression model (step forward method; P for factor entry set at 0.05, P for removing factor 0.10). A p-value of 0.05 was considered significant.

The study was approved by the Research Ethics, Governance & Integrity (REGI) Unit for University Hospital, Geelong.

4.4 Results

4.4.1 Demographics

During the study period, 843 patients underwent a resection and primary anastomosis for colorectal adenocarcinoma. There were 661 patients with colonic cancers and 182 with rectal cancers. Of these, 135 (16%) had known metastatic disease at the time of surgery, whilst 708 (84%) did not. Of the patients with metastases, only 19/135 (14%) were assessed as having potentially curable disease at initial presentation. Patients with and without metastases were similar in age, gender and smoking status. The patients with metastases had lower Elixhauser comorbidity scores ($p=0.005$, Mann- Whitney test), and were more likely to present as emergencies ($p<0.0001$)). A higher proportion of rectal cancer resections occurred in the group without metastases ($p=0.0039$). Diverting stomas were constructed in a higher proportion of patients without metastases ($p=0.015$), however this reflects the higher proportion of rectal resections in the group without metastases, and there was no difference between the groups when rectal ($P=0.89$) and colonic tumours ($p=0.55$) were considered separately. These findings are summarised in Table 4.1. The sites of metastatic disease are presented in Table 4.2.

Table 4.1: Patient characteristics.

	With metastases N=135	Without metastases N=708	P value
Male: Female	72:63	399:309	0.58
Age (Mean, 95% C.I.)	71 (70-72)	69 (67-72)	0.23
Elixhauser comorbidity score (Median, 95% C.I.)	2 (1-2)	2 (2-2)	0.005*
Smoker (current or past)	66 (49%)	314 (44%)	0.38
Emergency presentations	44/135 (33%)	107/708 (15%)	<0.0001*
Site of tumour			
Colon	119/135 (88%)	542/708 (77%)	
Rectum (include rectosigmoid)	16/135 (12%)	166/708 (23%)	0.0039*
Type of resection (colon tumours)			0.009*
Right colon	77 (65%)	294 (54%)	
Left colon	13 (11%)	38 (7%)	
Total/ subtotal colectomy	12 (10%)	56 (10%)	
Anterior resection	17 (14%)	155 (29%)	

Total	*119*	*542*	
Type of resection (rectal tumours)			0.42*
High anterior	1 (6%)	31 (19%)	
Low anterior	8 (50%)	69 (42%)	
Ultralow anterior	6 (38%)	63 (38%)	
Proctocolectomy	1 (6%)	3 (2%)	
Total	*16*	*166*	
Diverting stoma fashioned	15 (11%)	145 (22%)	0.015*
Diverting stoma (colon tumours)	4/116 (3%)	28/514 (5%)	0.55
Diverting stoma (rectal tumours)	11/16 (69%)	117/166 (70%)	0.89

NB: Overall there were more diverting stomas in the M0 group (145/708 (20%) vs. 15/135 (11%), p=0.015) but this is due to the higher percentage of rectal cancers in the M0 group. No difference when rectum and colon considered separately.

Table 4.2: Sites of metastatic disease.

Site	Number (Total 135)
Liver	61(45%)
Peritoneal	18 (13%)
Non- regional nodes	15 (11%)
Lung	10(7%)
Adrenal	1 (0.7%)
Spine	1 (0.7%)
Abdominal wall	1 (0.7%)

4.4.2 Peri- operative mortality

The overall peri-operative mortality rate was 32/843(3.8%). Peri- operative mortality rates grouped by potential risk factors are summarised in Table 4.3. The presence of metastases was associated with a higher peri-operative mortality rate (13/135 (9.6%) for patients with metastases vs. 19/708 (2.7%) for those without; relative risk 3.6; P=0.0003). This difference in peri- operative mortality was observed in patients who underwent elective operations (11/91 (12%) for patients with metastases vs. 12/601 (2.0%) for those without metastases; relative risk 6.0; p<0.0001), but not in the emergency surgery group (2/44 (4.5%) with metastases vs. 7/107 (6.5%) without metastases; p=0.93). On multivariate analysis, age at surgery and the presence of metastases were confirmed as independent predictors of mortality. None of the other potential risk factors listed in Table 4.3 were independent predictors of mortality.

Table 4.3 Peri- operative mortality rates

	Perioperative mortality group (n=32)	Perioperative survivors (n=811)	Analysis technique	P- value
Metastases				
Yes	13 (10%)	122 (90%)	Fisher's exact	<.001
No	19 (3%)	689 (97%)		
Age				
Median (IQR)	79 (75 – 83)	72 (63 – 79)	Mann-Whitney	<.001
Admission				
Emergency	9 (6%)	142 (94%)	Fisher's exact	.154
Elective	23 (3%)	669 (97%)		
Surgical site				
Colon	30 (5%)	631 (95%)	Fisher's exact	.028
Rectum	2 (1%)	180 (99%)		
Operation group				
High anterior	5 (3%)	173 (97%)	Pearson chi-squared	.112
Low anterior	2 (2%)	94 (98%)		

Right colon	15 (4%)	355 (96%)		
Subtotal/total	6 (8%)	65 (92%)		
Left colon	4 (8%)	48 (92%)		
Ultralow anterior	0 (0%)	76 (100%)		
Defunctioning stoma				
Yes	1 (0.6%)	159 (99.4%)	Fisher's exact	.019
No	31 (4.5%)	652 (95.5%)		

4.4.3 Anastomotic leaks

There were 54 anastomotic leaks in the 843 patients who had anastomoses performed (6.4%). Anastomotic leak rates grouped by potential risk factors are summarised in Table 4.4. In patients with metastases at presentation, leaks occurred in 17/135 (13%) patients, compared with 37/708 (5.2%) for those without metastases (Relative risk 2.5; p=0.0026). In the subgroup of patients who underwent elective surgery, leaks occurred in 11/91 (12%) of patients with metastases, and 32/601 (5.3%) of patients without metastases (relative risk 2.3; p=0.024). In the subgroup who underwent emergency surgery, however, leak rates were similar for patients with or without metastases (6/44 (14%) vs. 5/107 (4.7%); p=0.11). Diverting stomas were constructed in a total of 160/843 (19%) of cases. Anastomotic leak rates were similar for patients with or without diverting stomas (8/160 (5.0%) in patients with a diverting stoma, and 41/629 (6.7%) without (p=0.48)). On multivariate analysis, the presence of metastases was confirmed an independent predictor of anastomotic leakage. None of the other potential risk factors listed in Table 4.4 were independently predictive of anastomotic leak.

