

Evidence-based care for
older people with colorectal cancer:
a grey area

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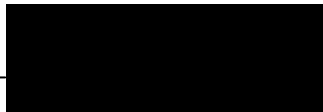
Declaration

This thesis is submitted to the University of Sydney in fulfilment of the requirements for the Degree of Doctor of Philosophy.

The work presented in this thesis is, to the best of my knowledge and belief, original except as acknowledged in the text. I carried out the research and compilation of this thesis under the supervision of Professor Jane Young, Sydney School of Public Health, and Professor Michael Solomon, Discipline of Surgery, University of Sydney. My specific contributions to jointly authored papers are outlined at the start of the relevant chapter.

I hereby declare that I have not submitted this material, either in full or in part, for a degree at this or any other institution.

Signature: _____



Date: 08/01/2014

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Abstract

Colorectal cancer is primarily a disease of ageing, yet older adults are underrepresented in both clinical and health services cancer research. There is evidence that older patients are less likely to receive guideline-recommended treatment than younger patients based on their age alone. However, treatment decision making for this group can be complex. This thesis presents a series of studies that explore the barriers to the evidence-based care of older people with colorectal cancer in New South Wales (NSW), with a focus on the receipt of adjuvant chemotherapy and radiotherapy. The chapters forming the body of the thesis consist of peer-reviewed published, accepted or submitted publications.

Chapter 1 provides an introduction to the role of age in cancer care and outcomes. People aged over 65 currently represent more than two-thirds of newly diagnosed colorectal cancer cases in NSW. With the ageing of the population, the number of older adults with colorectal cancer is expected to increase dramatically. This chapter describes the unique physiological, functional, social, life expectancy, quality of life, and cost-effectiveness considerations in treating this growing and heterogeneous group. Current evidence-based recommendations for colorectal cancer treatment are outlined, including the efficacy and potential adverse effects of surgery, chemotherapy and radiotherapy. Chapter 1 then summarises existing literature on the impact of age on the receipt of colorectal cancer care and on patient outcomes. Previously identified barriers to the implementation and acceptance of guideline-recommended treatment for older adults are described, as well as gaps and limitations of this research. Lastly, the specific aims of this thesis are outlined. These consist of: 1) exploring issues in the measurement of patient-reported outcomes that may affect patient care, 2) establishing current levels and predictors of adjuvant therapy receipt in NSW, 3) investigating physician and patient-based barriers to adjuvant therapy use, and 4) developing a risk model that could be used in chemotherapy decision making.

Patient-reported outcomes are increasingly being recognised as integral to both research and clinical practice for informing decision making and monitoring treatment effects.

Chapter 2 presents the results of two studies that explore issues in the measurement of patient-reported outcomes that may affect the treatment and care that older patients receive. This involved the use of existing prospectively collected data from participants in the control groups of pilot phases of a supportive care intervention following colorectal cancer surgery (n=57). In Study 1, the unmet supportive care needs of older and younger patients were compared at one month and three months after hospital discharge. Older age independently predicted significantly lower levels of unmet need in nearly all domains of the Supportive Care Needs Survey-Short Form 34. However, older patients were less likely than younger patients to report 'satisfied' needs, instead being more likely to report items were 'not applicable' at both one month (mean difference 29%, $p < 0.001$) and three months (mean difference 23%, $p = 0.01$). More than half of all older patients also had unmet needs at both time points. In Study 2, age differences in item non-response were explored in quality of life (QOL) assessments that had been completed using the Functional Assessment of Cancer Therapy-Colorectal at baseline, one month and three months after hospital discharge. Older age was significantly associated with non-response to a number of 'sensitive' questionnaire items (e.g. sex life, diarrhoea), as well as with greater levels of missing data overall. QOL in the social/family domain was overestimated when simple mean imputation was used to manage missing data. Where needs and QOL are not accurately captured or represented, older adults may be less likely to receive care that would enable them to better cope with their cancer and cancer treatment.

Chapter 3 establishes current levels of adjuvant therapy use for colorectal cancer in NSW and identifies patient and hospital-level predictors of treatment receipt. Linked population-based administrative and clinical data was used to examine the records of 580 people with lymph node-positive colon cancer, and 498 people with high-risk rectal cancer, who underwent surgery in NSW following their diagnosis in 2007/2008. Overall, 65-73% of eligible patients received chemotherapy and 42-53% received radiotherapy. Increasing age

was strongly associated with decreasing likelihood of receiving chemotherapy for lymph node-positive colon cancer ($p < 0.001$) and receiving radiotherapy for high-risk rectal cancer ($p = 0.003$), even after adjusting for confounders such as Charlson comorbidity score and American Society of Anesthesiologists (ASA) physical status. Other independent predictors of chemotherapy receipt included having an elective resection and having a current partner. Being discussed at a multidisciplinary team meeting also facilitated radiotherapy use. Adjuvant therapy rates varied widely between hospitals where surgery was performed. While chronological age alone continues to impact receipt of guideline-recommended adjuvant therapy, variation by hospital and other identified predictors indicates the potential to improve the care of older colorectal cancer patients in NSW.

Surgeons act as important gatekeepers to the care of patients after their cancer surgery. In **Chapter 4**, a survey of Australian and New Zealand colorectal surgeons was conducted to identify factors affecting their decisions to refer older patients to oncology. The self-administered survey consisted of three sections: 1) knowledge of current research evidence, 2) opinions on evidence and adjuvant therapy use in older patients, and 3) self-reported practice, or likelihood of referring a younger patient (60 years) and an older patient (80 years) across a range of different scenarios. Seventy percent of surgeons responded ($n = 102$). Surgeons were significantly less likely to refer an older patient than a younger patient for adjuvant therapy in all scenarios ($p < 0.001$), including when the patient had no other medical problems. The difference in referral recommendations was greatest when patients lived a long way from treatment, had a comorbid condition, or had little social support. There was larger variation in referral recommendations for older patients, and marked disagreement between surgeons in knowledge and opinion questions. Greater knowledge and more positive opinions predicted similar referral recommendations for older and younger patients ($p = 0.02$, $p = 0.01$). The lack of consensus among surgeons suggests that more research is needed both to predict the benefit and risks of treatment for older patients, and to determine how information from emerging evidence can best be used to assist physicians' treatment decisions.

Patients who decide not to undergo adjuvant therapy are typically older than those who accept treatment. **Chapter 5** reports the findings of a survey that aimed to identify potential barriers to adjuvant chemotherapy use in older patients by examining the associations between patient age, factors influencing chemotherapy treatment decisions, and preferences for information and decision-making involvement. A self-administered survey was completed by sixty-eight patients who had undergone surgery for colorectal cancer in a tertiary referral hospital in NSW within the previous 24 months. Fear of dying, health status, age, quality of life, and understanding treatment procedures and effects were significantly more important to older patients (aged ≥ 65 years) than younger patients in deciding whether to accept chemotherapy (all $p < 0.05$). Reducing the risk of the cancer returning and physician trust were important factors for all patients. While older patients preferred less information and less involvement in treatment decisions than younger patients, the majority of the older group wanted detailed chemotherapy information and rated many factors as important in their decision making. This study also revealed that surgeons' and patients' perceived barriers to adjuvant chemotherapy use may differ. Practical barriers such as distance to treatment were important to the colorectal surgeons surveyed in Chapter 4, but were not important to the older patients in this study. Through greater understanding and explicit assessment of patient preferences and perceived barriers to treatment, physicians may be better able to support older patients to make informed decisions about their care.

Taken together, the results of Chapters 3 and 4 imply that surgeon knowledge and views are a contributing factor to the age differences in adjuvant therapy receipt in NSW.

Chapter 6 describes the development of a mortality risk model that could be used by clinicians to assist the identification of patients who would benefit from discussion about adjuvant chemotherapy and their treatment preferences. All lymph node-positive patients aged ≥ 65 years who received surgery for colon cancer in NSW in 2007/2008 were identified using a linked population-based dataset ($n=1,550$). 12% of these patients did not survive the first year after surgery and therefore would not benefit from adjuvant chemotherapy.

A mortality risk model was built using multilevel logistic regression, and risk scores based on model predictors were summed for each patient. The risk model consisted of fourteen factors, including patient comorbidities, hospital admission factors, and other markers of frailty or health status. Age was not an independent predictor of mortality in the adjusted model. People with a total risk score of 0, 1 or 2 were considered at low risk (predicted one-year mortality of 3.0%), those scoring 3 to 6 at medium risk (7.5% mortality), and those with a score of 7 or above were considered at high risk of mortality (25.8% mortality). The model had good discrimination (AUC=0.79, 95% CI: 0.75-0.83) and calibration (p=0.46). The risk model may be useful in shifting the emphasis in treatment decision making from chronological age to the identification of those of any age who will live to benefit from these resources.

Chapter 7 provides an overview of the unique contributions of the research presented in this thesis. This includes the identification of a range of factors that impact the treatment of older colorectal cancer patients locally, and the potential of linked routinely collected data to monitor and generate evidence for an underresearched and at-risk patient group in NSW. This chapter also addresses the limitations and methodological issues that were encountered, and discusses implications of the work for clinical practice and for the future research that is needed to ensure greater understanding and improved outcomes for older people with colorectal cancer.

Arising from this thesis

Peer-reviewed publications

Jorgensen ML, Young JM, Harrison JD, Solomon MJ. Unmet supportive care needs in colorectal cancer: differences by age. *Supportive Care in Cancer* 2012; 20(6): 1275-81.

Jorgensen ML, Young JM, Dobbins TA, Solomon MJ. Does patient age still affect receipt of adjuvant therapy for colorectal cancer in New South Wales, Australia? *Journal of Geriatric Oncology*. [Accepted].

Jorgensen ML, Young JM, Solomon MJ. Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions, and practice. *Diseases of the Colon & Rectum* 2011; 54(3): 335-41.

Jorgensen ML, Young JM, Solomon MJ. Adjuvant chemotherapy for colorectal cancer: age differences in factors influencing patients' treatment decisions. *Patient Preference and Adherence* 2013; 7: 827-34.

Papers submitted for review

Jorgensen ML, Young JM, Solomon MJ. Older cancer patients and missing data in quality of life questionnaires.

Jorgensen ML, Young JM, Dobbins TA, Solomon MJ. A mortality risk prediction model for older adults with lymph node-positive colon cancer.

Awards

Early Career Researcher Award, NSW & ACT Cancer Epidemiology Network Meeting, Sydney, December 2011.

Early Career Award, Australasian Epidemiological Association Annual Scientific Meeting, Sydney, September 2010.

Oral presentations at conferences

Jorgensen M, Young J, Dobbins T, Solomon M. A mortality risk prediction tool for older adults with lymph node-positive colon cancer. Clinical Oncology Society of Australia (COSA) Annual Scientific Meeting, Adelaide, November 2013.

Jorgensen M, Young J, Dobbins T, Solomon M. A mortality risk prediction tool for older adults with lymph node-positive colon cancer. National Conference of Emerging Researchers in Ageing, Sydney, November 2013.

Jorgensen M, Young J, Dobbins T, Solomon M. The effect of patient age on receipt of adjuvant chemotherapy for node-positive colon cancer: a population-based health data linkage study, Clinical Oncology Society of Australia (COSA) Annual Scientific Meeting, Brisbane, November 2012.

Jorgensen M, Young J, Solomon M. What do older colorectal cancer patients want? Age differences in factors influencing chemotherapy treatment decisions, NSW & ACT Cancer Epidemiology Network Meeting, Sydney, December 2011.

Jorgensen M, Young J, Solomon M. Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions and practice. National Conference of Emerging Researchers in Ageing, Newcastle, October 2010.

Jorgensen M. Assessment of older cancer patients' needs. Australasian Epidemiological Association Annual Scientific Meeting, Early Career Workshop, Sydney, September 2010.

Jorgensen M, Young J, Solomon M. Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions and practice. Sydney Cancer Conference, July 2010.

Jorgensen M, King M, Harrison J, Young J. The curious case of the missing items: older patients and a quality of life questionnaire. Cancer Epidemiology Network Inaugural Meeting, University of Sydney, December 2009.

Jorgensen M, Young J, Solomon M. Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions and practice. University of Sydney Cancer Research Network Scientific Meeting, November 2009.

Jorgensen M, Young J, Harrison J, Solomon M. Unmet supportive care needs in colorectal cancer: differences by age. Health Services & Policy Research Conference, Brisbane, November 2009.

Poster presentations at conferences

Jorgensen M, Young J, Solomon M. A matter of opinion: age differences in colorectal cancer patients' and physicians' views on chemotherapy treatment decisions. Clinical Oncology Society of Australia (COSA) Annual Scientific Meeting, Brisbane, November 2012.

Jorgensen M, Young J, Solomon M. Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions and practice. Clinical Oncology Society of Australia (COSA) Annual Scientific Meeting, November 2010.

Jorgensen M, Young J, Solomon M. Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions and practice. Royal Australasian College of Surgeons Annual Scientific Meeting, Perth, May 2010.

Jorgensen M, Young J, Harrison J, Solomon M. Unmet supportive care needs in colorectal cancer: differences by age. Clinical Oncology Society of Australia (COSA) Annual Scientific Meeting, Gold Coast, November 2009.

1

Introduction

This chapter provides an overview of the role of age in cancer care and outcomes. There are several excellent reviews and resources about cancer in the older person,¹⁻⁶ each reflecting the authors' own areas of interest and expertise. While a truly comprehensive review is beyond the scope of this thesis, the following chapter summarises the unique challenges faced by older people with colorectal cancer and their physicians, with a focus on the factors that may contribute to age differences in treatment practices. Gaps and limitations of the existing literature are identified, and the specific aims and approaches of this thesis to filling these gaps are outlined.

1.1. Cancer and the older person

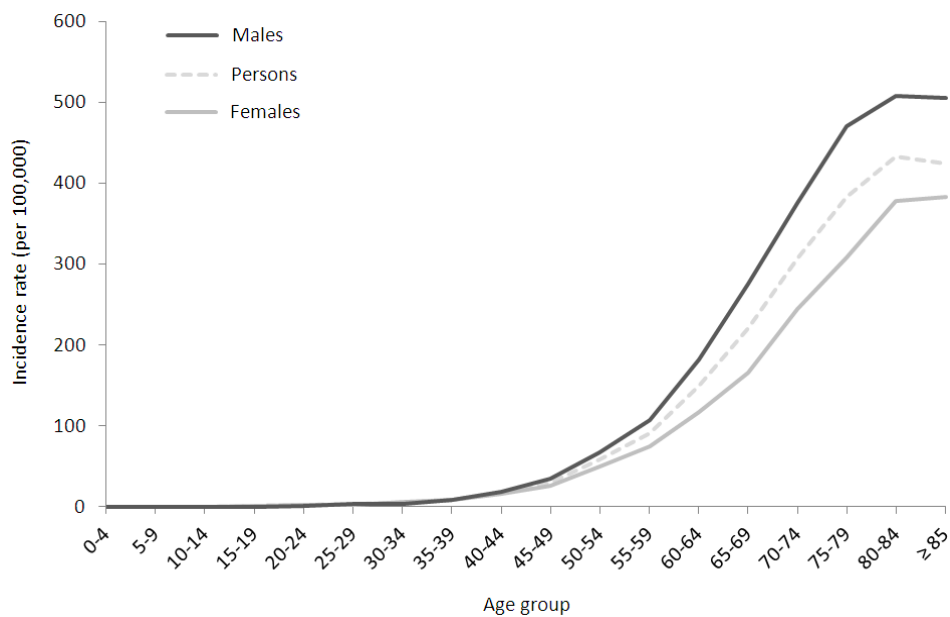
“If you’re not a paediatric oncologist, you’re a geriatric oncologist” (Lichtman, 2007).⁷

1.1.1. A growing population

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in the world, with over 1.2 million new cases and an estimated 608,700 deaths occurring in 2008.⁸ Australia has one of the highest incidence rates of CRC.⁹ It is the second most frequently diagnosed invasive cancer and the second most common cause of cancer death, accounting for 13% of the total cancer burden and 9% of cancer-related deaths in Australia.¹⁰ Five-year relative

survival from CRC in Australia is currently 66%.¹¹ The majority of colorectal cancers are adenocarcinomas (96%),¹² with approximately two thirds arising in the colon and one third in the rectum.¹³ Men have a higher lifetime risk of CRC than women, with 1 in 10 men and 1 in 15 women being diagnosed by the age of 85.¹⁴ Cases are relatively rare in those under 45 years, however incidence rates rise sharply with age until around 80 years (see Figure 1). CRC is therefore described as a disease of ageing.