Table 4.4 Anastomotic leak rates

	Anastomotic leak (n=54)	No anastomotic leak (n=789)	Analysis technique	P-value
Metastases				
Yes	17 (13%)	118 (87%)	Fisher's exact	0.003
No	37 (5%)	671 (95%)		
Age				
Median (IQR)	72 (67 – 78)	72 (63 – 79)	Mann-Whitney	0.852
Admission				
Emergency	11 (7%)	140 (93%)	Fisher's exact	0.586
Elective	43 (6%)	649 (94%)		
Surgical site				
Colon	42 (6%)	619 (94%)	Fisher's exact	0.865
Rectum	12 (7%)	170 (93%)		
Operation group				
High anterior	8 (4%)	170 (96%)		0.176

Low anterior	7 (7%)	89 (93%)	Pearson chi-squared	
Right colon	22 (6%)	348 (94%)		
Subtotal/total	9 (13%)	62 (87%)		
Left colon	5 (10%)	47 (90%)		
Ultralow anterior	3 (4%)	73 (96%)		
Diverting stoma				
Yes	8 (5%)	152 (95%)	Fisher's exact	0.478
No	46 (7%)	637 (93%)		
Elixhauser score				
Median (IQR)	3 (1 – 4)	2 (1 – 3)	Mann-Whitney	0.074

4.4.4 Long-term survival

The median survival after surgery was 167 months for patients without metastases, and 17 months for patients with metastases (P<0.0001). Anastomotic leak was associated with a significant reduction in overall survival (median survival 121 months for patients without anastomotic leak vs. 66 months in patients who had an anastomotic leak (p=0.016, Figure 4.1). If the patients who died peri- operatively are excluded from this analysis, however, long-term survival was similar between these groups (125 months for patients without anastomotic leak vs. 101 months in those with anastomotic leak; p=0.70). In the group of patients with metastatic disease, there was a similar trend to decreased survival in patients with anastomotic leaks (median survival 18 months for patients without anastomotic leak vs. 7.5 months for those with anastomotic leak; p=0.08), and long- term survival was similar if patients who died peri- operatively are excluded from the analysis (19 months for those without anastomotic leak vs 17 months for those with anastomotic leak; p=0.85).

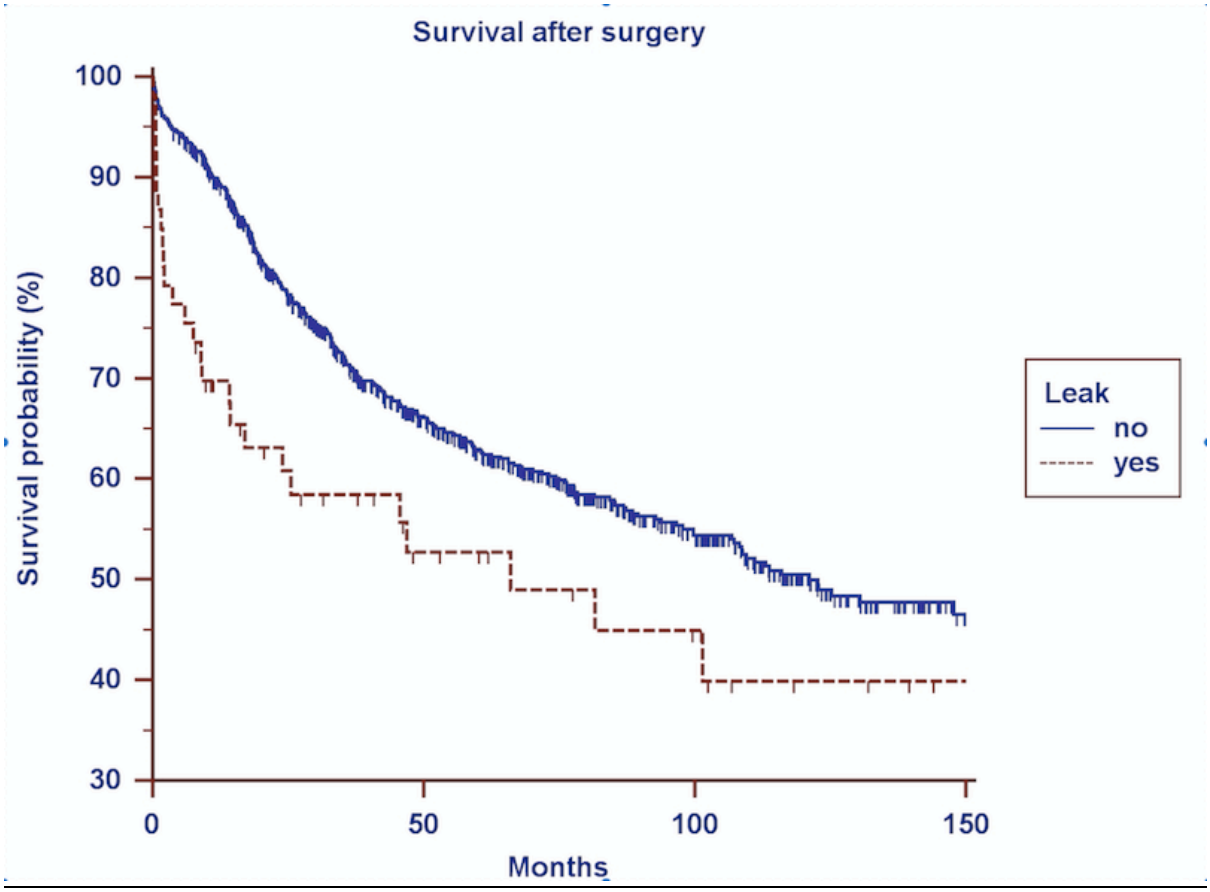

Figure 4.1 Survival after surgery

4.5 Discussion

Patients who underwent colorectal cancer resections with a primary anastomosis for colorectal cancer were almost three times more likely to have an anastomotic leak if they had metastases at the time of surgery than if they were operated on in the absence of known metastatic disease. The presence of metastases at the time of surgery was also associated with a four times higher peri- operative mortality rate. In patients with metastatic disease, anastomotic leak was associated with a high peri- operative mortality rate, but anastomotic leak did not appear to affect long- term survival beyond thirty days.