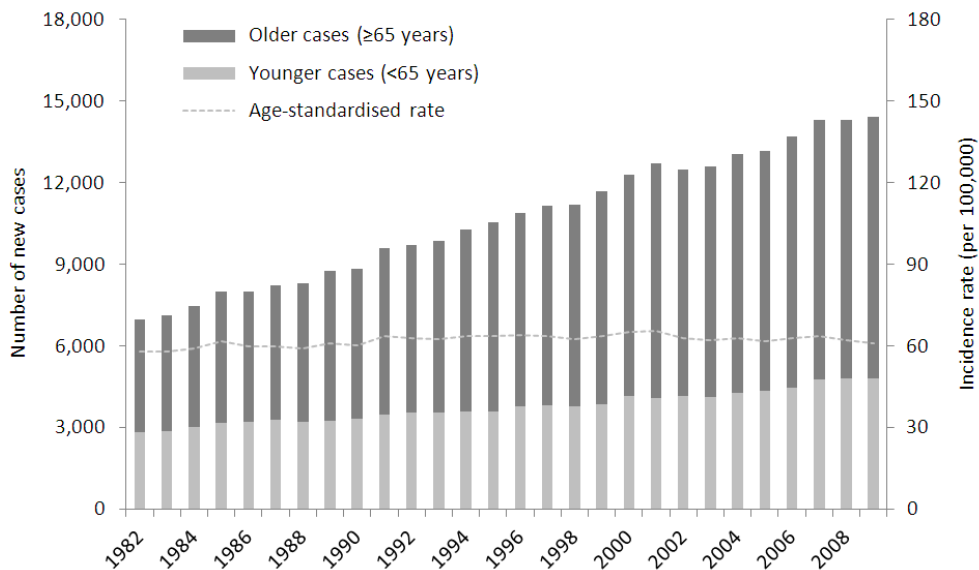
Figure 1. Age-specific colorectal cancer incidence rates by sex*



*Based on Australian Institute of Health and Welfare material¹⁴

The incidence of CRC in Australia has more than doubled in the last 30 years, from 6,970 cases in 1982 to 14,401 cases in 2009.¹⁴ By 2020, the number of new cases is projected to reach 19,960,¹⁵ an annual growth of over 3%. This outstrips the expected increase in the Australian population of 1% per year,¹⁶ indicating that CRC will present an ever-increasing burden on the healthcare system. The main driver of the increasing incidence of CRC is population ageing.¹⁵ While the age-standardised incidence rate has remained relatively stable since 1982, there has been a large increase in the number of new cases in those over 65 years (see Figure 2). People aged over 65 currently represent more than two thirds of newly diagnosed CRC cases,^{14,17} and the average age of diagnosis is nearly 70 years.¹⁰

Figure 2. Number and rate of new colorectal cancer cases by year and age group*



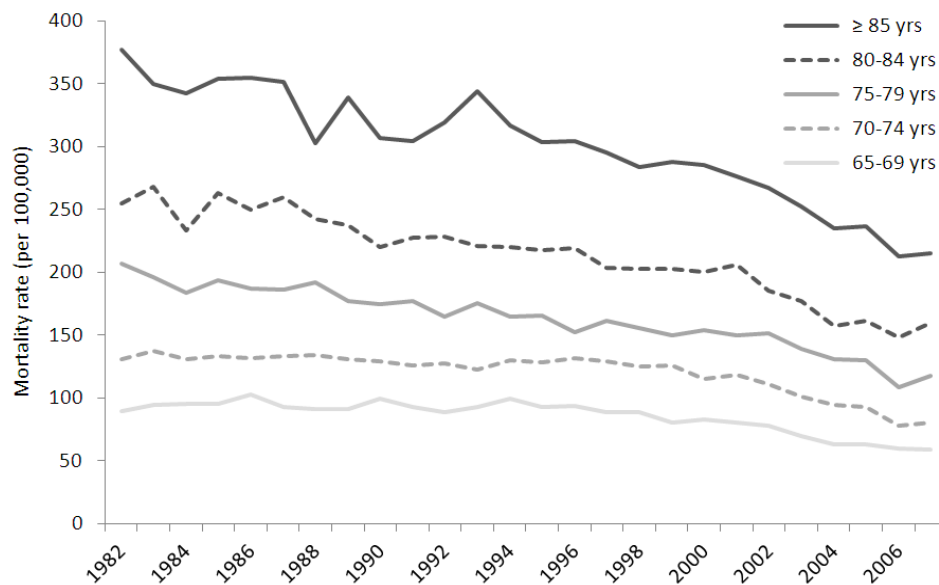
*Based on Australian Institute of Health and Welfare material¹⁴

Population ageing is generally defined as a rise in the median age of an area caused by increasing life expectancy and/or a decline in birth rates. Population ageing is occurring in nearly every country and region,¹⁸ and the speed of this ageing is likely to increase over the coming decades.¹⁹ In Australia, the median age of the population has risen from 28 years in 1970 to 37 years in 2012.^{20,21} People aged over 65 years currently make up more than 14% of Australia's population.²¹ With those born during the post-WWII baby boom now beginning to enter into old age, the percentage of people over 65 is projected to increase to between 20% and 22% by 2033.¹⁶ The number of people over 85 is also expected to more than double from 430,000 to nearly 1 million over the next 20 years.¹⁶ Given the expected increase in the number of older people and therefore the number of older CRC patients, the needs of this population require increasing attention.

Preventing illness and promoting good health throughout life are a core part of the national strategy to encourage participation and reduce the potential burden of future health care costs.²² CRC is particularly amenable to prevention and early detection, as most cancers are thought to originate from previously benign adenomas.²³ Improved detection through public awareness and screening could explain trends for increasing incidence rates of CRC

in older groups up to age 85,¹⁴ despite a flat age-standardised rate overall. The National Bowel Cancer Screening program, in operation since 2006, has been found to be effective in diagnosing people at earlier stages of disease,²⁴ though it remains limited in scope.²⁵ Other community screening programs, such as Rotary Bowelscan, have been reported to have significant reach.²⁶ While Australia has one of the highest incidence rates of CRC, it has fewer late stage diagnoses than many other countries and is a leader in CRC survival.¹³ Mortality rates among the elderly have also improved considerably (see Figure 3). Though 75% of the 4,047 CRC deaths in 2007 occurred in those over 65,¹⁴ improved survival means a growing number of older CRC survivors with unique health needs.^{27,28}

Figure 3. Colorectal cancer mortality rates by year and age group*



*Based on Australian Institute of Health and Welfare material¹⁴

Life expectancy should play a central role in treatment decisions.²⁹ Most of the life expectancy gains in the last few decades have been driven by people living longer into old age. Life expectancy at age 65 has increased since 1980 from 14 to 19 years for men, and from 18 to 22 years for women.³⁰ An important consideration alongside population ageing and cancer survivorship is the amount of remaining life spent in good health. Three major theories have emerged to explain how increases in life expectancy may affect health on a population level.³¹ The “compression of morbidity” theory suggests that increases in life

expectancy will be accompanied by a delay in the onset of disease.³² In the “expansion of morbidity” theory, the lives of people with chronic disease will simply be extended by life-sustaining medical care.^{33,34} The “dynamic equilibrium” theory highlights a delay in the progression of chronic disease, with a decreasing proportion of the life span spent in serious illness, but an expanding proportion of the life span with less severe illness.³⁵ A fourth more recent theory suggests an eventual emergence of a *very* old and frail population: an “epidemic of frailty”.³¹

While people with CRC have a reduced life expectancy compared to the general population (see Table 1), even those aged 80 have a life expectancy of 5-7 years, and could expect 3-4 years of self-reported good health.³⁶ Differing definitions and a complicated and fluid relationship between longevity and morbidity means there is yet no consistent evidence of a compression or expansion of disability among older populations.³⁷⁻⁴⁰ However, around half of the gains in life expectancy at age 65 between 1998 and 2009 in Australia were years with disability,⁴⁰ some of which were likely due to cancer sequelae. As the population ages, there will be a greater number of older people both with and without chronic health conditions. This means a growing and diverse population of older people with CRC who may also present with unique issues relating to the biology of ageing and cancer.

Table 1. Population and colorectal cancer (CRC) life expectancy in years by sex and age

Age	Males					Females				
	Aus ^a	Aus DFLE ^b	CRC III, 0 ^c	CRC III, 1-2 ^c	CRC surv HLE ^d	Aus ^a	Aus DFLE ^b	CRC III, 0 ^c	CRC III, 1-2 ^c	CRC surv HLE ^d
50	31.7	18.1	.	.	9.5	35.4	19.7	.	.	9.9
65	18.9	8.2	.	.	7.3	21.8	9.7	.	.	7.9
67	17.3	.	8.4	6.8	.	20.1	.	8.5	7.9	.
71	14.3	.	7.4	6.1	.	16.8	.	8.3	6.6	.
76	10.9	.	6.3	5.2	.	12.9	.	7.4	5.8	.
80	8.5	2.1	.	.	3.8	10.1	2.7	.	.	4.1
81	7.9	.	5.5	4.9	.	9.4	.	6.4	4.8	.
85	6.0	1.0	.	.	.	7.1	1.4	.	.	.

^aAll population life expectancy (Australia)³⁰; ^bAll population disability-free life expectancy (DFLE) (Australia)⁴⁰;

^cCRC stage III life expectancy, 0 or 1-2 comorbidities (USA)⁴¹; ^dCRC survivors healthy life expectancy (HLE) (Netherlands)³⁶

1.1.2. A disease of ageing

The strongest risk factor for cancer is age. However, there is no universally accepted view of the cause of this increased risk.⁴² One view holds that time is the risk factor rather than age. Time is required for neoplastic changes to take place in normal tissues, and the dose and duration of carcinogenic exposure increases over a person's lifetime regardless of any effects of ageing.^{43,44} Another view holds that age-related changes in physiology may provide a favourable environment for the initiation and growth of cancer cells.⁴⁵ Increasing evidence suggests the rise in cancer incidence with age results from the accumulation of cancer-causing cellular mutations *alongside* age-related changes in tissue microenvironment, gene silencing and telomere dysfunction.⁴⁶

As ageing involves genetic events that appear similar to those occurring in early cancer growth, cellular senescence and telomeres are often implicated in unifying theories of ageing and cancer.⁴⁷ Telomeres are gibberish DNA that act like shoelace tips in protecting chromosomes from fraying during cell division and replication. These regions progressively shorten with each division and therefore with age. When telomeres become critically short or DNA damage is sustained, cells can become inactive ("senescent") or die to prevent instability and tumour growth.⁴⁸ A cell that escapes from these normal controls and begins to become cancerous divides rapidly, and its telomeres quickly become very short. Shortened telomeres are thus a common feature of CRC tissue,⁴⁹ and have been associated with other age-related diseases and characteristics such as heart failure and immunosenescence.⁵⁰ Telomere length has also been proposed as a biomarker of ageing, as it appears to predict lifespan.^{51,52} The rate at which telomeres wear down varies between people and can depend on environmental stimuli (e.g. smoking).⁵³ Accumulation of senescent cells with age compromises tissue function and repair, but also appears to promote cancer growth by triggering inflammation in nearby cells and tissues.⁵⁴ Though still largely theoretical, increased understanding of the common pathways of cancer and ageing implies that older patients are not simply "adults who are old".

Paradoxically, age-related biological changes may also act to suppress cancer development and improve prognosis. While national cancer organisations typically aggregate incidence data for those aged over 85, researchers have noted a deceleration and decline in all-site cancer incidence and prevalence from between the ages of 75 and 84, and a decline in cancer mortality from age 90.^{55,56} Changes in screening practices or differential exposures to environmental carcinogens are potential contributing factors. However, a strong genetic component to exceptional longevity (e.g. clustering of centenarians in families) suggests that those living to the oldest ages have a survival advantage that protects them from ageing-related diseases like cancer.⁵⁷ Age-related declines in metabolism, rate of cell proliferation, and a high proportion of senescent cells may reduce the probability of malignant transformation and spread.⁵⁶ Indeed, the lower rates of metastatic disease reported in older people with CRC,⁵⁸ and the presence of less poorly differentiated tumours,⁵⁹ may help to explain improved survival in the very old.⁵⁷

However, other age-associated biological features may impact on treatment success. A greater proportion of older people present with right-sided colon cancers.⁶⁰ These are considerably more likely to be associated with microsatellite instability (MSI),⁶¹ the molecular fingerprint of a deficient DNA mismatch repair (MMR) system. Colorectal cancers with MSI have a better prognosis than microsatellite stable CRC,⁶² but their responses to fluorouracil-based chemotherapy regimens may be poorer.⁶³ However, MSI is only present in about 15% of cancers.⁶¹ Ageing-related changes in the way drugs affect the body (pharmacodynamics) and the way the body affects drugs (pharmacokinetics) may cause enhanced chemotherapy toxicity and reduced effectiveness.⁶⁴ Nonetheless, these factors do not prevent effective cancer treatment for the majority of older adults.⁶⁵ Individualised assessment of ageing and its effects is therefore required to ensure the most appropriate treatments, and therefore the best outcomes, are achieved.

1.1.3. Definitions of old age

While ageing is a universal reality, definitions of “old age” vary between countries and over

time. In the developed world, chronological time plays an important role in the definition. Old age is often linked to the age at which the state offers an age pension, currently 60 to 65 years in most countries.⁶⁶ However, changes in the social, political and economic environment have resulted in pension ages gradually being increased, and women's eligibility age brought into line with men. In many parts of the developing world, chronological time has little importance in the meaning of old age, and a loss of ability to perform roles and to actively contribute in society plays more into the definition.⁶⁷

This definition recognises that individuals with the same chronological age vary widely in their health and ability to function. Because of this heterogeneity, chronological age is not an accurate measure of the ageing process, remaining life expectancy, or how well a person will cope with treatment.⁶⁸ Individual biomarkers (e.g. telomere length, inflammation markers) are not yet adequately developed to be used exclusively to determine biological age.⁶⁹ The *consequences* of biological ageing are typically explained as a cumulative decline of physiological reserves across multiple systems.⁷⁰ Concepts such as loss of entropy, allostatic load or loss of homeostasis have been used to describe this decreased ability to cope with stress, in the presence of adequate baseline functioning.⁶⁵ Those with critically reduced reserves may be characterised as "frail".⁷¹ Though there is no consensus on the definition of frailty, it is generally conceptualised in one of two ways:⁷² as a "frailty phenotype" or syndrome identified by the presence of a number of criteria (e.g. weight loss, exhaustion, gait speed, grip strength, low physical activity),⁷³ or as a "deficit accumulation" model across a number of domains, including chronic disease, ability to manage daily activities, and physical signs.⁷⁴

Those that support the frailty phenotype model suggest that comorbidity, disability, and frailty are distinct clinical entities.⁷⁵ Comorbidities may be measured based on the presence of a number of chronic conditions, or as a comorbidity index reflecting the severity of a set of predefined conditions, for example the Charlson comorbidity index.⁷⁶ The prevalence of chronic conditions increases with age,⁷⁷ and the severity of comorbidities appears to have a

“dose-dependent” effect on overall survival of cancer patients.⁷⁸ However, there is minimal correlation between comorbidity and the ability to manage daily activities (functional status).⁷⁹ Functional status is frequently assessed in oncology research as a single performance status score, for example, the Eastern Cooperative Oncology Group (ECOG) score or the Karnofsky score.^{80,81} Ideally, evaluation of functional status for treatment decision making should be more extensive than assigning a performance status score,⁸² and may include assessment of independence in a checklist of self-care activities of daily living (ADLs) or activities for living independently in the community (instrumental ADLs).^{83,84} Social support can play an attenuating role on the effects of poor function.⁸⁵

However, the current gold standard in assessing physiological age is a comprehensive geriatric assessment (CGA), which identifies a suite of factors that better predict reduced life expectancy and underlying vulnerability than any single element alone.^{82,86-88} CGA commonly includes assessment of functional status, comorbidity, nutrition, mobility, polypharmacy, social support, mood, cognition, and the presence of geriatric syndromes such as falls and incontinence.⁸⁹ Because of the resource intensiveness of the CGA, a two-step approach to geriatric assessment is widely recommended.⁹⁰ This involves the use of screening tools to identify those requiring further full evaluation.

For practical reasons, a chronological definition of ageing is often used in research. Conventionally, old age has been defined as beginning at 65 years.⁹¹ The categorisation of “young old” (65-74), “old old” (75-84), and “oldest old” (85+) may have some usefulness in accounting for the diversity of this population.¹ The age of 70 has also been identified as a commonly used cutoff in the field of geriatric oncology.⁹² This is based on a sharp increase in the clinical signs of ageing,⁹³ though it is recognised that ageing-related bodily changes appear to start decades earlier. Various terms are also used to describe this population in research. One international media style guide suggests that “older” is preferable to “elderly” or “senior”.⁹⁴ In this thesis, any age cutoffs are explicitly defined within the chapter. The population will generally be described as “older”, implying that individuals are “older than” but not necessarily “elderly” or “frail”.

1.2. Age differences in treatment and outcomes

1.2.1. Recommended treatment: surgery

Surgery is the mainstay of curative treatment for colorectal cancer. In a population-based patterns of care study of 3,095 people diagnosed with colorectal cancer in New South Wales (NSW) in 2000, 96.4% received surgery (n=2,984).⁹⁵ Operative treatment for colon cancer should consist of en bloc removal of the involved bowel segment (“resection”), the associated lymphatic tissue to the origin of the feeding vessels (“apical nodes”), and any adjacent tissue or organs that are attached or adhered to the tumour.^{96,97} At least 12 lymph nodes be examined to confirm the absence of nodal involvement.⁹⁸ Nodes outside the field of resection that are suspected of being positive for disease should be sampled.⁹⁹ The type of bowel resection performed is determined by the tumour location. For example, a right hemicolectomy is the accepted treatment for tumours in the ascending colon.¹⁰⁰ People with disease that has metastasised to distant organs or tissues may still benefit curatively from surgery.⁹⁷ Following a resection, reconnection of the two healthy ends of the bowel (“anastomosis”) should be performed if possible. Laparoscopic-assisted colon surgery has been shown to have equivalent outcomes to conventional surgery when performed by experienced surgeons, and may also reduce morbidity.^{101,102}

Elective surgery for rectal cancer should be carried out by a specialist surgeon as it is more technically challenging and has greater potential for poor patient outcomes.⁹⁷ For many years, abdominoperineal resection (APR) was the standard treatment for rectal cancer.¹⁰³ APE includes the removal of the anus, rectum and part of the sigmoid colon. In a procedure called a colostomy, the end of the remaining colon is brought out permanently through the abdominal wall (“stoma”) and fixed to the surface of the skin, so faecal matter can leave the body. Advances in treatment techniques and equipment mean that preservation of the anal sphincter and avoidance of a permanent colostomy is now possible. A low anterior resection, where the colon is attached to the remaining part of the rectum, typically achieves superior rates of survival and recurrence¹⁰⁴ and is therefore the preferred treatment where a distal clearance margin of 1-2 cm can be achieved.⁹⁷

For tumours in the middle or lower third of the rectum, total mesorectal excision (TME) is recommended.⁹⁷ In this operation, the perirectal soft tissue envelope including the entire rectum (proctectomy) is removed to reduce local recurrence and the colon connected to the anus. Temporary stomas are typically created to give distal anastomoses at particular risk of leakage or breakdown time to heal. Local excision of some early colon or rectal cancers can be performed transanally i.e. using instruments inserted through the anus.⁹⁷

A note on the rectosigmoid junction

The site where the colon ends and the rectum begins is known as the rectosigmoid junction. There are no consistent anatomical or histological features to distinguish this region; a tumour is generally classified as rectal if its lower margin lies less than 16cm from the anal verge.¹⁰⁵ Because rectosigmoid junction cancers account for only 10% of cases,¹⁰⁶ they are typically combined with either colon or rectal cancers for research purposes. Similar rates of survival and recurrence suggest they may be better classified and treated with colon cancers,¹⁰⁷ however there remains no consensus in the literature. In this thesis, the categorisation of rectosigmoid junction cancers are defined where necessary.

1.2.2. Recommended treatment: adjuvant therapy

Adjuvant therapy refers to treatment that is given in addition to the primary or main treatment. In the context of cancer care, this includes radiation therapy or systemic treatments (chemotherapy, immunotherapy, hormone therapy). Treatment can be given adjuvantly (post-surgery) or neoadjuvantly (pre-surgery). Adjuvant therapy is intended to eliminate any residual micrometastatic disease after potentially curative surgery, in order to reduce the risk of recurrence and improve survival.¹⁰⁸ It is distinct from palliative chemotherapy or radiotherapy, which is typically used in advanced disease to alleviate symptoms, slow cancer progression, and prolong life.^{109,110} The anatomy and physiology of the human pelvis essentially dictates adjuvant therapy approaches to colon and rectal cancer. Radiotherapy is used primarily for rectal cancers, which tend to recur locally or



regionally because of the close proximity of the rectum to pelvic structures and organs and difficulties in achieving wide margins.¹¹¹ A systemic approach is more appropriate for colon cancers, as these tend to recur only at distant sites such as the liver and lungs.¹¹²

Specific adjuvant therapy recommendations are outlined in the current Australian clinical practice guidelines for colorectal cancer.⁹⁷ These guidelines broadly reflect those of the European Society for Medical Oncology (ESMO),^{113,114} the National Comprehensive Cancer Network (NCCN) in the USA,^{96,115} and the International Society of Geriatric Oncology.¹⁰⁸ Treatment approaches are guided by accurate staging of a tumour according to the extent of its spread. In Australia, it is recommended that both Australian Clinicopathological Staging (ACPS) and Tumor-Node-Metastases (TNM) staging are recorded.⁹⁷ Both of these are extensions of the original Dukes staging method that have evolved to better define treatment and prognosis.¹¹⁶

Australian clinical practice guideline recommendations for adjuvant therapy according to staging are highlighted in Table 2 and detailed below. Guidelines also exist for metastatic and recurrent colorectal cancer but are not outlined here.

Table 2. Staging and guidelines for adjuvant therapy⁹⁷

Stage	ACPS	TNM staging			TNM classification notes
		T	N	M	
0	-	Tis	N0	M0	Tis: Carcinoma <i>in situ</i> , confined to mucosa
I	A	T1	N0	M0	T1: Invades submucosa
I	A	T2	N0	M0	T2: Invades muscularis propria
II-A	B	T3	N0	M0	T3: Invades pericorectal tissues
II-B	B	T4a	N0	M0	T4a: Penetrates to surface of visceral peritoneum
II-C	B	T4b	N0	M0	T4b: Invades or adheres to other organs or structures
III-A	C	T1-2	N1	M0	N1: 1-3 positive regional lymph nodes
III-B	C	T3-4	N1	M0	
III-C	C	T1-4	N2	M0	N2: 4 or more positive regional nodes
IV	D	T1-4	N0-2	M1	M1: Distant metastasis

 Radiotherapy strongly recommended (rectal)  Chemotherapy strongly recommended (colon)

Strongly recommended (Level 1 evidence: systematic review)⁹⁷

- 1) People with resected Dukes C (i.e. node-positive) colon cancer should be considered for adjuvant chemotherapy.
- 2) Adjuvant preoperative or postoperative radiotherapy is recommended for high-risk (T3/4 or N+) rectal cancer.

Recommended (Level 2 evidence: randomised control trial)⁹⁷

- 1) There is a small but statistically significant benefit for the use of adjuvant chemotherapy in Stage II colon cancer. High risk sub-groups are more likely to benefit from adjuvant chemotherapy.
- 2) Preoperative therapy for rectal cancer may lower the incidence of late morbidity.
- 3) Where radiotherapy is indicated for rectal cancer, fluorouracil-based chemotherapy should be administered.

Recommended adjuvant therapy regimens

The standard of care following surgery for stage III colon cancer is six months of FOLFOX, which consists of oxaliplatin and fluorouracil (5-FU) with leucovorin (LV), every two weeks for 12 cycles.⁹⁶ This chemotherapy regime has increased disease-free survival and reduced recurrence compared to 5-FU/LV alone.¹¹⁷ Other treatment options include bolus 5-FU/LV/oxaliplatin (FLOX), capecitabine/oxaliplatin (CapeOx or XELOX). Single agent 5-FU/LV or capecitabine can be used if patients are felt to be inappropriate for oxaliplatin therapy.⁹⁶ Capecitabine is an oral prodrug of 5-FU with equivalent outcomes to 5-FU/LV and a better tolerability profile,¹¹⁸ making it particularly attractive for elderly patients, except in the case of renal impairment.¹⁰⁸ Adjuvant chemotherapy should be initiated within 8 weeks after surgery.¹¹⁹ Those with high-risk stage II colon cancer can also be considered for these adjuvant chemotherapy regimes.¹²⁰ A range of active drugs, either in combination or as single agents, may be used in metastatic and recurrent disease.⁹⁶ Radiotherapy in colon cancer is generally only considered for select patients with T4 tumours penetrating to a fixed structure or for patients with recurrent disease.⁹⁶

For patients with high-risk rectal cancer, preoperative radiation is preferred as it is more effective in reducing local recurrence and less toxic than postoperative treatment.¹¹⁴ Reducing tumour volume with preoperative radiation may also facilitate resection.¹¹⁵ The addition of 5-FU-based chemotherapy concurrent with preoperative radiation is recommended.¹²¹ Evidence of the effectiveness of postoperative chemotherapy following preoperative treatment is less clear.¹²² Recent studies have shown that capecitabine is equivalent to 5-FU in perioperative chemoradiation therapy.¹²³ Recommended doses of radiation are typically 45-50 Gy in 25-28 fractions to the pelvis using three or four fields.¹¹⁵ For patients treated with preoperative chemoradiation, an interval of 5 to 10 weeks prior to resection after completion of the five and a half week course is recommended to allow patient recuperation.¹¹⁵ Short-course radiotherapy may be appropriate in some situations.¹¹⁵ Radiation and chemotherapy are also used to manage metastatic and recurrent rectal cancer.

Specific age guidelines

The Australian Federal Age Discrimination Act (2004) states that taking a person's age into account when making healthcare decisions must be "reasonably based on evidence". A number of evidence-based clinical practice guidelines for colorectal cancer specifically outline that:

- Age alone should not be a contraindication for curative surgery in colon cancer¹²⁴
- Advanced chronological age should not be used to exclude patients from being offered adjuvant chemotherapy⁹⁷
- Age alone should not exclude any stage III colon cancer patient from consideration for adjuvant therapy¹⁰⁸
- Irrespective of age, a person who is functionally independent and without serious comorbidities should be a good candidate for most forms of cancer treatment.¹²⁴

However, the risk of comorbid conditions and functional impairment increases with age. These factors therefore need to be considered both in individual treatment decision making and in determining concordance with guidelines.

1.2.3. Age differences in treatment

Diagnosis and surgery

Differences between the treatment of older and younger people with CRC are apparent along the pathway of cancer care.^{125,126} Older people with CRC are more likely to have prolonged wait times from diagnosis to first cancer treatment,¹²⁷⁻¹³⁰ though emergency resection is also more common with advancing age.^{58,125,131,132} Many studies report that older CRC patients are less likely to undergo surgery than younger patients.^{58,125,126,133-135} While comorbidities can justifiably affect eligibility for surgery, age differences remain after accounting for this factor.¹³⁶⁻¹³⁸ Differences between younger and older patients also exist in rates of surgery for cancer recurrence.¹³⁹ However, the proportion of older patients receiving colorectal cancer surgery has increased considerably over time.¹⁴⁰⁻¹⁴²

Age differences in type of surgery for CRC are also apparent. Older people who do undergo resection are more likely to have less radical surgery than their younger counterparts,^{131,143} even after adjusting for comorbidities.¹³⁸ Laparoscopic colonic surgery appears to have at least equivalent outcomes to conventional open surgery^{101,102} and may in fact be of most benefit to the elderly.¹⁴⁴ Yet, increasing age is a significant predictor of non-receipt of laparoscopic surgery.^{145,146} A greater proportion of older people receive APR for rectal cancer,¹⁴⁷⁻¹⁴⁹ which can be associated with both higher rates of local recurrence and poorer survival than restorative rectal resection.¹⁰⁴ Inadequate lymph node evaluation (≥ 12 nodes) is also more likely with increased age.^{58,150-153}

Differences in adjuvant therapy receipt

Age differences in the receipt of guideline-recommended adjuvant therapy have been widely documented, both nationally and internationally, and across a range of cancer

types.¹⁵⁴⁻¹⁵⁸ Older people are less likely to receive adjuvant chemotherapy for stage III colon cancer.^{95,151,159-162} These differences remain after accounting for age-related factors such as comorbidities¹⁶³⁻¹⁷⁵ and physical function.^{176,177} Older patients are less likely to be referred to^{178,179} and seen by an oncologist,^{163,180} which are crucial factors in the receipt of chemotherapy.¹⁸¹ For stage II/III rectal cancer, increasing age is a predictor of non-receipt of radiotherapy,^{95,143,182-184} even when accounting for comorbidities,^{166,185-187} and is associated with decreasing use of combined chemoradiation.^{126,188} Older adults are also less likely to receive chemotherapy for metastatic CRC.^{170,189,190} However, adjuvant treatment rates are increasing over time.^{125,126,134,184,191,192}

A number of additional issues in the receipt of adjuvant chemotherapy exist. Older age is associated with significantly longer intervals from surgery to chemotherapy initiation.¹⁹³ Doses are routinely reduced even in older patients who are fit,¹⁹⁴ and the addition of oxaliplatin to the standard 5-FU/LV regime to increase survival is less likely with older age.¹⁹⁵⁻¹⁹⁷ Early discontinuation or a shorter than recommended treatment duration for older patients is also commonly reported.^{164,195,196,198}

Differences in follow-up

Increasing patient age is also associated with poorer follow-up care in cancer.¹⁹⁹ Older CRC survivors are less likely to receive care from both a primary care provider and oncology specialist,²⁰⁰ and have fewer physician visits overall.²⁰¹ They are less likely to receive preventative care including cholesterol testing and bone densitometry,²⁰⁰ and surveillance procedures such as colonoscopy.^{201,202}

1.2.4. Age differences in outcomes

There have been significant increases in colorectal cancer survival over recent decades in many developed countries,⁹ including for those over 70 years.¹⁴ However, differences continue to exist between younger and older patients for both short-term and long-term outcomes. Though greater levels of comorbidity among older people with CRC increases

the complexity of cancer management and affects survival,²⁰³⁻²⁰⁵ poorer treatment appears to contribute to age differences in outcomes.¹⁰⁸

Differences in perioperative outcomes

The incidence of 30-day operative mortality is frequently reported to increase with age,^{131,206,207} including after adjusting for comorbidity²⁰⁸⁻²¹⁰ and American Society of Anaesthesiologists (ASA) physical health status.^{58,210,211} Older age has been associated with longer length of stay^{132,210,212,213} and hospital readmission within 30 days,^{212,214} which may be the result of a greater frequency of post-operative complications.^{131,210,215} However, other studies report no age association with hospital readmission²¹⁶ or that older people are actually less likely to have an emergency readmission.²¹³

Side effects and complications of colorectal cancer surgery can include pain, wound healing and infection, anastomotic leakage, bowel dysfunction, urinary and sexual dysfunction, and issues related to the presence of a stoma.²¹⁷⁻²¹⁹ In a systematic review of surgical outcomes in rectal cancer, postoperative morbidity and complications were not consistently associated with age.²²⁰ However, complications such as anastomotic leakage may have a greater impact on the consequent survival of older patients.²²⁰ There have also been reports that increasing age is not associated with postoperative complications when ASA physical status is accounted for,²²¹ and that age is a predictor of higher rates of nonsurgical complications but not surgical complications.²²² Regardless of any age differences in perioperative outcomes, many researchers conclude that colorectal resection for older patients has acceptable levels of perioperative morbidity and mortality,^{212,223-225} particularly given that operative mortality has improved considerably over time.^{140,226}

Differences in survival

Longer term survival outcomes are often poorer for older adults with CRC, though there is large variation between countries.²⁰³ [Appendix 1.2](#) outlines the definitions for a number of commonly used survival measures. Many studies report that while overall five-year survival

of older patients is poorer, cancer-specific survival is not associated with age.^{131,223,227,228} That is, a substantial proportion of deaths in older people with CRC can be attributed to factors such as congestive heart failure, diabetes mellitus, and chronic obstructive pulmonary disease.²²⁹ However, some studies do report decreasing cancer-specific survival with age,^{140,143} and poorer relative survival for those older patients with metastatic disease or locally recurrent cancer.¹³⁹ Other findings suggest that after surviving the first year, older patients have the same relative survival as younger patients.^{230,231} This indicates a prolonged effect of surgery and anaesthesia on those with reduced reserves.⁷⁰

Conflicting findings may be partly explained by differing methods for estimating cancer survival.²³² Nonetheless, suboptimal treatment appears to be a major contributor where poorer outcomes are reported.^{108,143,233} Increased rates of radical resection for older patients have produced marked improvements in five-year relative survival for this group.^{140,141,226,234} Poorer outcomes may also be explained by age differences in factors such as adequate lymph node evaluation, which is important for treatment planning and is associated with survival.^{235,236} Similarly, longer time to adjuvant chemotherapy initiation, early discontinuation, and dose reduction are all associated with poorer CRC survival.^{119,237-241} Underuse of laparoscopy in older patients may increase rates of complicated postoperative recovery,²⁴² potentially resulting in further omission, delay and discontinuation of adjuvant chemotherapy.²⁴³ Moreover, deviations from practice recommendations may add to the perception that treatment is less effective for older patients, resulting in further undertreatment.

Differences in efficacy and toxicity of adjuvant therapy

In an analysis of pooled data from seven randomised trials with surgery-alone control arms, the addition of 5-FU based adjuvant chemotherapy improved five-year disease-free survival in node-positive colon cancer patients from 42% to 58% and five-year overall survival from 51% to 64%.²⁴⁴ Older adults with node-positive colon cancer derive the same benefit from these regimes as younger patients in terms of disease-free and relative survival.^{245,246}

However, the absolute survival benefits are smaller with age due to competing causes of death.^{245,247} It also remains uncertain whether the addition of oxaliplatin to 5-FU-based therapies increases survival in those aged over 70.^{117,246,248}

Meta-analyses of randomised trials indicate that radiotherapy improves cancer-related and overall survival compared to surgery alone, in addition to considerably reducing rates of local recurrence.^{249,250} While the magnitude of the reported survival benefits are relatively small, preventing recurrence is a key treatment aim as pelvic recurrent rectal cancer has dismal prognosis and poor quality of life.²⁵¹ The addition of preoperative chemotherapy to radiotherapy improves local control but does not appear to improve disease-free or overall survival.²⁵² Nonetheless, the evidence suggests the efficacy of radiotherapy and combined chemoradiation is the same irrespective of patient age.^{108,253}

Chemotherapy side effects are most apparent in healthy cells that multiply quickly, as these drugs indiscriminately target rapidly dividing cells. A substantial proportion of patients experience nausea and vomiting, despite the availability of modern antiemetics.^{254,255} Diarrhoea, oral mucositis, neutropenia, and cognitive dysfunction are also frequently reported.²⁵⁶⁻²⁵⁹ Chemotherapy-induced anaemia can be a contributor to the fatigue experienced by many cancer patients.²⁶⁰ Peripheral neuropathy caused by oxaliplatin may persist for a number of years for a small subset of patients.²⁶¹ Radiotherapy targets cancer cells within a treatment field, but may also affect normal tissues within this field. Acute side effects of pelvic radiotherapy include diarrhoea, skin problems, fatigue, urinary frequency, sexual dysfunction and pain.^{262,263} Late (long-term) effects are less common with modern techniques, but typically involve anorectal and sexual function.²⁶⁴ Generally, physical and functional well-being is improved by three or more years after diagnosis for most CRC survivors.²⁶⁵

Most evidence suggests that there are minimal age-related increases for fit older patients in toxicity of chemotherapy^{124,245,266,267} and radiotherapy.^{124,253,268,269} However, poorer health among older patients may enhance the risk of treatment-related complications.²⁷⁰

Predictors of severe chemotherapy toxicity for older patients identified in prospective studies include instrumental ADL score, falls, self-rated health and ECOG performance status.^{271,272} The role of comorbidity in adjuvant treatment is less clear and will depend on the specific condition. Significant survival benefits from chemotherapy without increases in toxicity-related hospitalisation have been reported for those with chronic obstructive pulmonary disease, heart failure, and diabetes.²⁷³ However, having diabetes does appear to increase the risk of recurrence, as well as short-term and long-term mortality.^{274,275} While those with comorbidities generally have less potential to benefit from adjuvant therapy, it is difficult to determine from current research whether poorer survival is a consequence of the comorbid condition, reduced tolerability, or decreased treatment use.²⁷⁶

In the absence of specific comorbid diagnoses, reduced organ function associated with the ageing process may increase chemotherapy toxicity. Careful monitoring and dose reduction for older people may therefore be required,¹²¹ particularly in combined chemoradiation.²⁷⁷ Decreases in renal blood flow can affect clearance of chemotherapy agents that are renally excreted.²⁷⁸ However, 5-FU is primarily metabolized by the liver,²⁷⁹ and the consequences of age-related changes in hepatic metabolism on chemotherapy are not well understood.²⁸⁰ Decreased secretion of gastric enzymes and splanchnic blood flow with age may impact the absorption of orally administered agents such as capecitabine.²⁷⁸ The prevalence of anaemia also increases with age,²⁸¹ and appears to be a risk factor for chemotherapy toxicity.²⁷² Greater levels of polypharmacy in older age and the possible interactions with chemotherapy drugs is an additional concern.²⁸² For older women with rectal cancer, increased risk of pelvic fracture following radiotherapy has been reported.²⁸³

Toxicity in clinical trials is rated according to defined objective criteria, such as the National Cancer Institute (NCI) common terminology criteria.²⁸⁴ Subjective toxicity is the extent to which people's well-being is influenced by objective toxicity measures.²⁸⁵ There is evidence that quality of life (QOL) is not significantly poorer for older patients with CRC who receive adjuvant therapy compared to those who do not,²⁸⁶ although it is not clear whether

chemotherapy or radiotherapy differentially affects the QOL of older patients compared to younger patients.^{263,287} The recent development of a patient-reported version of the NCI common terminology criteria²⁸⁸ may help to accelerate the move towards increased collection and reporting of QOL measures. Generally, older patients report similar or better QOL than their younger counterparts in the longer term,²⁸⁹ and QOL following surgery does not appear to differ by age.^{220,290} However, older patients may be less willing to sacrifice any level of impairment of function or QOL during treatment.