A large prospective Australian study by Sammour et al.[155] found no significant difference in the 5-year overall survival for colorectal cancer patients whose had anastomotic leak versus those who had not, after correcting for confounding factors including age, gender, ASA score, cancer stage, and after the exclusion of early deaths within 120 days (early deaths were accounted for by septic complications resulting from anastomotic leak). This finding was supported by another Western Australian study on patients undergoing ultra-low anterior resection for rectal cancer which reported no significant difference in either the long-term survival or local recurrence rate between those who did and did not have a leak.[156]

There is not only great variability in the reported anastomotic leak rates after colorectal resection, but there is also conflicting evidence as to how the presence of metastases influences the risk of leak. A recent meta- analysis including 22 studies of anastomotic leak rates following low anterior resections for rectal cancer reported rates of 3% to 28%, with a total of 974/10,343 (9%) suffering anastomotic leaks.[157] Alves et al reported anastomotic

leaks in 43/707 (6%) colorectal resections with primary anastomosis for cancer.[158] They described a number of risk factors for anastomotic leak, but did not examine whether metastases influenced this risk. Nikolian et al. recently reported a much lower anastomotic leak rate of 2.7% (244/9192) in an American series of colorectal resections for all indications, though their analysis of risk factors did not include metastases.[159] Bakker et al, reported an anastomotic leak rate of 1176/15667 (7.5%) for colorectal cancer resections with primary anastomoses in the Dutch colorectal audit;[160] but they did not find tumour stage to be associated with anastomotic leak in 131/1785 (7.3%) patients with stage IV disease, compared with 1045/13883 (7.5%) patients with stage I-III cancers).[160] However, a Swiss retrospective study reported a four- fold higher rate of anastomotic leakage after colorectal resections for cancer in patients with metastatic disease (6/94 (6.3%) vs. 7/406 (1.7%).[161]

In patients with colorectal cancer with potentially resectable liver metastases, there is ongoing controversy regarding the optimal surgical approach. Traditionally, the primary tumour has been resected first, and the metastases, when there are appropriate indications, resected later. Recently there are advocates for other approaches, including synchronous bowel and liver resections or performing the liver resection first (sometimes following neo adjuvant therapy) with later resection of the primary tumour.[154] One argument against operating on the primary tumour first is the concern that anastomotic leakage may lead to significant delays in chemotherapy or metastasectomy.

There is also ongoing controversy regarding the benefit of resecting the primary tumour in patients with colorectal cancer and non- resectable metastases. Scogins et al published the first paper which compared outcomes for primary resection versus a non- operative

approach for colorectal cancer with non- resectable metastases.[162] They compared 66 patients who had undergone resection of the primary tumour, with 23 who did not. They reported 5% mortality and 30% morbidity rates for surgery, but no survival advantage was conferred by resecting the primary tumour. In the non- operative group, only 2/23 patients developed bowel obstruction requiring later surgery, and none were complicated by significant bleeding or perforation of the tumour. A later meta- analysis of short-term outcomes after resection or non-operative management of primary colorectal cancers in the presence of non-resectable metastases pooled the outcomes for 850 patients, 536 of whom were treated surgically initially.[163] The overall surgical mortality rate was 3% (ranging from 0 to 5% in the reviewed studies) with an overall surgical morbidity rate of 12% (ranging from 19% to 47% in the reviewed studies).

In a large meta- analysis of 21 studies, Clancy et al concluded that resection of the primary tumour may confer a long- term survival benefit to patients with colorectal cancer and non-resectable metastases. [152] However, all current studies are subject to significant selection bias, as they are all retrospective. Cirocchi et al published a Cochrane review examining the seven studies of patients with incurable metastases and asymptomatic primary tumours (in which group the decision to operate or not is typically more controversial).[153] They found no evidence that resecting the primary tumour improves survival in these patients, nor did it appear to reduce the likelihood of requiring later emergency surgery. No randomized trials have addressed these questions to date.

Recent improvements in chemotherapy have increased survival for patients with incurable colorectal cancer, which may increase the risk of complications from the primary tumour

occurring over time. The introduction of agents such as bevacizumab may also directly increase the risk of complications (particularly bleeding) from the primary tumour. This question was specifically addressed in the NSABP C-10 trial[164] - a prospective cohort study of 90 patients who received FOLFOX6 chemotherapy with bevacizumab for patients with colon cancer with non- resectable metastases in whom the primary tumour was not resected. After two years, the overall rate of major morbidity related to the primary tumour was 16%. Two patients died from complications of their primary tumour, and one patient died. The authors concluded that this approach did not compromise survival, nor did it result in an unacceptable rate of complications from the primary tumour, so 'these patients can be spared initial non- curative resection of their asymptomatic primary.

This study was limited by being retrospective, with selection bias affecting the outcomes presented. The patients with metastases were more likely to have emergency surgery than the group without metastases, and this may partly explain the higher anastomotic leak rate. On the other hand, the patients with metastases who were selected for resection and primary anastomosis were less likely to have significant comorbidities, and were less likely to have rectal resections than the group without metastases. These factors would be expected to contribute to a lower anastomotic leak rate in the group with metastases relative to those without metastatic disease. The number of anastomotic leaks was too small to allow meaningful subgroup analyses for emergency vs. elective or for rectal vs. colonic operations.

4.6 Conclusion

In conclusion, metastatic disease increases the risk of anastomotic leak after colorectal resections with primary anastomoses. Although those with leaks had a higher peri-operative mortality rate, long- term survival was unaffected for those who survived beyond the peri-operative phase.

Metastatic progression of colorectal cancer in a regional setting

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This chapter has been submitted to

ANZ Journal of Surgery for publication

5.1 Abstract

Background:

Understanding of the risk of metastatic progression in colorectal cancer can help to inform decisions and determine follow up for colorectal cancer patients.[163] To date, only one study in NSW had described the patterns of progression to metastatic disease in Australia.[163]

Aim:

This study primarily aims to evaluate the patterns and risk factors of metastatic progression for colorectal cancer in regional Victoria. The secondary aim is to assess if the identified risk factors are similar to those of the NSW population.

Methods:

All non-metastatic CRC patients who underwent curative resection from Jan 2002 - Dec 2009 at University Hospital, Geelong, were retrospectively recruited into this study from a database which was maintained prospectively. Patients were followed until December 2014 for subsequent metastases. The annual hazard ratio (aHR) for metastatic CRC was derived from the annual rate of failure by the initial stage at diagnosis. Cox regression analysis was performed to establish factors associated with progression to metastatic disease.

Results:

There were 345 and 158 patients diagnosed with non-metastatic (stage I-III) colon and rectal cancer respectively between 2002-2009. Metastatic progression was significantly higher for patients with stage III disease (colon cancer - aHR 4.42; rectal cancer - aHR 3.34), for patients

with severe comorbidities (aHR 2.18), colon cancer patients with lowest socioeconomic status (aHR 2.03), and lymphovascular invasion (aHR 2.94). Gender difference, tumour location, and geographical location did not show any statistically significant effects on metastatic progression.

Conclusion:

The patterns and risk factors for metastatic CRC disease progression within a region in Victoria, were different from those seen in NSW.[166] It is necessary to assess a wider sample of the Victorian population before determining surveillance strategies for the higher-risk patient groups in Victoria.

5.2 Introduction

Colorectal cancer (CRC) is estimated to be the third most common cancer, and the second leading cause of cancer-related death in Australia in 2019.[165] At the time of initial diagnosis, 10-35% of patients will have clinically detectable metastasis.[166] A further 30-40% of patients will eventually develop metastasis after curative resection of their primary tumour.[167] Metachronous metastases remain the main reason for CRC-related death. Despite improvements in chemotherapy regimens and aggressive resection of metastatic CRC, the 5-year mortality is approximately 15%.[167] Thus, the ability to predict the risk of metastatic progression could improve surveillance strategies. Luo et al. in 2016 published an analysis of localised and regional CRC progression to metastatic disease, and the influence of sociodemographic status and disease characteristics on the risk of metastatic progression within a New South Wales (NSW), Australia population.[168] It is, however, uncertain if these patterns could be extrapolated and applied to other regions of Australia.

5.3 Methods

This study is a retrospective analysis of a prospectively maintained colorectal cancer database from Barwon Health, Geelong (a regional university hospital in Victoria). All patients who underwent resection for non-metastatic colorectal cancer with curative intent from 1 January 2002 until 31 December 2009 were included. There were 528 CRC cases (364 colon cancer, 164 rectal cancer), of which 25 cases died within four months of diagnosis and therefore excluded. The last date of follow up was 31st December 2014 for subsequent metastatic progression. This study was approved by the Research Ethics, Governance & Integrity (REGI) Unit for University Hospital, Geelong.

Patient demographics were recorded along with the socioeconomic status (SES) based on the patient's residential postcode at diagnosis. Comorbidities were scored using the Charlson comorbidity index (CCI) and classified as mild (CCI scores of 1-2), moderate (CCI scores of 3-4), or severe (CCI scores ≥ 5). The geographical location of residence at diagnosis was classified as major cities, inner regional, and outer regional, according to the Australian Standard Geographical Classification Remoteness Structure.[167] The Index of Relative Socio-Economic Disadvantage derived from the 2001 Census grouped scores based on levels of education, employment and housing into quintiles, providing estimation for the level of SES.[168]

Disease characteristics included the year of diagnosis, the stage at diagnosis, primary tumour location, and the need for adjuvant or neo- adjuvant chemo or radio- therapy. The stage of tumour was recorded according to the TNM staging system, based on histopathology and

perioperative imaging. The stage at diagnosis was defined as the highest degree of spread within four months after initial diagnosis (as defined by the Victorian Cancer registry). Subsequent metastatic disease was identified beyond four months following the initial diagnosis by reviewing the hospital's electronic medical records (BOSSnet) for radiology results, clinic follow-up notes, or by speaking to the patients, their general practitioners, or next of kin.

The time to development of metastatic disease was calculated from the date four months after the initial CRC diagnosis. Patients had lifelong clinical follow up wherever possible. When patients were lost to clinical follow up (73 patients), attempts were made to contact the patient or their family or general practitioner to confirm if they were alive and if metastatic recurrence had occurred.

Colon and rectal cancers were analysed separately. The cumulative incidence for metastatic progression and the differences in time to metastatic disease by initial stage at diagnosis were estimated using Kaplan Meier and log-rank test. The annual hazard ratio (aHR) for metastatic CRC was derived from the annual rate of failure by the initial stage at diagnosis. Cox regression analysis was used to identify the risk factors associated with metastatic progression. All analysis was performed using Medcalc software. $P<0.05$ was considered statistically significant in a multivariate model.

5.4 Results

5.4.1 Patient demographics and risk analysis

This study included 503 patients diagnosed with non-metastatic (Stage I-III) CRC during 2002-2009 (Table 5.1). Of these, 345 were diagnosed with colon cancer (58.8% localised, 41.2% regional) and 158 with rectal cancer (55.1% localised, 44.9% regional). The median age of diagnosis was 72.4 years for colon cancer and 70.1 years for rectal cancer. Overall, 201 (40.0%) patients had no comorbidities, 196 (39.0%) had mild, 80 (15.9%) had moderate and 26 (5.1%) had severe comorbidities.

After a median follow up of 6.2 years (range 0.2 – 13.0), 117 (23.3%) patients were diagnosed with distant recurrent disease. Of these, 89 (54 colon cancer, 35 rectal cancer) patients had detectable metastases within three years from initial diagnosis, and 16 patients had detectable metastases between 3 to 5-years (11 colon cancer, 5 rectal cancer). Twelve patients (7 colon cancer, 5 rectal cancer) were diagnosed with metastatic disease beyond 5 years.

The overall cumulative metastatic CRC incidence was 20.9% at 5 years and 23.3% at 10 years. For both colon and rectal cancer, Stage III cases had a significantly higher cumulative incidence of metastatic disease than those with Stage I / II (Figure 5.1 and 5.2). This was also consistent with a higher annual hazard ratio for metastatic CRC (Figure 5.3 and 5.4). The annual hazard for metastatic progression decreased significantly over time for those patients with Stage III disease, and after 5 years, it is observed to demonstrate convergence with annual hazard ratios in patients diagnosed with Stage I and II disease.