1.2.5. A focus on adjuvant therapy

This brief review suggests that pervasive age differences exist in the receipt of guideline-recommended adjuvant therapy for older CRC patients. Where a person is more likely to die of a comorbid condition than of cancer, or where poor health limits the ability to withstand treatment, these decisions will be clinically appropriate. However, an increasing number of individuals reach old age without measurable loss of functional capacity and free of severe medical conditions. These older adults are as likely to benefit from standard cancer treatment as younger adults do, with equal or at least manageable toxicity.

Chemotherapy and radiotherapy treatment decisions would appear to be more complex than surgical decision making for CRC, as surgery is now the mainstay of curative treatment. Given the expected growth in the number and proportion of older cancer patients, further exploration of the barriers and facilitators to the use of adjuvant therapy is required to ensure equal access to care and improved outcomes for this population. This thesis therefore largely focuses on exploring the reasons for the differences in adjuvant treatment of older CRC patients. The use of the term “difference” instead of “disparity” is a deliberate choice. While historically meaning “a large difference”, to many, disparity implies an inequity or an injustice rather than a simple inequality.²⁹¹ This term may not reflect the many shades of grey in decision making for older CRC patients.

1.3. Factors that may influence age differences in treatment

1.3.1. Underrepresentation in research

While older patients make up the majority of CRC cases, they are underrepresented both in clinical trials and in health research generally. Older people make up only between 22% and 32% of clinical trial participants.²⁹²⁻²⁹⁴ The median age of patients in clinical trials is 10 years younger than the median age of CRC incidence,¹¹³ and little data is available for patients older than 80 years.¹²⁴ Reasons for this underrepresentation can be broadly separated into barriers to opportunity to participate in trials, barriers to awareness of trials, and barriers to acceptance of trial enrolment.²⁹⁵

Of 323 cancer trials recruiting adults in Australia in 2009, 11.1% had a maximum age criteria of 60 or above, with 70-79 years being the most frequent age cut-off.²⁹⁶ Exclusion criteria such as comorbidities and functional status are also major contributors to the underrepresentation of older people in clinical trials,²⁹⁵ though older people are still less likely to be offered participation even when these factors are not present.²⁹⁷ Studies have generally found only small differences between the willingness of older and younger patients to participate in trials.²⁹⁷ However, they are less likely to actively seek them out,²⁹⁸ and report other barriers to participation such as transport.²⁹⁹ While there is increasing attention on and participation of older people in research,³⁰⁰ most clinical trials conducted to date have not addressed the most pressing issues in ageing and cancer, such as the impact of comorbidities, reduced physiologic reserve and polypharmacy on treatment tolerance, or changes in drug pharmacokinetics and pharmacodynamics.³⁰¹ There is therefore less certainty regarding the safety and effectiveness of adjuvant therapy for the very old and those with poorer fitness and functionality, resulting in fewer evidence-based guidelines for this population and potentially contributing to practice variation.

Older people are underrepresented in virtually all aspects of health-related research.³⁰² A Medline search was conducted using Medical Subject Headings (MeSH) to determine the

total proportion of cancer literature focusing on cancer and ageing (see [Appendix 1.3](#)). Of over two million articles indexed to cancer, 23.7% of articles were also indexed to a subject heading of “aged” or “aging”. Only 0.33% were indexed with an ageing field as a primary focus of the article. A colorectal cancer-specific search yielded similar findings, with just 423 articles focusing on issues of the older patient in CRC (0.29%). A recent literature review of the QOL of cancer survivors, for example, noted that just 4 of 173 identified studies focused on older patients.³⁰³ More non-interventional epidemiologic studies are required alongside clinical trials to ensure improved understanding of the unique needs of older patients and the causes of health inequalities.

1.3.2. Issues in measurement

Inequalities in health care access and outcomes have emerged as a public policy concern over the last few decades.³⁰⁴ Originally focusing on racial and ethnic subgroups, more recently the scope has been expanded to include other priority populations such as women, people with disabilities, those living in rural areas, and older people. A lack of consistency across studies in adjusting for confounders is an issue that has been documented in racial and ethnic disparities research.³⁰⁵ In the cancer field, the effect of older age on surgical and adjuvant therapy outcomes remains conflicting because of limitations in measuring and adjusting for comorbidities and health status.^{306,307} This is a particular concern where population-based observational cohorts are used to generate evidence for treatment effectiveness, as lower rates of non-cancer deaths or early separation of survival curves may indicate methodological biases in favour of the treated group.^{306,308,309} These measurement issues may add an additional layer of complexity for clinicians when considering the evidence.

Issues also appear to exist in the measurement of patient-reported outcomes (PROs) such as quality of life (QOL) and supportive care needs. PROs are increasingly being recognised alongside traditional survival and recurrence measures as integral to both cancer research and treatment decision making.³¹⁰⁻³¹² These measures are particularly valuable in

comparing a growing range of treatment options for an ageing population with increasingly complex health problems.³¹³ Despite carrying a more substantial burden of disease and disability, older people with CRC generally report similar or better QOL and similar or fewer unmet needs than younger patients.³¹⁴⁻³¹⁶ It is possible that these contradictory findings result from a number of identified concerns, including a lack of elderly-specific tools to encompass the scope of relevant issues,³¹⁷ underreporting of symptoms,³¹⁸ or missing data due to patient attrition.³¹⁹ The potential implications of these factors for older patients' care and outcomes should be examined further.

1.3.3. Patient-based factors

Patients who decide not to undergo adjuvant therapy are significantly older than those who accept treatment.^{165,166,175,320-322} Much of the recent focus on older cancer patients has been through a geriatric lens, i.e. exploring the impact of ageing-related conditions on cancer and physician decisions for cancer treatment. However, understanding the decision-making processes of older patients may require greater exploration from a gerontology perspective, i.e. including social, cultural, psychological, lifespan and life course concepts.⁴

Barriers to adjuvant therapy use in older cancer patients identified in previous studies include side effects, QOL, stage of life considerations, social support, transportation and costs.³²³⁻³²⁷ However, older patients may also be more vulnerable to forgoing worthwhile treatment because of limited insight into their diagnosis and prognosis, or perceptions of treatment benefits and risks.³²⁸ This vulnerability could result from a number of interrelated factors including poorer health literacy,^{329,330} difficulties processing and remembering information,³³¹ cognitive and sensory deficits,³³² asking physicians fewer questions,³³³ and typically preferring less information and less involvement in treatment decision making.³³⁴⁻³³⁶ Older patients may have more negative attitudes and beliefs towards adjuvant treatment,³³⁷ and appear to have a greater degree of cancer fatalism,^{338,339} perhaps from growing up in a time when cancer survival was much poorer.⁶⁸ However, less is known about whether these factors uniquely affect the adjuvant therapy decision making of older cancer patients.

Those over 65 years report significantly fewer discussions about chemotherapy.³³⁷ The involvement of older patients in decision making discussions may also be challenged by physician assumptions that they prefer a passive role,³²⁹ perceptions that their cognition or communication is deficient,³⁴⁰ or the reportedly poorer responsiveness and communication that physicians have with older patients in the clinical encounter.^{329,332} This is a major concern, given that most older patients are willing to consider chemotherapy³⁴¹ and the primary determinant of treatment decisions is physician advice.³⁴²

1.3.4. Translation of evidence

Evidence-based practice (EBP) is the use of current best evidence in conjunction with clinical expertise and patient values to guide health care decisions.³⁴³ A significant gap often exists between scientific evidence or research-based guidelines and actual clinical practice.³⁴⁴ The study of the methods, interventions and variables that influence the adoption of EBPs by individuals or organisations is described as translational research.³⁴⁵ General factors identified in systematic reviews of EBP translation include lack of knowledge or awareness, physician attitudes and characteristics, evidence barriers, organisational or system barriers, and lack of support to implement guidelines.^{346,347}

Many of these areas have been previously implicated in the uptake of adjuvant therapy in older cancer patients. Previous physician surveys have revealed that both surgeons and oncologists are less likely to recommend adjuvant therapy for older patients based on their age alone.³⁴⁸⁻³⁵¹ Differences in treatment recommendations and receipt have been associated with physician characteristics such as younger age and higher volume.^{159,351,352} Physicians with less awareness of current evidence generally,³⁵³ or of geriatrics specifically,⁶⁸ may assume that treatment would cause a loss of function simply on the basis of patient age. Negative age-related value judgments have also been implicated in surgeons' general decision-making processes,³⁵⁴ and may reflect wider attitudes of society about ageing.³⁵⁵ The associations between physician knowledge and attitudes and how these directly influence adjuvant therapy recommendations requires further exploration.

Institutional and health system factors may also explain age differences in adjuvant therapy receipt. The number of oncologists within a patient's residential area is associated with greater access to chemotherapy after surgery.¹⁷⁴ Significant variation between hospitals in rates of adjuvant chemotherapy for colon cancer has been noted,^{173,356} and may be explained by hospital characteristics such as running an accredited cancer surgery program.³⁵⁷ Colorectal surgeons have also been found to hold significantly stronger preferences against all adjuvant options compared with oncologists.³⁵⁸ Referral to oncology is therefore a crucial factor in receipt of chemotherapy among older patients.¹⁸¹ Higher oncology consultation rates appear to be associated with surgeons who work closely with oncologists, both in teaching hospitals and small hospitals,^{359,360} and these surgeons are less likely to have patients "get lost in the system".³⁶¹ Nevertheless, older patients remain less likely to receive adjuvant therapy even after seeing an oncologist.^{175,185}

Clinicians often report high satisfaction with clinical practice guidelines, but may consider them impractical or too rigid to apply to individual patients.³⁶² For older patients, the increasing prevalence of comorbidity appears to contribute significantly to variation in physician recommendations.³⁴⁹ Research to guide clinicians on the impact of treatment on these vulnerable adults is sparse. While screening and subsequent comprehensive geriatric assessment have been suggested as an effective approach to identify those at risk of chemotherapy toxicity,³⁶³⁻³⁶⁵ there remains little consensus on which screening tool clinicians should use or which CGA elements should be included.^{89,366} However, practice variation and reduced rates of treatment appear to exist even for fit older patients.

1.3.5. Is it worth it?

A substantial debate in the literature exists over whether older patients are actually overtreated.^{306,367-369} Certainly, these adjuvant therapy decisions require careful consideration of present-day risks against less well-defined future gains, for a sub-population that is not as robust as their younger counterparts. Older patients clearly have lower potential for absolute survival benefits from adjuvant therapy in terms of years left

to live, and may place a different value on the risk of adverse effects and logistical challenges of treatment. Treatment decisions also occur against a backdrop of increasing public focus on health expenditure and the rising costs of cancer treatment,³⁷⁰ as well as frequent discussion about the impending “silver tsunami” that is portrayed as set to cause “unimaginable chaos” for public services.³⁷¹

Cost-effectiveness is therefore an important concept in the treatment of older patients. Benefits are typically measured in terms of the number of quality-adjusted life years gained,³⁷² which accounts for both the quantity and quality of life lived. It is increasingly argued that cost-effectiveness analysis should take into consideration social concerns,³⁷³ as opposed to valuing every year of “quality” life equally regardless of the person who gains it. There is a general societal preference to prioritise the health of younger adults over older adults.^{372,374} This may be due to a number of reasons including the potential for productivity, remaining life expectancy, and the “fair innings” principal.³⁷⁵ However, there is also a strong community desire to reduce health inequalities and prioritise disadvantaged groups. Johnstone and colleagues believe that much of the political debate around population ageing in Australia represents “demographic alarmism”, that is both misleading and harmfully prejudicial to the health and social welfare of older Australians.³⁷¹ There is also substantial push-back from community groups against perceived ageism in cancer treatment.³⁷⁶ A law banning age discrimination in the provision of healthcare was fully implemented in the UK in 2012, following public reports of poor treatment and outcomes of older patients in the National Health Service.³⁷⁷

While the acquisition cost of 5-FU/LV chemotherapy is less than A\$1,000 for an average course,³⁷⁸ the current recommendation to incorporate oxaliplatin in this regime for an additional A\$12,000³⁷⁸ perhaps deserves further economic consideration for older patients, given the unclear survival benefits.¹²⁴ These costs occur alongside administration costs (\approx A\$5,000)³⁷⁹ as well as the costs of any adverse events.³⁸⁰ However, the costs of not receiving recommended adjuvant therapy may far outweigh this, both in terms of the very

high treatment costs for recurrent metastatic cancer³⁸¹ as well as substantial loss of quality and quantity of life. Eighty percent of recurrences arise within the first two years after resection, and the median survival following recurrence in stage III CRC is 12.5 months.³⁸² The average life expectancy of a 70 year old in Australia is 15-17 years.³⁰ This suggests that older patients are a vulnerable population from which valuable and sometimes lifesaving therapy is withheld. Yet, considerable grey areas mean there is a need to further explore how these decisions are made by both patients and clinicians.

1.4. Specific gaps in existing literature

1.4.1. Shifting focus to the “whole person”

The move towards patient-centred models of health care in the last few decades³⁸³ appears to be a promising step for patients in terms of satisfaction and perceived quality of care.³⁸⁴

A key attribute of these models is holistic care, i.e. recognising and responding to the complete needs of the whole person.³⁸⁵ Health measures most relevant to older adults (e.g. comorbidity, functional status) are rarely incorporated into oncology clinical trials.^{386,387}

Many risk tools only incorporate a limited evaluation of health status,^{388,389} despite general acknowledgement that treatment decisions should be based on the assessment of individual life expectancy and predicted treatment tolerance and not on chronologic age. Typically, comorbidity is the sole health-related factor used in the exploration of age differences in treatment^{125,126} and in barriers to the treatment of older patients.³⁵¹

Much of the research exploring patient preferences for adjuvant therapy also focuses on weighing survival benefit against treatment toxicity.³⁹⁰ While survival and toxicity are clearly central to these decisions, this emphasis tends to ignore the impact of logistical, social and emotional drivers on treatment decision making. The fact that patient and treatment characteristics are not a consistent predictor of preferences,³⁹¹ and the willingness of many patients to consider even negligible benefits sufficient to make chemotherapy worthwhile,³⁹² imply that there are important “whole person” considerations requiring further exploration.

1.4.2. Relativity

If two percent of a treatment group die compared to four percent of a control group, this finding can be presented as a two percent absolute risk reduction, or a more impressive-sounding 50% lower risk of death. Relative or proportional reductions in risk are not readily understood by most patients.³⁹³ Physicians' interpretations of the magnitude and significance of research findings can also be affected by the reporting of results in exclusively relative terms.³⁹⁴ In patient-reported outcomes research, age is often presented solely as a relative predictor, potentially affecting clinicians' perceptions about the treatment and care that older patients need.

Relativity may also sometimes be underused when exploring the barriers to adjuvant treatment receipt. A number of studies focusing on barriers to treatment have involved older people only. While providing an important overview of the issues, this can make it difficult to determine what is uniquely different about the decision-making processes and barriers for older patients in comparison to their younger counterparts.

1.4.3. A local context

Australia has a land mass roughly the size of the continental United States and a population of just under 23 million people.²¹ While it is one of the least densely populated countries in the world, Australia is highly urbanised. One third of Australia's population resides in New South Wales (NSW), and 64% of these people live in the Greater Sydney region.³⁹⁵ More than a quarter of Australians were born overseas (26%),³⁹⁶ a considerably higher proportion than Canada, the USA, or the UK. Australian life expectancy and health is among the highest in the world.³⁹⁷ However, some groups have notably poorer health status, such as those living in rural and remote areas³⁹⁸ and Aboriginal and Torres Strait Islander peoples (three percent of the population).³⁹⁹ As the most populous state, NSW is a representative sample of the sociocultural and geographic diversity of the country, though with fewer people living in remote areas.

Australia has a taxpayer-funded universal health care system (Medicare), supplemented by a substantial private sector that is involved both in health care delivery and financing. Medicare consists of three components – medical services (including visits to general practitioners and other medical practitioners), hospital treatment as a public patient, and prescription pharmaceuticals.³⁹⁷ Since 1993, the Australian Pharmaceutical Benefit Scheme (PBS) has insisted on appropriate economic evidence before authorising public funding of a new drug.⁴⁰⁰ The recommended regimes of capecitabine and 5-FU for stage III colon cancer, either alone or in combination with oxaliplatin, are all PBS listed. Surgery and chemotherapy administration are covered by Medicare for anyone electing to be treated as a public patient, and are also covered by private health insurance. Radiotherapy has been found to be cost-effective in rectal cancer.⁴⁰¹ However, outpatient radiotherapy is not covered by private insurance, which can result in substantial out-of-pocket costs in parts of the country where the only radiotherapy centre is a private facility.⁴⁰²

Despite a steadily growing population of older people with cancer, geriatric oncology in Australia is in its infancy.⁴⁰³ Australia's cultural diversity, expansive distances, medical funding from public resources and generally high health outcomes, also mean that barriers and attitudes in the uptake of adjuvant therapy may be different to other countries and regions. In addition, the investigation of Australia-specific issues in treatment receipt and the development of tools based on local data may give findings greater clinical credibility.