Table 5.1: Baseline characteristics of colorectal cancer patients

Characteristics	Cancer type				Total number of cases	
	Colon		Rectal			
	n (% within cancer type)				n (% within total)	
Age at diagnosis (years)						
<60	49	(14.2)	36	(22.8)	85	(16.9)
60-69	93	(27.0)	41	(25.9)	134	(26.6)
70-79	132	(38.2)	61	(38.6)	193	(38.4)
80+	71	(20.6)	20	(12.7)	91	(18.1)
Sex						
Male	187	(54.2)	97	(61.4)	284	(56.5)
Female	158	(45.8)	61	(38.6)	219	(43.5)
Charlson Comorbidity Index						
None (score 0)	130	(37.7)	71	(44.9)	201	(40.0)
Mild (score 1-2)	134	(38.8)	62	(39.2)	196	(39.0)
Moderate (score 3-4)	63	(18.3)	17	(10.8)	80	(15.9)
Severe (score ≥ 5)	18	(5.2)	8	(5.1)	26	(5.1)

Year of Diagnosis						
2002-2005	151	(43.8)	72	(45.6)	223	(44.3)
2006-2009	194	(56.2)	86	(54.4)	280	(55.7)
Geographical location						
Major cities	217	(62.9)	107	(67.7)	324	(64.4)
Inner regional	118	(34.2)	48	(30.4)	166	(33.0)
Outer regional	10	(2.9)	3	(1.9)	13	(2.6)
Socio-economic status						
1st quintile (most disadvantage)	83	(24.0)	41	(25.9)	124	(24.6)
2nd quintile	80	(23.2)	32	(20.3)	112	(22.2)
3rd quintile	26	(7.5)	14	(8.9)	40	(8.0)
4th quintile	132	(38.3)	56	(35.4)	188	(37.4)
5th quintile (least disadvantage)	24	(7.0)	15	(9.5)	39	(7.8)
Stage at diagnosis						
I	64	(18.6)	36	(22.8)	100	(19.9)
II	139	(40.3)	51	(32.3)	190	(37.8)
III	142	(41.1)	71	(44.9)	213	(42.3)

Primary tumour location						
Sigmoid colon	134	(38.9)				
Caecum and appendix	65	(18.8)				
Ascending / hepatic flexure of colon	59	(17.1)				
Transverse colon	49	(14.2)				
Splenic flexure / descending colon	32	(9.3)				
Synchronous	6	(1.7)				
Rectosigmoid			27	(17.1)		
Rectum			131	(82.9)		
Type of surgery						
Elective	274	(79.4)	146	(92.4)		
Emergency	71	(20.6)	12	(7.6)		
Total	345	(100.0)	158	(100.0)	503	(100.0)

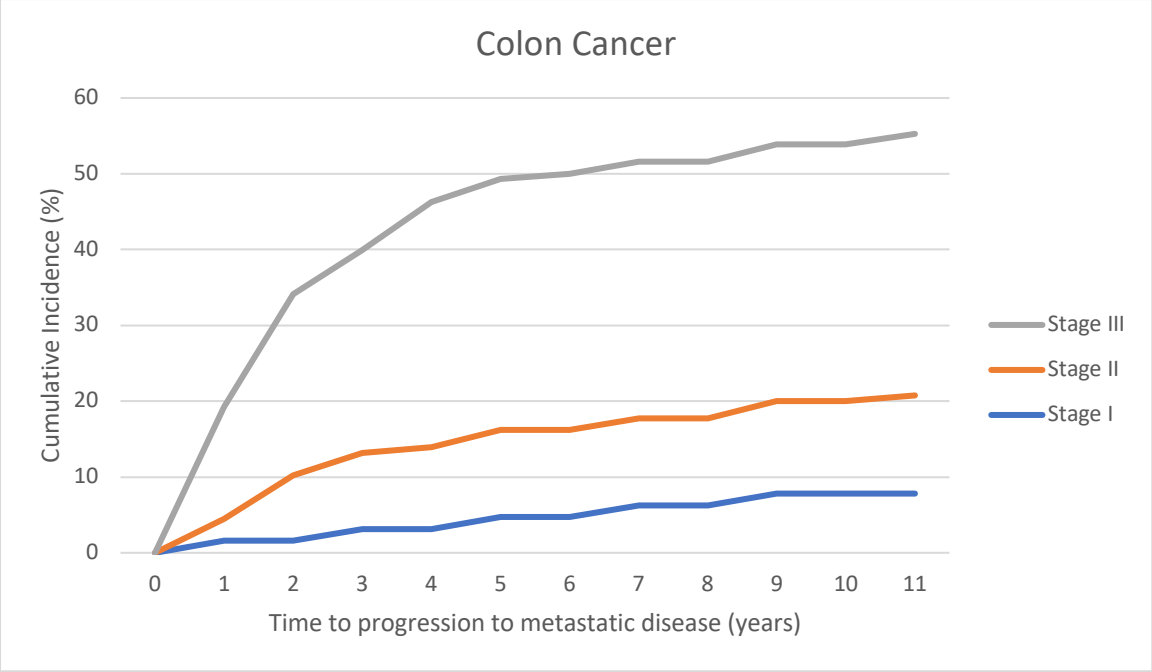

Figure 5.1: Cumulative incidence rate of metastatic colon cancer by stage at initial diagnosis

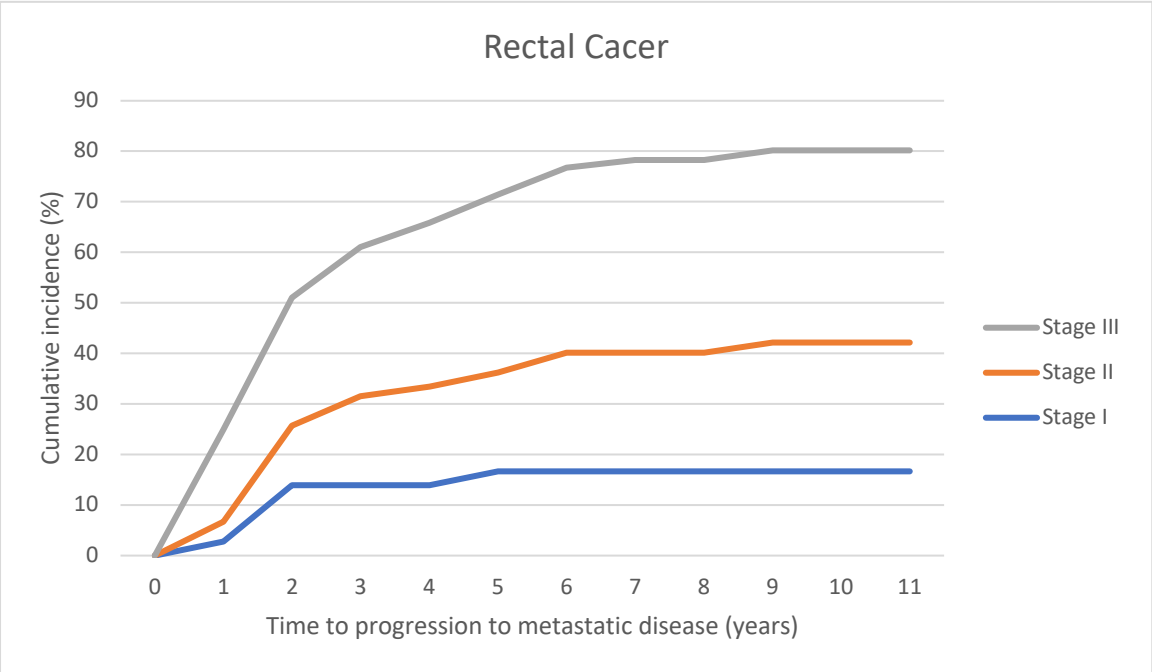

Figure 5.2: Cumulative incidence rate of metastatic rectal cancer by stage at initial diagnosis