1.5. Thesis aims and hypotheses

Older people with CRC are a growing and underresearched group who appear to be vulnerable to poor treatment and outcomes. The overall aim of this thesis is to explore the barriers to evidence-based care for older people with colorectal cancer, with a focus on receipt of guideline-recommended adjuvant therapy. More specifically, the aims of this thesis are:

- 1) To explore issues in the measurement of patient-reported outcomes that may contribute to age differences in treatment, by:
 - a. Quantifying differences in the levels of need and unmet need of older and younger colorectal cancer patients in the three months following surgery
 - b. Determining age differences in levels of missing data and the effect of imputation methods on estimates of older patients' quality of life after colorectal cancer surgery
- 2) To establish current levels of adjuvant therapy utilisation for colorectal cancer in NSW and determine patient and hospital-level predictors of treatment receipt
- 3) To investigate physician-based and patient-based barriers to the receipt of adjuvant therapy, by:
 - a. Identifying factors that affect colorectal surgeons' decisions to refer older patients for adjuvant therapy and determining relationships between surgeon knowledge, opinions and self-reported practice
 - b. Exploring the association between patient age, factors that influence patients' chemotherapy treatment decisions, and preferences for information and involvement in treatment decision making
- 4) To develop a mortality risk model that could be used by clinicians to assist adjuvant chemotherapy decision making

It is hypothesised that:

- 1) a. Older patients with colorectal cancer will have lower levels of post-operative unmet need but a greater proportion of met needs compared to younger patients
- b. Greater levels of missing data in quality of life questionnaires will be associated with older age and multiple imputation of missing data will more accurately estimate quality of life than simple mean imputation
- 2) Rates of adjuvant therapy utilisation for colorectal cancer in NSW will have increased from previously measured rates and patient age and hospital of surgery will be a significant predictors of adjuvant therapy receipt
- 3) a. Patient age will affect colorectal surgeon's decisions to refer older patients for adjuvant therapy and surgeon knowledge and opinions will be associated with self-reported practice
- b. Older patients will place greater importance on physician recommendations for adjuvant chemotherapy and maintaining quality of life than younger patients and will prefer less information and involvement in treatment decision making
- 4) A mortality risk model for chemotherapy decision making with good discrimination and calibration will be able to be developed using linked population-based data

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Appendix 1.2. Definitions of survival and life expectancy

Term	Definition
Overall survival (all-cause)	Proportion of people who are alive at a given time point after cancer diagnosis or treatment, or the probability of being alive
Cancer-specific survival	Cancer survival in the absence of other causes of death, based on each person's recorded cause of death
Relative survival	Cancer survival in the absence of other causes of death, based on an adjustment using a comparable cancer-free cohort
Disease-free survival	Proportion of people who are alive and cancer free at a given time point
Progression-free survival	Proportion of people who have not experienced any new cancer growth or spread at a given time point
Life expectancy	Average remaining years of life a person can expect to live at a given age
Disability-free life expectancy	Average remaining years of life expectancy without disability*
Healthy life expectancy	Average remaining years of life expectancy in good health*

*Definitions of "disability" and "good health" may differ

Appendix 1.3. Proportion of literature focusing on cancer and ageing*

MeSH headings	Medline search							
	1	2	3	4	5	6	7	8
Neoplasms	X	X	X	X				
Colorectal neoplasms					X	X	X	X
<i>AND</i>								
Aged ^b , <i>OR</i>		X	X	X ^a		X	X	X ^a
Ageing, <i>OR</i>		X	X	X ^a		X	X	X ^a
Geriatrics, <i>OR</i>			X	X ^a			X	X ^a
Health services for aged, <i>OR</i>			X	X ^a			X	X ^a
Geriatric assessment, <i>OR</i>			X	X ^a			X	X ^a
Geriatric nursing, <i>OR</i>			X	X ^a			X	X ^a
Geriatric psychiatry			X	X ^a			X	X ^a
<i>Hits</i>	2,556,938	605,621	608,718	8,468	147,997	50,978	51,161	423
<i>% of cancer research</i>	100.00	23.67	23.81	0.33	100.00	34.45	34.57	0.29

*Medline search to end of 2012

^aArticles in which the subject term (or sub-branches) are considered to be the primary focus of the article

^bSub-branches include "Aged, 80 and over" and "Frail elderly"

2

Measurement

This chapter uses existing prospectively collected data to examine issues in the measurement of patient-reported outcomes (PROs) that may affect the treatment and care that older patients receive.

Adjuvant therapy decisions for this population involve careful consideration of the risks of treatment against potential survival benefits. These risks are increasingly being measured using PROs such as quality of life and supportive care needs. Accurate ascertainment, analysis and reporting of PROs in research is therefore required to inform patients' and clinicians' treatment decision making. Issues in the measurement of PROs may also be important considerations in monitoring the effects of treatment on older individuals.

This chapter is presented as the following papers:

1. Jorgensen ML, Young JM, Harrison JD, Solomon MJ. Unmet supportive care needs in colorectal cancer: differences by age. *Supportive Care in Cancer* 2012; 20(6): 1275-81.
Available: <http://link.springer.com/article/10.1007/s00520-011-1214-9>
2. Jorgensen ML, Young JM, Solomon MJ. Older cancer patients and missing data in quality of life questionnaires. [Submitted]

CONTRIBUTION STATEMENT

Dear co-authors,

RE: Jorgensen ML, Young JM, Harrison JD, Solomon MJ. Unmet supportive care needs in colorectal cancer: differences by age. *Supportive Care in Cancer* 2012; 20(6): 1275-1281.

I would like to use the above paper as one of the chapters of my PhD thesis and request your permission to do so. As one of the requirements of the Academic Board of the University of Sydney, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author contributions

Jorgensen ML conceived and designed the analysis, reviewed the literature, analysed and interpreted the data, drafted the manuscript. **Young JM** conceived and designed the original research protocol, analysed and interpreted the data, critically revised the paper. **Harrison JD** designed the original research protocol, original patient recruitment and data collection, interpreted the data, critically revised the paper. **Solomon MJ** conceived and designed the original research protocol, interpreted the data, critically revised the paper. All authors read and approved the final draft of the manuscript.

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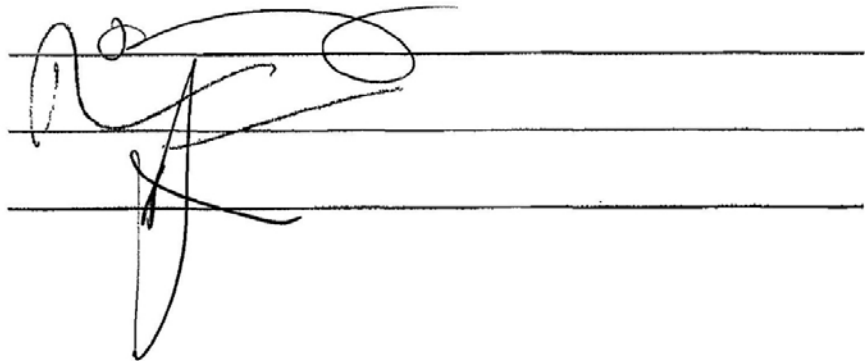
Kind regards,

Mikaela Jorgensen

Jane M Young

James D Harrison

Michael J Solomon



Study 1. Unmet supportive care needs in colorectal cancer: differences by age

2.1.1. Abstract

PURPOSE: Cancer is primarily a disease of ageing, yet the unmet supportive care needs of older cancer patients are not well understood. This study aims to explore how unmet needs differ by age over the 3 months following colorectal cancer surgery.

METHODS: Control groups from pilot phases of an ongoing randomised trial completed the Supportive Care Needs Survey-Short Form 34 (SCNS-SF34) at one and three months following hospital discharge (n=57). Multiple regression was used to investigate whether age was an independent predictor of unmet needs in each of the five SCNS-SF34 domains. The proportion of patients with unmet needs and the pattern of item responses were compared between patients aged <65 and ≥ 65 years at both time points.

RESULTS: Older age independently predicted significantly lower levels of unmet need than younger age in nearly all SCNS-SF34 domains. However, more than half of all older patients had unmet needs at both time points (56% and 65%), and age differences in unmet needs were less apparent by 3 months. Older patients were less likely than younger patients to report 'satisfied' needs, as older patients were significantly more likely to report items were 'not applicable' at both one month (mean difference 29%, $p<0.001$) and three months (mean difference 23%, $p=0.01$).

CONCLUSIONS: While older patients reported lower levels of unmet need than younger patients, the high prevalence of unmet needs and age differences in item response patterns indicate that further research is needed to determine whether older patients' needs are being accurately captured.

This is an author-created version of the accepted manuscript. The final publication is available at www.springerlink.com.

2.1.2. Introduction

Colorectal cancer is primarily a disease of the elderly. More than 65% of colorectal cancer cases occur in patients over 65 years of age,² and this figure is expected to rise with population ageing.²⁹ Yet little is known about how older patients cope with cancer and cancer treatment.

Supportive care includes treatment to optimise cancer patients' physical comfort and functional ability, as well as non-tumour specific treatment such as social, informational, economic, psychological and spiritual support.^{1,16} When needs for supportive care are not met, patients' quality of life and satisfaction with care may be affected.⁵ Vulnerable patient groups can be identified through exploring socio-demographic and clinical predictors of unmet needs. Predictors of unmet needs vary across studies, and include income, advance disease and depression.¹⁶ Patients with poor health status and those lacking social support, for example, are more likely to have higher levels of unmet need.¹⁶ These factors have been associated with increasing age.^{9,26,34} However, older patients are generally reported to have lower levels of unmet need than younger patients across a range of cancer types.^{4,6,14,28,30-33}

The cause of these conflicting findings is difficult to determine as patient age is not often the focus of unmet needs research. For example, previous studies have not explored whether older patients have lower levels of unmet need because they are more likely to have their needs 'met' than their younger counterparts. The absolute prevalence of unmet needs in older patients is also difficult to determine from previous research, as relative comparisons of levels of unmet need are typically used. While valuable, these relative comparisons may ignore the impact that any unmet needs have on patients who are older and perhaps more unwell. In addition, unmet needs are not often measured prospectively

over time.¹⁶ Apparent age differences in unmet needs could be affected by the timing of assessment, as older patients tend to recover more slowly from cancer treatment.¹⁰ Thus, more research is needed to provide a clearer picture of age-related differences in supportive care needs.

A greater understanding of the needs and unmet needs of older patients is also vital to ensuring that the best decisions are made for treatment and care. It has been suggested that many older people do not report their health care needs for a range of complex reasons.³⁵ This may mean that they are less likely to receive care which could improve their health outcomes, and may in turn affect physicians' decisions about suitability for adjuvant treatment such as chemotherapy.²² Given the conflicting predictors of unmet needs in previous research and the unexplored issues in the unmet needs of older patients, the aims of this study were to determine (a) whether age independently predicts unmet needs over the three months following colorectal cancer surgery, and (b) whether the extent of need and unmet needs differs by age.

2.1.3. Method

Participants

The study used existing data collected from participants in the control groups of two trials of a supportive care intervention for people with colorectal cancer, which were approved by their local area health service ethics review committees. Control groups were used so that the measurement of their needs would not be affected by the receipt of an intervention. Eligibility criteria and recruitment processes were identical for both studies. All patients aged over 18 years who were admitted to Royal Prince Alfred Hospital, Sydney for surgery for colorectal cancer between July and December 2006 (for study 1)³⁸ and between June 2007 and June 2008 (for study 2)¹⁵ were assessed for eligibility. Patients were considered ineligible if they were discharged to another health facility (such as a hospice), died during admission, or were cognitively impaired such that they could not give informed consent or complete questionnaires.

Procedure

Prior to discharge from hospital, baseline demographic and clinical information was obtained. Several outcomes were assessed at baseline, one month and three months after discharge from hospital as part of the aforementioned supportive care intervention trials.^{15,38} Unmet supportive care needs were measured using the Supportive Care Needs Survey- Short Form 34 (SCNS-SF34).⁷ Responses to this survey at both one and three months formed the dataset for the present analyses.

The SCNS-SF34 is a validated self-administered questionnaire that asks patients to rate their level of need for additional support over the last month on a range of items in five needs domains.⁷ These are psychological, health system and information, physical and daily living, patient care and support and sexuality. Patients are asked whether each item is 'not applicable' (no need), 'satisfied' (need already satisfied), 'low need', 'moderate need' or 'high need' (need for additional help). Standardised scores are calculated for each domain (possible range 0–100).²³ The instrument has high internal consistency and convergent validity with three other measures of psychological well-being.⁷

Data analysis

Participants were divided into 'younger' (<65 years) and 'older' (≥65 years) age groups for analysis. The age of 65 was selected to divide the sample as (1) this was the median age of the sample, and (2) this cut-off is frequently used to define older age.²⁵ Mean standardised scores in each of the five SCNS-SF34 domains at one and three months were calculated for the younger and older groups.²³ Demographic/clinical characteristics (e.g. education, cancer site) of both age groups were compared using t-tests and chi-square tests.

Multiple regression analyses were used to test for independent associations between demographic/clinical characteristics and (1) mean scores for all five needs domains at both one and three months, and (2) the mean differences in domain scores between one and three months, to determine independent predictors of change in unmet needs scores over

time. A manual backwards elimination approach to modelling was used. Any of the demographic/clinical characteristics measured at baseline which indicated a possible relationship to domain scores ($p < 0.25$) were included in the base models.¹⁷ Plots of each demographic/clinical variable against domain scores were also examined for outliers and approximate linearity before inclusion in the models. Variables with the least effect on domain scores were dropped out of the models one at a time until all predictors were statistically significant. Age, as the variable of interest, was retained in all models. Only the results for the final models in all five needs domains at both one and three months are presented, as multiple regression was used primarily to determine independent associations between age and domain scores.

The extent of supportive care needs was measured in two ways. The proportion of patients who reported any unmet needs ('low/moderate/high need') was calculated for both time points and compared between younger and older patients using chi-square tests. The study also investigated whether older patients were more likely than younger patients to have their needs 'met' ('satisfied'). The mean differences in the proportion of 'not applicable' and 'satisfied' responses were compared between older and younger patients using independent samples t-tests at both one and three months.

2.1.4. Results

Of 57 patients, 28 were younger than 65 years of age and 29 were aged 65 and over (see Table 1). Older patients were significantly less likely than the younger patients to have completed high school or tertiary education ($p = 0.02$), be employed ($p < 0.001$), live with others ($p = 0.02$), receive adjuvant therapy ($p = 0.04$) and have no comorbid conditions ($p = 0.05$). All other characteristics were comparable between age groups.

Table 1. Characteristics of participants by age group at baseline

Characteristic	Younger group, n (%)	Older group, n (%)	p level
Total participants	28 (100)	29 (100)	
Age in years (mean/SD)	50.9 (11.6)	74.3 (6.3)	<.001**
Male	14 (50)	19 (66)	.24
Born in Australia	17 (61)	18 (62)	.92
English spoken at home	23 (82)	23 (80)	.79
Completed high school or tertiary education	20 (71)	9 (31)	.02*
Employed full or part time	19 (68)	5 (17)	<.001**
Private health insurance	12 (43)	8 (28)	.23
Lives alone	5 (18)	14 (48)	.02*
Site of cancer			.88
Colon	13 (46)	13 (45)	
Rectosigmoid	2 (7)	4 (14)	
Rectal	13 (46)	12 (41)	
Dukes stage of cancer			.81
A	7 (25)	6 (21)	
B	9 (32)	6 (21)	
C	8 (29)	10 (34)	
D	2 (7)	3 (10)	
Non-cancerous tumour ^a	2 (7)	4 (14)	
Metastatic disease	3 (11)	2 (7)	.61
Received adjuvant therapy	14 (50)	7 (24)	.04*
One or more comorbid conditions	12 (43)	20 (69)	.05*

^aPathological stage identified after randomisation, all surgically treated with curative intent; *p≤0.05; **p≤0.01

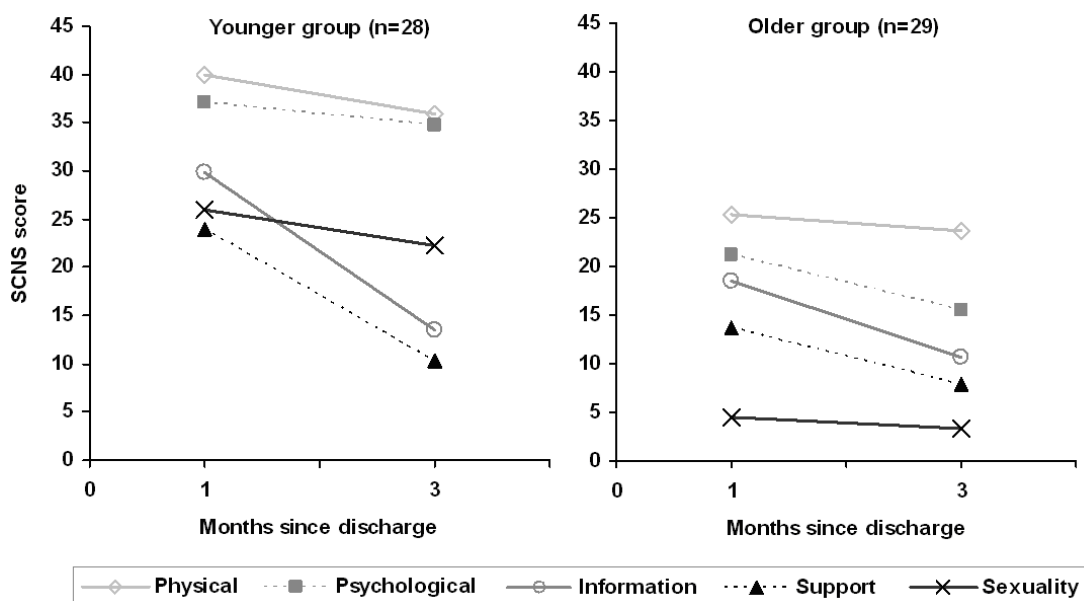
Decreasing age independently predicted unmet needs for nearly all domains at both time points (see Table 2). Older patients had significantly lower levels of unmet need in all SCNS-SF34 domains except patient care/support at one month after hospital discharge. At three months, older patients had significantly lower levels of unmet need in all SNCS-SF34 domains except patient care/support and health system/information. Unmet needs were highest in both groups in the physical and psychological domains (see Figure 1). Notably, the older group had very low scores for unmet needs in the sexuality domain. While levels of unmet need decreased over time for both age groups, the decrease in mean scores tended to be larger in the younger group. These results were not significant however.

Table 2. Multiple regression results for age and other independent predictors

Domain	Time ^a	Model statistics	Variable	b (95% CI)	p level
Psychological	1 m	$R^2_{adj}=0.096$, $F_{1,49}=6.34$, $p=0.02$	Age	17.1 (3.5-30.7)	.02*
	3 m	$R^2_{adj}=0.19$, $F_{2,44}=6.42$, $p=0.004$	Age	22.3 (8.3-36.3)	.003**
			Private health	16.3 (1.7-30.8)	.03*
Diff	$R^2_{adj}=-0.02$, $F_{1,44}=0.34$, $p=0.57$	Age		.57	
Physical & daily living	1 m	$R^2_{adj}=0.12$, $F_{1,50}=7.64$, $p=0.008$	Age	16.5 (4.5-28.4)	.008**
	3 m	$R^2_{adj}=0.06$, $F_{1,45}=4.11$, $p=0.05$	Age	15.1 (0.2-29.9)	.05*
	Diff	$R^2_{adj}=0.15$, $F_{3,42}=3.68$, $p=0.02$	Age		.12
			Cancer stage	13.8 (1.9-25.8)	.03*
		<i>n</i> in household	14.9 (0.7-29.2)	.04*	
Sexuality	1 m	$R^2_{adj}=0.30$, $F_{4,44}=6.20$, $p<0.001$	Age	17.6 (4.4-30.7)	.01**
			Gender	18.0 (5.1-31.0)	.008**
			Comorbidity	17.5(1.5-33.6)	.03*
			Cancer site	13.8 (0.0-27.5)	.05*
	3 m	$R^2_{adj}=0.42$, $F_{4,41}=9.05$, $p<0.001$	Age	15.8 (4.4-27.2)	.05*
			Gender	19.2 (8.2-30.1)	.001**
			Comorbidity	18.0 (4.1-31.9)	.01**
			Cancer site	13.2 (1.6-24.8)	.03*
Diff	$R^2_{adj}=0.12$, $F_{2,40}=3.78$, $p=0.03$	Age		.60	
		Metastases	22.6 (5.7-39.6)	.01**	
Health system & information	1 m	$R^2_{adj}=0.22$, $F_{3,47}=5.75$, $p=0.002$	Age	11.0 (1.0-20.9)	.03*
			Metastases	20.1 (3.1-27.1)	.02*
			Language	12.9 (0.2-25.6)	.05*
	3 m	$R^2_{adj}=0.01$, $F_{1,44}=1.47$, $p=0.23$	Age		.23
Diff	$R^2_{adj}=0.15$, $F_{2,42}=4.93$, $p=0.01$	Age		.11	
		Gender	12.8 (2.9-22.8)	.01**	
Patient care & support	1 m	$R^2_{adj}=0.04$, $F_{1,49}=3.02$, $p=0.09$	Age		.09
	3 m	$R^2_{adj}<0.001$, $F_{1,44}=1.01$, $p=0.32$	Age		.32
	Diff	$R^2_{adj}=0.05$, $F_{1,43}=3.11$, $p=0.09$	Age		.09

^a1 m = 1 month, 3 m = 3 months, diff = difference (3 months – 1 month); * $p\leq 0.05$; ** $p\leq 0.01$

Figure 1. Levels of unmet need by domain and age group*

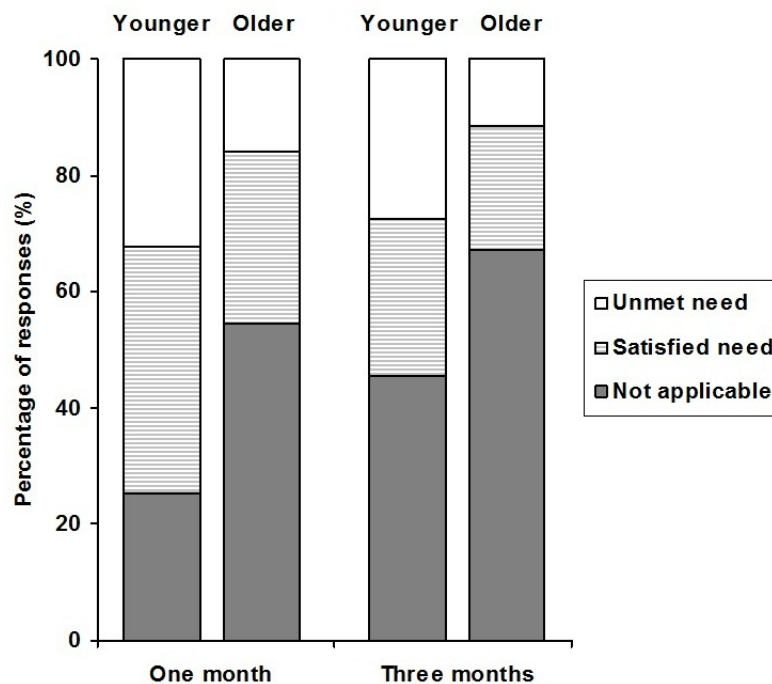


*Higher scores indicate higher levels of unmet need

A number of other factors also independently predicted unmet needs. For example, gender, comorbidity and type of cancer predicted unmet needs in the sexuality domain at both one and three months (model $p < 0.001$). Other predictors of domain scores included language, stage of disease, private health insurance and living alone (see Table 2).

A significantly greater proportion of younger patients than older patients had unmet needs at one month (89% vs 56%; $\chi^2 = 7.137$, $p = 0.008$). However this difference was no longer significant at three months (79% vs 65%; $\chi^2 = 1.142$, $p = 0.29$). The pattern of item responses was also calculated (see Figure 2). Older participants reported items were 'not applicable' (no need) significantly more often than younger participants. This occurred both at one month (54% vs 25%, $p < 0.001$, 95% CI 14.4–43.5) and three months (67% vs 44%, $p = 0.01$, 95% CI 5.1–41.0). Consequently, older patients were significantly less likely than younger patients to report 'satisfied' needs at one month (29% vs 42%, $p = 0.04$, 95% CI 0.9–24.4). At three months they were only as likely as younger patients to report 'satisfied' needs (19% vs 23%, $p = 0.52$, 95% CI 8.1–15.9).

Figure 2. Percentage of answers in each response category by age group



2.1.5. Discussion

In this study, age was the most frequent independent predictor of unmet needs. Older patients reported significantly lower levels of unmet need compared to younger patients in nearly all SCNS-SF34 domains at both one and three months after surgery for colorectal cancer. However, a considerable proportion of older patients had unmet needs, and age differences in unmet needs were less apparent by three months. Older patients were also less likely than younger patients to report ‘satisfied’ needs, as they were significantly more likely to report that items were ‘not applicable’ (no need).

Many other studies have similarly reported that older patients have significantly lower levels of unmet need compared to younger patients, across a range of cancer types.^{4,6,14,28,30-33} Yet the absolute prevalence of unmet needs in older cancer patients is unclear. In this current study, more than half of all older patients still had some unmet needs at both one and three months after hospital discharge. While younger patients may express greater unmet needs, it is possible that older patients have less capacity to cope

with any level of unmet needs due to poorer general health and lower levels of social support.²⁶ In addition, the unmet needs scores of older patients did not decrease as much as younger patients over time, and the proportion of older patients with unmet needs actually increased from one to three months. This suggests that their unmet needs are potentially more persistent and harder to address. The impact of unmet needs on older patients therefore requires further exploration.

This study was unique in comparing the extent of 'met' and 'unmet' need by age. One priority of needs assessment is to determine whether existing healthcare resources are meeting the needs of a given population.³⁶ There is widespread recognition that older cancer patients are a vulnerable group requiring special evaluation throughout treatment.²⁷ Without reporting the extent of 'met' needs, it may therefore be assumed that the low unmet needs of older patients are due to high levels of 'met' need. However in this study, older patients were less likely than younger patients to report 'satisfied' needs. Instead, older patients were significantly more likely than younger patients to report that items were 'not applicable' (no need). Other results from this study suggest that the large proportion of 'not applicable' responses may not truly reflect an absence of need in the older cohort. Older patients had significantly higher levels of comorbidity and were more likely to live alone. These are two factors which have consistently been identified as putting older patients at risk of increased need for assessment and care.¹¹ Contradictory predictors of unmet needs may therefore indicate that older patients are less likely than younger patients to express their needs for help.

Stoic attitudes of older patients have been found to account for age-related differences in the reporting of chronic pain, for example.³⁷ Other traditionally taboo issues such as psychological or sexuality needs may be underreported because of cohort attitudes. In this study decreasing age had the strongest association with unmet needs in the psychological domain at three months, and second strongest at one month. Similar findings for psychological unmet needs were reported by Smith and colleagues.³⁰ Issues around age

differences in the reporting of sexuality have been discussed in quality of life research¹² and could account for the very low mean score for older patients in this domain. Sanson-Fisher and colleagues commented that older patients may keep their needs private in the belief that they should be able to cope.²⁸ Older patients may also underreport needs as they are worried about being a burden to the cancer team or their family,²⁴ worried that they will lose their independence if they report problems,²¹ or may minimise their problems in order not to fulfil negative stereotypes about age.³⁵ Qualitative research examining the attitudes of older patients towards the expression of unmet needs is warranted.

Studies focusing on the needs of older patients are scarce,¹⁸ despite increasing commentary on the unique and complex management of older cancer patients. Age differences in unmet needs and the high proportion of 'not applicable' responses imply that older patients have a different needs profile to younger patients. Age-specific instruments have been suggested in quality of life research,^{13,19} both to capture additional information about older patients and to overcome identified measurement issues. Some quality of life instruments, for example, have demonstrated a heavy response burden and increased requirement for interview administration with advancing age.⁸ Older patients, who are particularly vulnerable to the effects of poor health literacy,³ may also have difficulty distinguishing between level of need when completing unmet needs assessments.²⁰ Developing age-specific unmet needs instruments may ensure that older patients' needs are accurately identified and measured.

This was a small study, and the results should be interpreted with caution. For example, unmet needs were only explored at one and three months after hospital discharge. A recent systematic review of cancer patients' unmet supportive care needs identified that predictors of unmet needs, including age, were highly variable in all domains at all time points.¹⁶ In this current study, levels of unmet need similarly depended not only on age, but also the timing of assessment from discharge and other demographic and clinical predictors. Predictors of unmet needs also did not explain much of the variability in some

of the unmet needs domains. These results suggest that needs should be monitored throughout each individual patient's journey and interventions tailored accordingly. In addition, more insight is needed to determine whether older patients' low unmet needs scores genuinely reflect low levels of need or a reluctance to disclose needs. Without more information to determine how age-related factors affect outcomes and their measurement, decisions about treatment and care for this growing population will continue to be problematic.

Acknowledgments

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Jorgensen ML conceived and designed the analysis, reviewed the literature, analysed and interpreted the data, drafted the manuscript. **Young JM** conceived and designed the original research protocol, interpreted the data, critically revised the paper. **Solomon MJ** conceived and designed the original research protocol, interpreted the data, critically revised the paper. All authors read and approved the final draft of the manuscript.

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Study 2. Older cancer patients and missing data in quality of life questionnaires

2.2.1. Abstract

BACKGROUND: For older adults with cancer, treatment decision making often involves careful consideration of the predicted impact of treatment on quality of life (QOL). However, issues may exist in the measurement and management of QOL data in cancer research. This study aimed to determine whether increasing age was associated with item non-response in the Functional Assessment of Cancer Therapy-Colorectal (FACT-C) and whether methods commonly used to manage missing data produced unbiased QOL estimates.

METHODS: Control groups from pilot phases of a randomised trial completed the FACT-C at baseline, one and three months following hospital discharge (n=57). Extent of item non-response was examined and mean patient age compared between responders and non-responders. A checklist was applied to determine whether the suggested simple mean imputation method should be used for the missing items. Complete case and multiple imputation methods were also compared.

RESULTS: Missing data was greatest at one month after discharge. Non-responders were significantly older than responders for the items “sex life”, “diarrhoea”, and “body appearance”. Older age was also associated with greater levels of missing data overall. QOL in the social/family domain was overestimated when simple mean imputation was used for the “sex life” item.

CONCLUSIONS: Older age is a risk factor for item non-response in the FACT-C, and a commonly used imputation method may overestimate QOL. Exploring reasons for missing items, checking of missing data patterns and imputation methods, and transparency of reporting in patient-reported outcomes research is required to ensure the QOL of older patients is accurately represented.

2.2.2. Introduction

Missing data are inconvenient yet inevitable in most patient-reported outcomes research. The amount and reasons for missing data need to be determined for results to be appropriately analysed and interpreted. Loss of data through missing or incomplete questionnaires can reduce power to detect change over time or differences between groups. False conclusions may be drawn if there is a systematic difference between responders and non-responders and missing data are not handled adequately. However many studies reporting patient health-related quality of life (QOL) outcomes do not provide any details about missing data.¹⁻³ Without transparency of reporting, the reader cannot determine whether authors' conclusions are valid.

Colorectal cancer is primarily a disease of older age, with more than half of all cases occurring in those over 65 years.⁴ Accurate measurement and reporting of QOL is particularly important for this growing patient group, as treatment decisions often involve a delicate balance between extension of life and the predicted impact of treatment on QOL.^{5,6} However, older adults appear to be at risk of inadequate and inaccurate measurement of QOL. Older patients are often excluded from clinical trials due to comorbidities or functional status limitations.⁷ These premorbid health conditions and a higher risk of postoperative morbidity⁸ may contribute to missing or incomplete questionnaires when older patients are actually included in research.⁹ While increasing age has previously been reported to be associated with item non-response in a number of QOL instruments,¹⁰⁻¹⁴ it is not often explored whether this missingness matters – that is, whether non-response is associated with QOL or whether it can be managed adequately using the methods suggested by the QOL instrument developers. Further exploration of these potential biases is needed to ensure that patient-reported outcomes such as QOL are utilized in clinical decision making² and that the QOL of older adults undergoing cancer treatment is being accurately represented.

General guidelines do exist for the management of missing data in QOL research. Simple mean imputation is typically recommended when there are less than 5% missing data and multiple imputation when this figure is larger.¹⁵ The use of simple mean imputation when >50% of items in a subscale and >80% of all items are completed has been suggested for the commonly used Functional Assessment of Cancer Therapy (FACT) instrument.^{10,16} A syntax package that accompanies the colorectal version of this questionnaire is based on these calculations.¹⁷ While unquestionably useful, such recommendations may dissuade researchers from assessing their particular data for patterns of missingness and bias. Cheung and colleagues (2006) investigated the use of the simple mean imputation procedure for the FACT-General in a culturally-diverse Singaporean population.¹⁸ Our study focused on another potentially vulnerable group – older colorectal cancer patients – and aimed to determine 1) the extent of missing data, 2) whether age was a significant predictor of item non-response, and 3) whether methods commonly used to manage missing data produce unbiased estimates in the FACT-Colorectal quality of life instrument.

2.2.3. Method

Participants

Data from control group participants of two trials of a supportive care intervention for people with colorectal cancer were used for the analysis.^{19,20} Control groups were used as their questionnaire completion would not be affected by the receipt of intervention. Both trials used identical eligibility criteria and recruitment processes, and participant characteristics (as listed in Table 1) did not significantly differ between the studies. All eligible patients who received surgery for colorectal cancer at Royal Prince Alfred Hospital, Sydney were invited to participate. Those who were under 18 years, had cognitive impairment, died during admission, or were discharged to another health facility (such as a hospice) were considered ineligible. All participants gave informed consent to be included in the trials and approval was received from their local area health services ethics review committees.

Questionnaire

Baseline demographic and clinical information was obtained prior to discharge from hospital. As part of a comprehensive assessment of needs and QOL, participants self-completed the Functional Assessment of Cancer Therapy – Colorectal (FACT-C) at baseline and at one and three months after discharge from hospital.

The FACT-C is a self-report quality of life questionnaire designed for use with colorectal cancer patients.²¹ It consists of 27 core items which assess patient concerns in four domains: physical, social/family, emotional, and functional well-being. An additional 12 items address site specific concerns related to colorectal cancer. Each item is rated on a 0 to 4 Likert type scale. Item responses are combined to produce subscale scores for each domain, and then summed to produce a total score. Higher scores reflect better QOL.

If missing items are present, it is suggested that subscale scores be estimated from the mean of the items that have been completed (simple mean imputation). This method is recommended only when more than 50% of the items in a subscale are answered.

Calculating total FACT scores from subscale scores is considered appropriate as long as the overall item response rate is greater than 80%.¹⁶ Prorated subscale scores and total scores can be performed automatically using the FACT-C scoring program for SPSS or SAS.¹⁷

Data analysis

Extent of missing data

Rates of non-response for each FACT-C item were tabulated. The percentage of participants who had none, one, two, or three or more FACT-C items missing at each time point were also calculated. Data from participants who were lost to follow up were excluded from each time point analysis.

Association with age

To determine whether age was associated with missing data, the mean age of responders was compared to non-responders for items with greater than 5% missing data at baseline, one month and three months using t-tests. Similarly, t-tests were used to compare the mean age of participants with few missing items overall (none or one item) to those with more missing data (two or more items).

Assessment of simple mean imputation

The checklist proposed by Fayers and colleagues¹¹ was then applied to establish whether the suggested simple mean imputation method would be appropriate for the data:

- (i) *Patients with missing items should be similar to other patients.* Part (i) was addressed by examining the association between missing items and patient age (as above). The overall QOL (mean total FACT-C score) was also compared between responders and non-responders for these missing items, and between those with few or more missing items overall.
- (ii) *Items with missing data should not behave differently from other items in their subscale (domain) or be correlated with external factors.* For part (ii), the two missing items most strongly associated with age were used as examples of how to apply the checklist:
 - a) *Items comprising the scale should all have similar mean values.* The mean value of the item with missing data was compared to the mean value of the other subscale items.
 - b) *The scale should not be ordered or hierarchical.* That is, where an item builds on a previous item e.g. “I can walk 5 metres”; “I can walk 10 metres”.