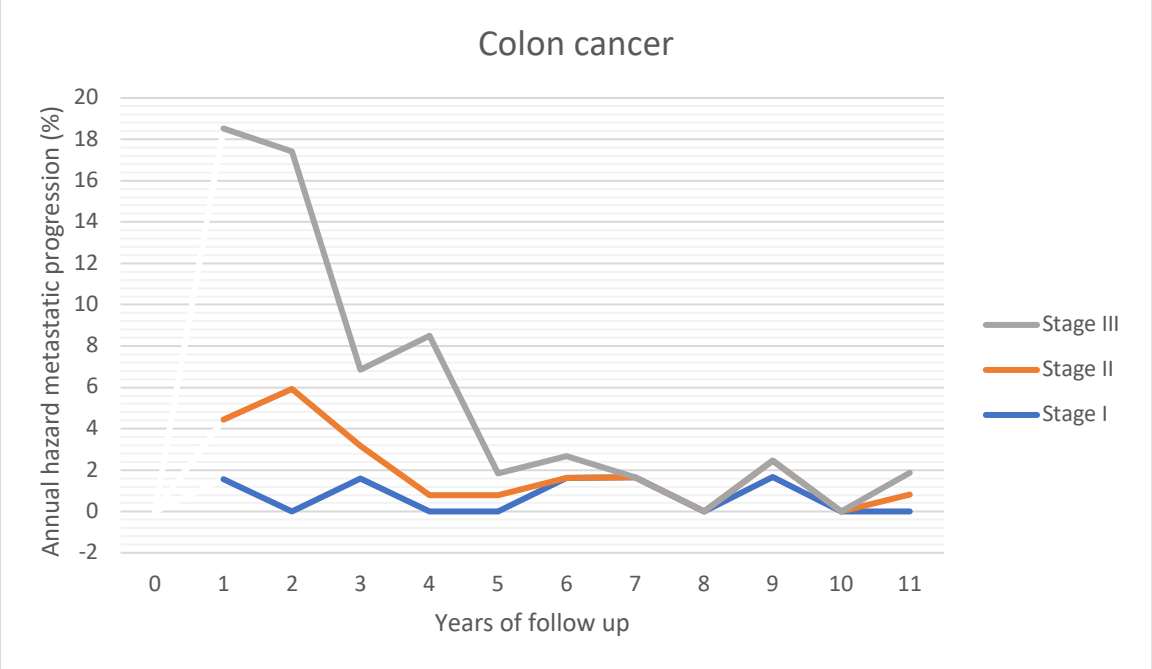

Figure 5.3: Annual hazard of metastatic colon cancer by stage at initial diagnosis for cases

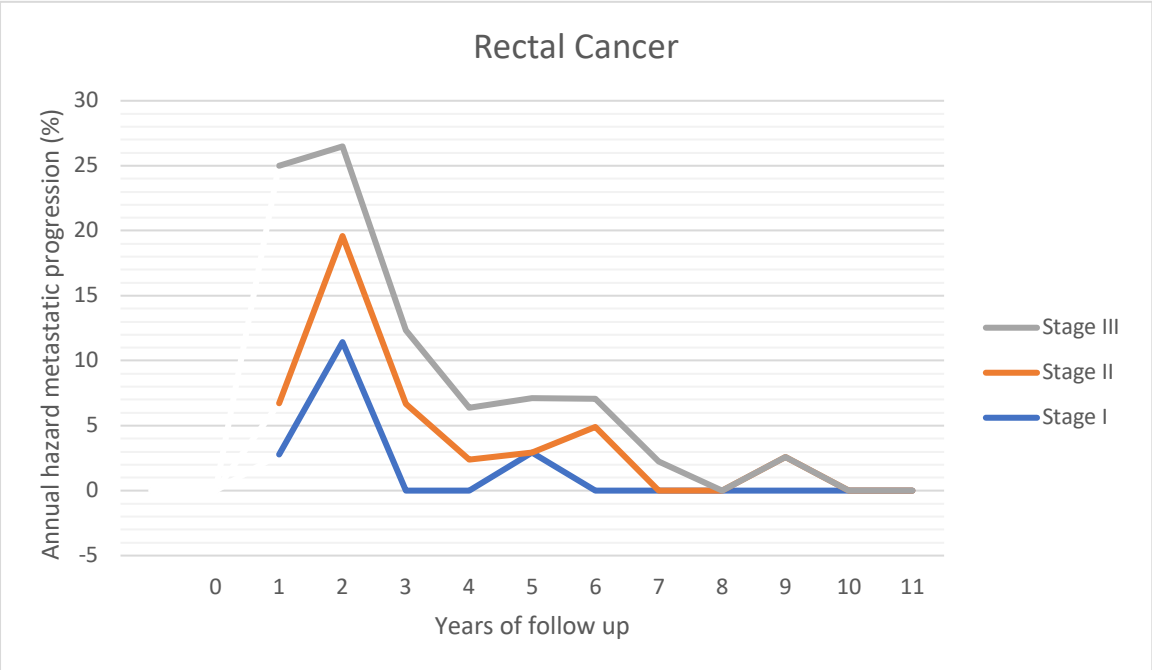

Figure 5.4: Annual hazard of metastatic rectal cancer by stage at initial diagnosis for cases

Tables 5.2 and 5.3 presents the results of the multivariate analysis stratified by cancer site. For both colon and rectal cancer, metastatic progression was significantly higher for patients with Stage III disease [(aHR 4.42 for colon cancer (95% CI 1.74 to 11.23), aHR 3.34 for rectal cancer (95% CI 1.36 to 8.22)], in patients with severe comorbidities (aHR 2.18, 95% CI 0.26 to 0.86), in colon cancer patients with lowest socioeconomic status (aHR 2.03 95% CI 1.23 to 3.34) and in those with lymphovascular invasion (aHR 2.94 95% CI 1.70 to 5.06). Gender difference, tumour location, and geographical location did not show any statistically significant effects on metastatic progression. The colon cancer patients were five times more likely to have poorer prognosis following progression to metastatic disease.