- c) *Items within a scale should be strongly correlated.* A correlation matrix was used to determine the level of correlation between the item with missing data and other items in the subscale.
- d) *Items should have similar between-patient standard deviations.* Standard deviations of the missing data item and other subscale items were compared.
- e) *Items should not be strongly correlated with external or baseline variables.* Correlations between mean item scores and external factors (e.g. living arrangements, presence of an ostomy appliance) were examined.

Comparison with other methods

A complete case analysis was then used to determine the size and direction of any bias resulting from the use of the simple mean imputation method. For the two example items, answers to that item were removed from the data of complete cases then the domain scores were estimated using simple mean imputation. The resulting imputed mean domain score was then compared to the real mean domain score for the complete cases.

Multiple imputation was also performed on the data of all participants for all of the domains where items were significantly associated with age, using the PROC MI command in SAS. Each missing value was replaced by five simulated values to reflect the uncertainty about imputed values.²² Multiple imputation also assumes that missingness is not completely random but depends on observed data (e.g. age). Thus, other items in the domain and participant characteristics listed in Table 1 were included in the imputation model. The mean domain scores for all participants produced by simple mean imputation and multiple imputation were compared.

2.2.4. Results

The characteristics of the 57 participants are presented in Table 1. The mean age of participants was 63 years (median 65 years; range 27 to 86 years). 5 (9%) of the 57 participants were lost to follow up by one month and a further 5 participants by three months. Of these 10 participants lost during the course of the study, 8 no longer wanted to participate and 2 were too sick to continue. Age and QOL in the previous assessment was not significantly associated with loss to follow up at either time point.

Table 1. Characteristics of participants at baseline

Characteristic	n (%)
Total participants	57 (100)
Mean age in years (SD)	63 (15)
Male	33 (58)
Born in Australia	35 (61)
English spoken at home	46 (81)
High school or tertiary education	29 (51)
Employed full or part time	24 (42)
Private health insurance	20 (35)
Lives alone	19 (33)
Site of cancer	
Colon	26 (46)
Rectosigmoid	6 (11)
Rectal	25 (44)
Dukes stage of cancer	
A	13 (23)
B	15 (26)
C	18 (32)
D	5 (9)
Non-cancerous tumour ^a	4 (7)
Received adjuvant therapy	21 (37)
One or more comorbid conditions	32 (56)

^aPathological stage identified after surgery and randomisation; all patients surgically treated with curative intent

Extent of missing data

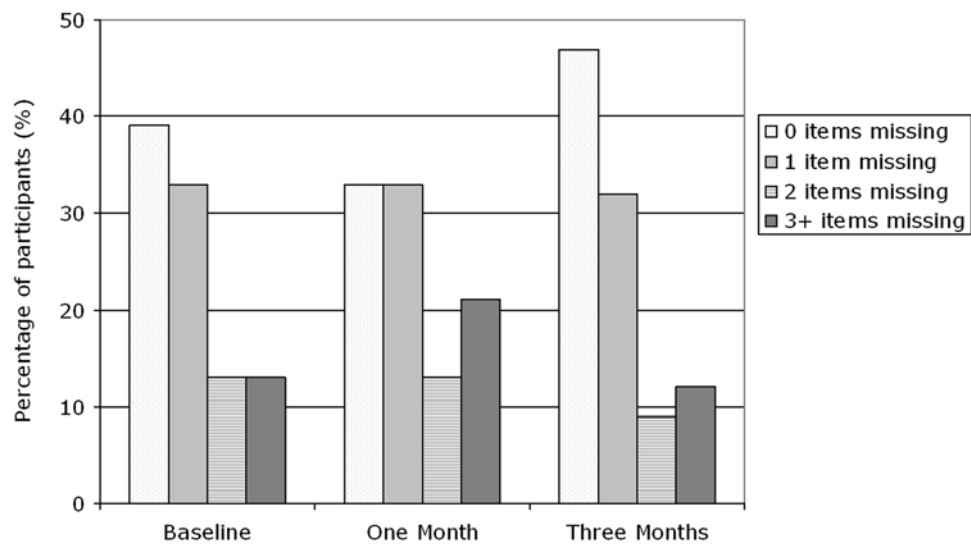
Seven questionnaire items had a non-response rate of over 5% at either baseline, one month or three months after hospital discharge (see Table 2). These appeared to be the more sensitive or potentially “not applicable” items. The most commonly missed item was “I am satisfied with my sex life” (54% at one month), followed by “I feel close to my partner (or main support)”, “I like the appearance of my body”, “I have diarrhoea”, “I have control of my bowels”, “My work (including work at home) is fulfilling” and “I am losing weight”. For the “sex life” question, participants have the option to check a box if they prefer not to answer. At one month, 75% who did not answer the question checked this box (n=21).

Table 2. FACT-C items with a non-response rate of over 5% at each time point

FACT-C item	Missing data		
	Baseline, n (%)	One month, n (%)	Three months, n (%)
I am satisfied with my sex life	29 (51)	28 (54)	24 (51)
I feel close to my partner (or main support)	3 (5)	11 (21)	6 (13)
I like the appearance of my body	5 (9)	7 (13)	.
I have diarrhoea	3 (5)	6 (12)	3 (6)
I have control of my bowels	3 (5)	6 (12)	.
My work (including work at home) is fulfilling	4 (7)	3 (6)	.
I am losing weight	.	4 (8)	.

Most participants had none or only one item missing from their questionnaires. At baseline, 39% of participants had complete data, 33% had one item missing, 13% had two items missing and the remaining 13% had three or more items missing. A similar distribution of missing data was seen at one and three months after discharge (see Figure 1), though there was a greater proportion of patients with three or more items missing at one month (21%).

Figure 1. Percentage of participants with FACT-C items missing at each time point



Association with age

Non-responders were significantly older than responders for the items “I am satisfied with my sex life” (one and three months), “I like the appearance of my body” (baseline), and “I have diarrhoea” (baseline and three months) (see Table 3). Increasing age was also associated with greater levels of missing data overall. Those missing two or more items tended to be older than those with none or one item missing, although this was only significant at one month (mean age 69 vs 59 years, $p=0.01$).

Table 3. Significant associations between age and item non-response at each time point

Time point	FACT-C item	% missed item	Mean age (SD) completed item	Mean age (SD) missed item	Test result
Baseline	Diarrhoea	5	62 (15)	80 (6)	$t_{55}=2.06, p=0.04$
	Appearance of body	9	62 (15)	75 (5)	$t_{55}=2.02, p=0.05$
1 month	Sex life	54	57 (13)	67 (14)	$t_{50}=2.71, p=0.009$
3 months	Sex life	51	58 (13)	66 (15)	$t_{45}=2.04, p=0.05$
	Diarrhoea	6	61 (15)	81 (5)	$t_{45}=2.33, p=0.02$

Assessment of simple mean imputation

The results of the Fayers and colleagues checklist¹¹ for determining whether simple mean imputation would be appropriate for the data were as follows:

- (i) *Patients with missing items should be similar to other patients.* While patients with the missing items listed above were older than responders, the overall QOL of responders and non-responders only differed significantly for one of these items. At baseline, those who missed the “body appearance” item had a significantly lower overall QOL than those who responded (mean FACT-C score 66 vs 92, $p=0.02$). People with more missing items overall only tended to have poorer QOL than those with none or one item missing at baseline (mean FACT-C score 80 vs 92, $p=0.09$).
- (ii) *Items with missing data should not behave differently from other items in their subscale (domain) or be correlated with external factors.* “I am satisfied with my sex life” (one month) and “I have diarrhoea” (three months) were the two missing items most strongly associated with age and were used as examples for applying part (ii) of the checklist:
 - a) *Items comprising the scale should all have similar mean values.* The “sex life” item had a lower mean value than other items in the social/family domain (1.3 vs >3.1). The “diarrhoea” item from the colorectal specific domain had a similar mean score to other domain items (1.7 vs 1.3-2.8).
 - b) *The scale should not be ordered or hierarchical.* Items in the social/family or colorectal specific domain did not build on other items in their domain.
 - c) *Items within a scale should be strongly correlated.* “Sex life” did not correlate significantly with any other items in the domain. “Diarrhoea” was significantly correlated with three other items in its domain (“swelling or cramps” $p<0.01$, “losing weight” $p<0.01$, “appetite” $p<0.05$).

- d) *Items should have similar between-patient standard deviations.* The standard deviation of the “sex life” item was greater than other domain items (1.4 vs <1.0). For the “diarrhoea” item, the standard deviation was similar to other domain items (1.6 vs 1.1-1.7).
- e) *Items should not be strongly correlated with external or baseline variables.* “Sex life” scores were hypothesised to be associated with participants’ living arrangements. Indeed they were, with participants who lived alone having a significantly higher score (mean 3.0) than those who lived with others (mean 1.1) ($p=0.03$). Any imputation method should therefore allow for this factor. Scores for the “diarrhoea” item were not associated with presence of an ostomy appliance ($p=0.42$) or any other tested factor (age, gender, language, stage).

Based on the checklist, it appears that using simple mean imputation method for the “sex life” item could lead to biased results.

Comparison with other methods

The complete case analysis showed that the size and direction of bias resulting from simple mean imputation for the “sex life” item in our dataset was a 2 point overestimate of QOL (see Table 4). The imputed mean social/family domain score (23.6) was significantly higher than the real mean domain score (21.6) for the complete cases ($p<0.001$). This difference is greater than the minimally clinically important difference for this domain.^{23,24} When the same procedure was applied to the “diarrhoea” item, the imputed and real mean colorectal specific domain scores for complete cases were statistically similar (14.4 vs 14.1, $p=0.17$).

Simple mean imputation also produced a higher mean score than multiple imputation when the data of all participants were used to calculate one month social/family domain scores (22.6 vs 21.7, $p=0.002$). While only a one point difference, this multiple imputation score was closer to the real mean of the complete cases (21.6). The mean social/family domain score at three months was also overestimated by simple mean imputation

compared to multiple imputation (22.2 vs 21.4, $p=0.008$). For the colorectal specific domain where items were also significantly associated with age, both imputation methods produced similar domain scores at baseline ($p=0.98$) and at three months (see Table 4).

Table 4. Two examples comparing imputation methods for mean domain scores

FACT-C item (domain)	Complete cases			p	Non-complete cases		All participants		p
	n	Mean (SD) score real	Mean (SD) score SI ^a		n	Mean (SD) score SI ^a	Mean (SD) score SI ^a	Mean (SD) score MI ^b	
Sex life (social)	21	21.6 (3.8)	23.6 (4.4)	<.001	28	23.3 (5.2)	22.6 (4.7)	21.7 (4.5)	.002
Diarrhoea (colorectal)	42	14.1 (5.2)	14.4 (5.2)	.17	4	20.0 (4.2)	14.6 (5.4)	14.6 (5.3)	.97

^aSI = simple mean imputation; ^bMI = multiple imputation

2.2.5. Discussion

In this study, non-responders were significantly older than responders for the FACT-C items “sex life”, “diarrhoea”, and “body appearance”. Older age was also associated with greater levels of missing data overall. Sensitive or potentially “not applicable” items were most commonly missed by all participants, and the greatest amount of missing data occurred at one month after discharge from hospital. QOL in the social/family domain was significantly overestimated when simple mean imputation was used for the “sex life” item.

Increasing age appears to be a considerable risk factor for item non-response in QOL questionnaires. In our study, those missing two or more FACT-C items were significantly older than those with none or one item missing at one month after discharge. Similar findings have been noted in other reports.^{10,12-14} The types of items that older patients omit also appear to be comparable across QOL instruments. For example, questions about symptoms (“acid indigestion”) and the body (“self conscious when nude”) were less likely to be responded to by older patients in studies using the EORTC QLQ-C30.¹¹ These items are similar to the “diarrhoea” and “body appearance” FACT-C items in our study. While these associations between age and missingness should be noted, exploring whether estimates of QOL are affected is of greater importance.

The major concern with missing data is that QOL will be overestimated due to poorer QOL of non-responders.²⁵ While older cancer patients would appear to be at risk for poorer QOL than younger patients due to greater morbidity, the opposite is generally reported in the literature.²⁶⁻²⁹ However, it is difficult to determine whether the QOL of older patients is being accurately represented, as many studies exclude patients with missing data or do not disclose analysis methods.³⁰ In our study, those missing two or more items tended to have poorer overall QOL at baseline, and overall QOL was poorer for non-responders to the “body appearance” item. This means that QOL could be overestimated if these (predominantly older) people are excluded from analysis. QOL may be further overestimated as a result of the tendency for older adults to minimize their problems due to stoic attitudes³¹ or worries about being a burden.³² For example, older colorectal cancer patients are significantly more likely than their younger counterparts to report that their needs are “not applicable”.³³ Without accurate information about their needs and QOL, older patients may be less likely to receive care which would enable them to better cope with their cancer and cancer treatment.

Efficace and colleagues (2007) suggest that poor methodological rigour in QOL reporting could contribute to the underutilization of this research in clinical decision making.² This may help to explain why there is considerable variation between physicians in chemotherapy recommendations for otherwise healthy older colorectal cancer patients,³⁴ despite reports that QOL is not significantly impacted.³⁵ While the quality of QOL reporting has improved over time,² missing data was addressed in less than a third of randomized controlled trials with QOL outcomes from 2002-2008¹ and non-response is not mentioned in a validation study of the FACT-G for older patients with cancer.³⁶ In our study of the 39 item FACT-C, the majority of participants had none or only one or two items missing (85%). This is similar to the findings of Fairclough and colleagues (1996) for the 28 item FACT-G, where 90% of participants answered all or missed only one item.¹⁰ This amount of non-response may not impact on a large study’s power to detect differences, but can be a problem for small pilot studies if missing data are not managed.

Sexuality items appear to cause the most difficulty in QOL assessment. Considerable non-response rates to such items have been noted in studies using the Rotterdam Symptom Checklist¹¹ and on the FACT-G in a Singaporean population.¹⁸ More than half of participants did not respond to the “sex life” question at all time points in our study. A psychometric analysis of the Spanish version of the FACT-G revealed that the “sex life” question did not fit well with other items.³⁷ In our study, the “sex life” item had a lower mean score, greater standard deviation and low correlation with other items in the social/family domain. Simple mean imputation may therefore result in biased estimates as the average of other items in the domain is used to estimate the subscale score.¹¹ The complete cases analysis showed that the size and direction of the bias from simple mean imputation in the social/family domain was a 2 point overestimate of mean QOL, which is greater than the reported minimally clinically important difference for this domain.^{23,24} Simple mean imputation also produced a higher estimate than multiple imputation for the mean social/family domain score of all participants. This means that the QOL of older patients, who are less likely to complete the “sex life” item, may be overestimated in this domain if the suggested simple mean imputation method is used.

Exclusion of the “sex life” item when calculating domain scores has been suggested.¹⁸ However exploring the reasons why older participants do not answer certain questions may provide insights for how to manage this question without losing information on an important aspect of cancer recovery. In our study, 75% of those who did not answer the “sex life” item checked a box to indicate that they “preferred not to answer it”. Older patients may have found the question too personal or offensive, or they may have felt that this question was not applicable to them, being more likely to live alone and perhaps viewing sexuality as dependent on having a partner. The 25% of non-responders who did not check the “prefer not to answer” box could have less systematic reasons for missing that particular item. Ageing issues such as poorer eyesight and cognitive or physical difficulties are possible explanations for missingness that is not item specific.⁹

Prevention is usually preferable to analytical cure. Missing data may be reduced through selecting QOL assessment tools with a known higher item response rate in older patients.^{38,39} Age-specific instruments for the assessment of QOL issues that are unique to older adults have also been proposed,³ though missingness does not appear to have been addressed as yet in the recently developed EORTC QLQ-ELD15 questionnaire for older patients.⁴⁰ Where research involves patients of all ages, other suggested prevention strategies include using practice questions⁴¹ and considering where assessment takes place.⁴² In our study, the FACT-C may have had higher non-response rates as it was the last questionnaire in a comprehensive assessment of needs and QOL. Compliance with QOL assessment can also be affected by different factors at various time points.⁴³ The greater item non-response occurring at one month after hospital discharge in our study may indicate that this is a difficult time period for cancer patients, where greater attention to individual QOL is required and where particular care should be taken in evaluating non-response.

This was a small study and analysis of missingness was not an a priori aim. Nevertheless, increasing age was associated with non-response for a number of items, and using simple mean imputation as suggested for the FACT-C resulted in overestimates of QOL scores. While guidelines for analysis methods are useful, patterns of missing data should be checked in all datasets to avoid biased results. Multivariable analysis for non-response was also not performed in our study, meaning that other factors could be influencing missingness. Nevertheless, older patients represent an at-risk group who should be considered during study design to ensure that valuable information is not lost. Ultimately, greater transparency of reporting is needed so that readers can assess whether the QOL of those at risk of missing data is being accurately represented.

Acknowledgements

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3

Local context

This chapter examines the effect of patient age on receipt of adjuvant therapy in NSW. While age differences in adjuvant therapy receipt have been documented extensively worldwide, it is important to routinely monitor the treatment of at-risk patient groups as well as identify other local factors that may hinder or facilitate adjuvant therapy use.