Table 5.2 Multivariate cox regression analysis for metastasis in colon cancer

Variables	Cases	% of metastasis	Hazard ratio	95% CI	P value
Stage at diagnosis					
I	64	7.8	1		
II	139	12.9	1.62	0.60-4.39	
III	142	34.5	4.42	1.74-11.23	<0.001
1st quintile (most disadvantage)	83	28.9	2.03	1.23-3.34	0.006
Lymphovascular invasion	38	50.0	2.94	1.70-5.06	<0.001

Table 5.3 Multivariate cox regression analysis for metastasis in rectal cancer

Variables	Cases	% of metastasis	Hazard ratio	95% CI	P value
Stage at diagnosis					
I	36	16.7	1		
II	51	25.5	1.66	0.63-4.38	
III	71	38.0	3.34	1.36-8.22	0.012
Comorbidity Index					
None	71	21.1	1		
Mild	62	38.7	2.72	1.41-5.24	
Moderate	17	23.5	1.47	0.49-4.45	
Severe	8	37.5	2.18	0.63-7.56	0.027

5.4.2 Perioperative therapy

Of the 345 colon cancer patients, 111 (32.2%) patients had received adjuvant treatment; 109 had chemotherapy, and 2 had chemoradiotherapy. Of the 158 rectal cancer patients, 26 (16.5%) patients had long course chemoradiotherapy, 12 (7.6%) patients had short-course radiotherapy, and 61 (38.6%) had adjuvant therapy either in the form of chemotherapy, chemoradiotherapy or radiotherapy only (Table 5.4).

Table 5.4 Colorectal cancer patients receiving adjuvant therapy

Adjuvant therapy (Rx)	Colon cancer		Rectal cancer		
	Stage II n=139	Stage III n=142	Stage I n=36	Stage II n=51	Stage III n=71
Chemotherapy	15	94	2	8	29
Chemoradiotherapy	1	1	0	4	14
Radiotherapy	0	0	0	2	2
Subtotal	16 (11.5%)	95 (66.9%)	2 (5.6%)	14 (27.5%)	45 (63 .4%)
Total receiving Rx	111		61		

5.4.3 Survival analysis

5-year survival for colorectal cancer patients in this cohort from stage I to III was 80 months, 75 months and 62 months respectively (Figure 5.5).

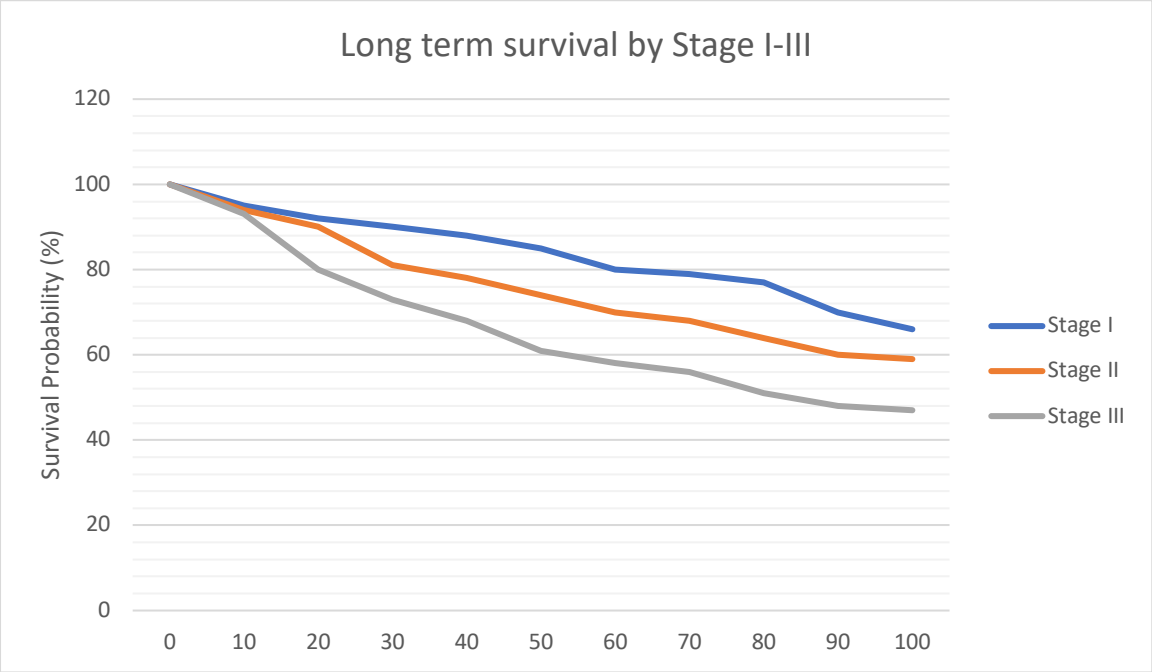

Figure 5.5: Kaplan-Meier survival curve for Stage I to III colorectal cancers

5.5 Discussion

In a regional teaching hospital within Victoria, the incidence of metachronous cancer was 23.3% after a median follow up of 6.2 years for patients who had CRC resection for curative intent. This rate was similar to Luo's NSW population study.[168] The majority of the patients (76%) with metachronous metastatic CRC were detected within 3 years. The above was not an unexpected finding, highlighting the importance of endorsing the recommendations given by the Australian Colorectal cancer surveillance guidelines. The guidelines aim to achieve early detection of metachronous cancer, or when they are still at the asymptomatic stage where further endeavours of curative surgery might be possible.

A higher risk of metastatic progression was observed in colon cancer patients living in areas of lowest socioeconomic status (SES) corresponding to findings observed in some studies globally that have shown poorer outcomes in rural communities and patients with low SES.[169-172] Interestingly, this was not observed in the rectal cancer group. Given that the stage of colon cancer at diagnosis was accounted for and that our treatment provision was comparable to national standards (approximately 60% of colon cancer patients had been offered neoadjuvant or adjuvant therapy), we speculate that the SES disparities may be partly due to differences in patient factors. Patients with lower SES are usually associated with a higher incidence of unhealthy lifestyle behaviours such as smoking and excessive alcohol usage, which may be the driving factors for cancer progression.[173]

Another positive finding was the significant correlation found between the moderate to severely comorbid rectal cancer patients and a higher risk for metastatic progression.

Although it was beyond the scope of this study to evaluate the underlying reasons for this observation, there are several possibilities proposed. Firstly, diseases such as diabetes[174], obesity,[175] inflammatory bowel disease[176] have been shown to contribute to the aetiology of colorectal cancer, and this association might result in a more aggressive form of colorectal cancer. Secondly, comorbid patients are more likely to be offered less aggressive adjuvant therapy and at times, even precluded patients from receiving it.[177-178] Thirdly, patient compliance might be affected, and follow up interfered when patients have difficulty keeping up with the numerous appointments intended for their various health issues — all these leading to a more advanced spread.

Beyond the pathological stage at diagnosis, other critical prognostic determinants for CRC include histological features (i.e., presence of lymphovascular invasion, perineural invasion, extramural invasion, and histologic tumour differentiation).[179] In this study, we found a consistently higher risk of developing metastatic disease in colon cancer cases with lymphovascular invasion. This observation, however, was not seen in patients with rectal cancer. It is possible that the pathological grade of cancer or histological type – both of which were unfortunately neither assessed in this study – might also be associated with metastatic risk, and should therefore be part of any future studies. We believe that these histological risk factors could guide our medical oncologists in tailoring more aggressive adjuvant therapy for the higher-risk patient groups.[167]

The strength of this study lies in its long term follow up, completeness of follow up, and excellent quality of notification of subsequent cancer episode. When the patients were lost to clinical follow up (73 patients), where clinical or survival status was uncertain, exhaustive

attempts were made to contact the patient or their family or general practitioner in order to locate the patient or to confirm if and when they had developed metastasis or died; thus, enabling us to calculate the true rate of metastatic progression. However, no study is without limitations. Firstly, this was a single regional centre study containing only a small dataset, not without its inherent selection bias. Secondly, this study did not allow for analysis such as pathological grade or type that may be valuable information on the risk of metastatic progression. Moreover, some metastases may have remained undetected. Nonetheless, with complete follow up achieved, any potential underestimation would at least have been minimised.

5.6 Conclusion

This study provided a summary of the patterns and risk factors for metastatic CRC disease progression within a region in Victoria, patterns, identifying risk factors that were different from those seen in NSW.[168] In South Western Victoria patients with lower socioeconomic status, severe comorbidities, and lymphovascular invasion had a higher risk for metastatic progression. In our study, advanced age, gender, and rurality were not risk factors. Due to the inconsistencies observed in ours and the NSW population study,[168] there is a need to perform similar studies in other regions. Their findings should help determine surveillance strategies for higher-risk patients in Australia.

Summary

Colorectal cancer (CRC) accounts for the highest expenditure on cancer care in Australia. Despite being one of the commonest cancers in both men and women in Australia, and the incidence increasing over the last two decades, colorectal cancer outcomes have generally improved with a fall in age-adjusted mortality, suggesting a health system well-equipped for the detection and management of CRC. However, the survival outcome of CRC patients within Australia still varies with geography, population density, and between health services. Some of the literature reports poorer outcomes regional, rural and remote patients.

The systematic review in chapter two established that regional and rural patients in Australia generally experienced worse CRC outcomes. However, the prognosis varied between the different regional and rural populations. Patient demographics, cancer characteristics and treatment varied with geographical location. There is also limited data available for CRC follow up and psychosocial outcomes. Although there is a need to improve data collection and reporting, it is likely that many rural/regional patients with CRC are not able to access all modalities of care and this may unduly influence their colorectal cancer outcomes. We need better, more comprehensive data collection at a population-level to better understand this geographical variation, inform governmental health policy and ensure the best possible outcomes in all regions. There is an opportunity to use data linkage to obtain some of the relevant data, and to establish a more holistic and longitudinal understanding of rural regional CRC, and so minimising the expense of data collection.

The third chapter[180] of this thesis analysed a prospectively maintained registry kept over a period of thirteen years from 2002 to 2014, that had accumulated 1079 patients who had undergone surgery at the University Hospital Geelong for CRC (744 colon cancers and 335 rectal cancers). Chapter three reports that the overall number of operations per year have increased over time (p=0.037) but the proportions of elective and emergency surgery remained similar over this period (p=0.75). This consistent proportion of elective cases persisted in spite of the Federal Government introducing a National Bowel Cancer Screening Program in 2006. The median survival after surgery by stage was 123 months, 141 months, 76 months and 17 months for stage I to IV CRC respectively. The two-year survival rate after surgery was approximately 40%. Overall, there were significant improvements observed in both peri-operative mortality and long- term survival of CRC patients at this major regional centre. The improvement in survival occurred despite an increasing proportion of comorbid patients undergoing surgery, and despite there being no change in tumour stage at diagnosis over the study period at UHG.

In chapter four,[181] I found that metastatic disease increases the risk of anastomotic leak after colorectal resections with primary anastomoses. Metastatic disease was present in 16% (135 of 843 patients) and was associated with an increased risk of anastomotic leakage (13% vs. 5%, p=0.003) and a higher peri- operative mortality rate (9.6% vs. 2.8%, p=0.0003). Patients with anastomotic leakage had a reduction in the overall survival (121 months vs. 66 months, p=0.02). Although those with leaks had a higher peri- operative in-hospital 30-day mortality rate, long- term survival was unaffected for those who survived beyond the peri- operative phase. Further studies are indicated to determine whether the higher leak rate is due to an

altered immune response induced by malnutrition, the primary cancer and/or the liver metastases themselves.

In chapter five, I analysed 503 patients (345 colon and 158 rectal) with non-metastatic (stage I-III) CRC who had resections and were followed up for at least five years. Metastatic progression was, as expected, significantly higher for patients with stage III disease (aHR 4.42 for colon cancer 95% CI 1.74 to 11.23, aHR 3.34 for rectal cancer 95% CI 1.36 to 8.22), and those with lymphovascular invasion (aHR 2.94 95% CI 1.70 to 5.06). Metastatic disease was also more likely to eventuate in those with severe comorbidities (aHR 2.18, 95% CI 0.26 to 0.86), and in colon cancer patients with the lowest socioeconomic status (aHR 2.03 95% CI 1.23 to 3.34). Gender, tumour location and geographical location (rural or regional) were not associated with metastatic progression. The identified risk factors were different from those previously reported from NSW. Before determining surveillance strategies to target higher-risk-of-progression patient groups in regional Victoria, these findings would require confirmation from similar studies conducted in other regions of rural/regional Victoria, such as Bendigo, Albury / Wodonga, Latrobe Valley, or Shepparton.

All Australians, regardless of their domicile, age, gender or ethnicity should be able to access the care they need to ensure the best possible colorectal cancer outcomes. These outcomes include not only disease-free survival but also psychosocial wellbeing. This thesis supports the need to perform similar studies based on registries, data linkage, and health system information systems, to derive better outcome data from every region.

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