This study is one of the first analyses to use treatment data from the NSW Clinical Cancer Registries (ClinCR). ClinCRs were established in five health service areas in 2006, with a sixth registry commencing in 2007. Data are collected for patients treated within public facilities only. Items comprise a minimum data set developed by NSW Oncology Groups. Because the combined registry data have not been used previously, considerable data cleaning and harmonisation was required. The quality and usefulness of the data was examined before the commencement of the current study, with consultation from an advisory group of data managers, coders, and clinicians. Further information is available in [Appendix 3.1](#) and in a full report online: <http://ses.library.usyd.edu.au/handle/2123/8936>

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CONTRIBUTION STATEMENT

Dear co-authors,

RE: *Jorgensen ML, Young JM, Dobbins TA, Solomon MJ. Does patient age still affect receipt of adjuvant therapy for colorectal cancer in New South Wales, Australia? Journal of Geriatric Oncology. [Accepted].*

I would like to use the above paper as one of the chapters of my PhD thesis and request your permission to do so. As one of the requirements of the Academic Board of the University of Sydney, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author contributions

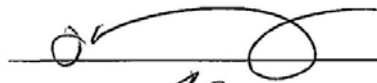
Jorgensen ML conceived and designed the study, data cleaning and harmonisation, analysed and interpreted the data, drafted the manuscript. **Young JM** designed the study, data acquisition, interpreted the data, critically revised the paper. **Dobbins TA** designed the study, data cleaning and linkage, interpreted the data, critically revised the paper. **Solomon MJ** interpreted the data, critically revised the paper. All authors read and approved the final draft of the manuscript.

If you agree with the contributions outlined above and give permission for this paper to be a part of my thesis, please sign next to your name below. Your support is greatly appreciated.

Kind regards,

Mikaela Jorgensen

Jane M Young



Timothy A Dobbins



Michael J Solomon



Does patient age still affect receipt of adjuvant therapy for colorectal cancer in New South Wales, Australia?

3.1. Abstract

OBJECTIVES: To investigate the effect of patient age on receipt of stage-appropriate adjuvant therapy for colorectal cancer in New South Wales, Australia.

MATERIALS AND METHODS: A linked population-based dataset was used to examine the records of 580 people with lymph node-positive colon cancer and 498 people with high-risk rectal cancer who underwent surgery following diagnosis in 2007/2008. Multilevel logistic regression models were used to determine whether age remained an independent predictor of adjuvant therapy utilisation after accounting for significant patient, surgeon and hospital characteristics.

RESULTS: Overall, 65-73% of eligible patients received chemotherapy and 42-53% received radiotherapy. Increasing age was strongly associated with decreasing likelihood of receiving chemotherapy for lymph node-positive colon cancer ($p < 0.001$) and radiotherapy for high-risk rectal cancer ($p = 0.003$), even after adjusting for confounders such as Charlson comorbidity score and ASA physical health status. People aged over 70 years for chemotherapy and over 75 years for radiotherapy were significantly less likely to receive treatment than those aged less than 65. Emergency resection, intensive care admission, and not having a current partner also independently predicted chemotherapy nonreceipt. Other predictors of radiotherapy nonreceipt included being female, not being discussed at multidisciplinary meeting, and lower T stage. Adjuvant therapy rates varied widely between hospitals where surgery was performed.

CONCLUSION: There are continuing age differences in adjuvant therapy utilisation in NSW that are not explained by patients' comorbidities or health status. Further exploration of these complex treatment decisions is needed. Variation by hospital and patient characteristics indicates opportunities to improve patient care and outcomes.

3.2. Introduction

Colorectal cancer is primarily a disease of ageing, with those over 65 years accounting for two-thirds of all incident cases.¹ Surgical resection is the mainstay of curative treatment. To reduce the risk of recurrence after surgery, current clinical practice guidelines recommend that all lymph node-positive colon cancer cases be considered for adjuvant chemotherapy, and all high-risk (T3-4 or N+) rectal cases be considered for adjuvant preoperative or postoperative radiotherapy, regardless of patient age.² However, increasing age was an independent predictor of non-concordance with adjuvant treatment guidelines in a patterns of care study conducted in the state of New South Wales (NSW), Australia in 2000.³ Similar findings have been reported internationally.⁴⁻⁷

The collection of patient and treatment information to determine patterns of care often requires resource- and time-intensive surveys of clinicians or medical record audits. There is now potential to conduct such studies in NSW using routinely collected data. Clinical Cancer Registries (ClinCR) have been in operation in public facilities in NSW since 2006 and contain comprehensive staging and treatment information that is not routinely collected elsewhere. When linked to other health datasets, ClinCR data may be able to be used to monitor the uptake of evidence-based guidelines and identify those at risk of suboptimal treatment.

Determining whether treatment variation is due to patient, physician or hospital characteristics requires the use of multilevel modelling techniques and adequate adjustment for factors such as preoperative health. This often does not occur in population-based studies. Since rates of appropriate treatment among older colorectal cancer patients appear to be increasing over time,^{8,9} it is also important to routinely examine whether age remains a barrier to the implementation of evidence-based cancer care.

The aim of this study was to use a linked population-based dataset to examine the effect of patient age on the receipt of stage-appropriate adjuvant therapy for colorectal cancer in NSW.

3.3. Materials and methods

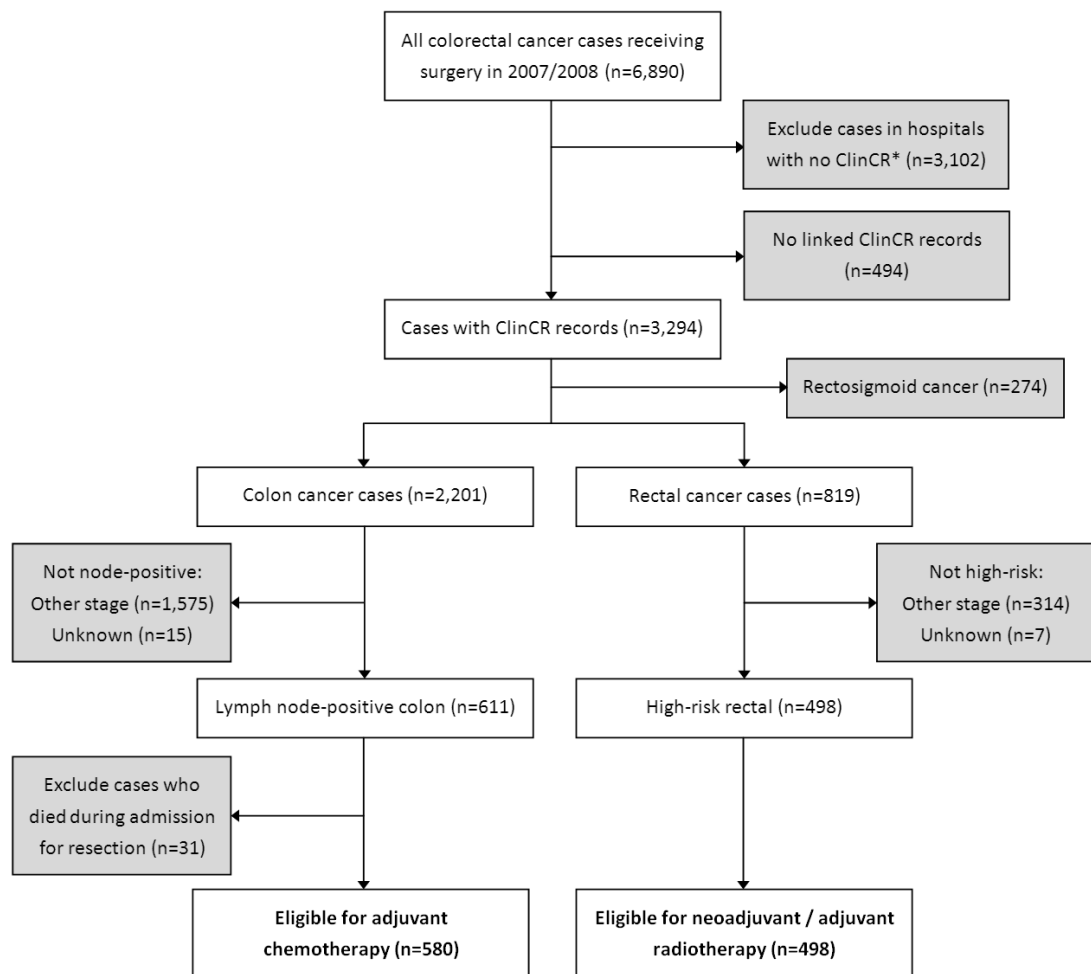
Data source

One-third of Australia's population resides in NSW. People with a colon, rectosigmoid junction or rectal cancer mandatorily registered by the population-based NSW Central Cancer Registry (CCR) in 2007 and 2008 formed the basis of a linked dataset. Hospital separations data from the NSW Admitted Patients Data Collection (APDC) and records from the NSW Registry of Births, Deaths and Marriages (RDBM) were linked by the Centre for Health Record Linkage (CHeReL) to the CCR cohort. Linkage to the Clinical Cancer Registry (ClinCR) was also possible for 85% of people receiving surgery in a public hospital in 2008,¹⁰ providing in-depth information on cancer staging, adjuvant therapy, and specialist consultations that was not available in the CCR. These data are based on a minimum dataset that is collected locally then collated through a central information exchange. The cohort was restricted to the first unique cancer of any person who had an admission for a surgical resection in the month of their diagnosis or thereafter. The study was approved by the NSW Population & Health Services Research Ethics Committee.

Determining chemotherapy and radiotherapy receipt

Because chemotherapy and radiotherapy data are only available from the ClinCR, those receiving surgery in private hospitals and the two area health services where ClinCR data is not collected were excluded (see Figure 1).

Figure 1. Flowchart defining the denominator for receipt of adjuvant chemotherapy and radiotherapy



*Private hospitals and Greater Western/Greater Southern Area Health Service

According to current national clinical practice guidelines, all lymph node-positive (N+M0 or stage III) colon cancer cases should be considered for adjuvant chemotherapy, and all high-risk rectal cases (T3-4N0M0 or T1-4N+M0 or stage II/III) should be considered for adjuvant preoperative or postoperative radiotherapy.² Those with any other stage of cancer at diagnosis were excluded from the cohort. People with colon cancer who died during admission for their resection were also excluded as they could not receive postoperative chemotherapy. Rectosigmoid junction cancers were not included in the analysis, as there is a lack of consensus in the literature on whether these cancers should be classified with colon or rectal cancers. All those with a ClinCR record containing any details of

chemotherapy commencement (for node-positive colon) or radiotherapy commencement (for high-risk rectal) were considered to have received adjuvant therapy.

Identifying predictors of chemotherapy and radiotherapy receipt

Multivariable cross-classified multilevel logistic regression models were used to determine predictors of receipt of chemotherapy and radiotherapy.¹¹ Because surgeon and hospital data were available, three-level models were fitted to take into account the clustering of patients by surgeon and the clustering of surgeons within hospitals. Cross-classified models were used as some surgeons performed resections at more than one hospital. Any available patient, surgeon or hospital characteristic that indicated a possible univariate relationship with adjuvant therapy use ($p < 0.25$) were initially included in multivariable models. Characteristics are listed in Tables 1 and 2, and included Charlson comorbidity score,¹² socioeconomic disadvantage (SEIFA),¹³ remoteness (ARIA),¹⁴ and surgeon and hospital caseload (divided into patient quintiles). Backwards elimination was used to exclude non-significant predictors one at a time until all variables were significant ($p < 0.05$) or their exclusion worsened model fit.

Sensitivity analyses

Although those undergoing surgery in a private hospital were excluded from the ClinCR cohort, some people may have received adjuvant treatment in a private facility that was not recorded in the ClinCR. A series of sensitivity analyses were undertaken to examine the potential impact of missing treatment and covariate data.

- 1) Chemotherapy sensitivity model: It is likely that many people receiving chemotherapy in the private sector would have private health insurance, as Australians are entitled to treatment free of charge in public hospitals. For this sensitivity model, all those with private insurance or no insurance status recorded were additionally assumed to have received chemotherapy.

- 2) Radiotherapy sensitivity model: Outpatient radiotherapy is not covered by private health insurance, however there were only 18 facilities (5 private) that a patient could attend in NSW in 2008.¹⁵ For this model, all patients whose nearest radiotherapy centre was private were additionally assumed to have received radiotherapy. A patient's nearest facility was calculated based on road distance between postcode centres using GIS software. 72.8% of people who had radiotherapy recorded attended their nearest radiotherapy centre.

- 3) Health status sensitivity models: Poor functional status predicts treatment outcomes independently of comorbidity and age.¹⁶ A measure of functional status, the Eastern Cooperative Oncology Group (ECOG) performance status, was only recorded for 24.6% of the ClinCR cohort. The American Society of Anesthesiologists (ASA) physical health status score may be a useful alternative¹⁷ and was available for 83.8% of the cohort. However, it could not be included in the original models as the characteristics of those who had ASA recorded differed from those who did not. Additional complete-case models including ASA score were therefore built for both chemotherapy and radiotherapy receipt, to determine whether age remained a significant predictor when a measure of health status was included.

Comparing rates of oral chemotherapy to a secondary data source

Capecitabine, an orally-administered chemotherapy drug, was approved for use as a single-agent adjuvant treatment for stage III colon cancer in 2005. There was concern about the adequacy of recording of capecitabine, as it does not require a physical consultation for administration and prescription rates increase with patient age.¹⁸ Rates of solitary capecitabine use in the ClinCR cohort were therefore compared to another data source that has been used previously to describe adjuvant therapy use.¹⁹ The Biogrid Australia Colorectal Cancer Database is a prospective data repository that contains detailed information on staging and treatment from five hospitals in Victoria and Tasmania, Australia. Data for those diagnosed with stage III colon cancer from 2006 to 2009 (inclusive) were used.

3.4. Results

Of the state-wide cohort of 6,890 people with colorectal cancer treated in 105 hospitals, 3,294 (47.8%) had a ClinCR record that could be used to determine adjuvant therapy receipt. People who had a ClinCR record were similar to those who did not have a ClinCR record with regard to sex, age, and site of cancer (all $p > 0.05$, see Table 1). However, people with a ClinCR record were significantly more likely to be disadvantaged, have no private health insurance, have had their resection following emergency admission, have a higher Charlson comorbidity score, and live in a less remote location.

Rates of chemotherapy and radiotherapy receipt

Of 580 people with lymph node-positive colon cancer in the ClinCR cohort, 65.2% had a chemotherapy ClinCR record (95% CI: 61.3-69.1%). There was a steady decline in chemotherapy receipt by increasing age (see Figure 2). Of 498 people with high-risk rectal cancer, 41.6% had a radiotherapy record (95% CI: 37.2-45.9%). Radiotherapy rates decreased with increasing age, though not as markedly as for chemotherapy.

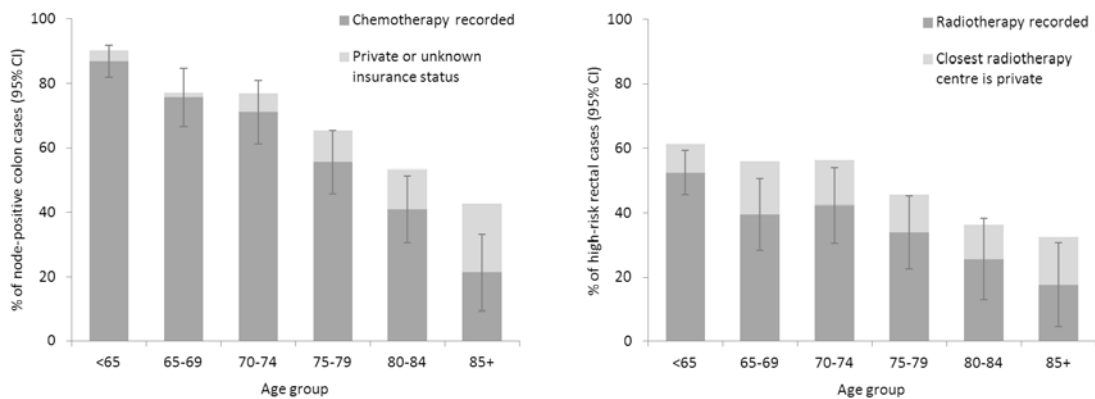
In the chemotherapy sensitivity analysis, where all people with private health insurance were assumed to have received treatment, the estimated proportion receiving chemotherapy increased to 72.6% (95% CI: 68.9-76.2%). In the radiotherapy sensitivity analysis, where all people whose nearest radiotherapy centre was private were assumed to have received treatment, estimated radiotherapy use increased to 53.2% (95% CI: 48.8-57.6%).

Table 1. Characteristics of patients receiving surgery for colorectal cancer in NSW, 2007-08

	ClinCR cohort, n (%)	Rest of NSW, n (%)	p value
Sex			0.754
Male	1,795 (54.5)	1,946 (54.1)	
Female	1,499 (45.5)	1,650 (45.9)	
Age at diagnosis (mean/SD)	68.7 (12.5)	68.3 (11.9)	0.145
0-59	732 (22.2)	810 (22.5)	
60-69	857 (26.0)	1,055 (29.3)	
70-79	1,029 (31.2)	1,046 (29.1)	
80+	676 (20.5)	685 (19.0)	
Site of cancer			0.964
Colon	2,201 (66.8)	2,411 (67.0)	
Rectosigmoid junction	274 (8.3)	301 (8.4)	
Rectum	819 (24.9)	884 (24.6)	
Socioeconomic disadvantage (SEIFA)*			<0.001
1 Least disadvantaged	533 (16.2)	860 (23.9)	
2	616 (18.7)	570 (15.9)	
3	604 (18.3)	848 (23.6)	
4	776 (23.6)	792 (22.0)	
5 Most disadvantaged	764 (23.3)	522 (14.5)	
Remoteness (ARIA)			<0.001
Highly accessible	2,554 (77.5)	2,153 (59.9)	
Accessible	592 (18.0)	1,044 (29.0)	
Moderately accessible/remote	148 (4.5)	399 (11.1)	
Discharged to nursing home	62 (1.9)	23 (0.6)	<0.001
Born in Australia	2,093 (63.5)	2,850 (79.3)	<0.001
Private health insurance	666 (20.2)	2,644 (73.5)	<0.001
Resection following emergency admission	539 (16.4)	127 (3.5)	<0.001
Degree of spread of cancer*			<0.001
Localised	1,143 (34.7)	1,468 (40.8)	
Regional spread	1,618 (49.1)	1,625 (45.2)	
Distant metastasis	523 (15.9)	337 (9.4)	
Charlson Index (comorbidity)			<0.001
0	2,665 (80.9)	3,132 (87.1)	
1	313 (9.5)	259 (7.2)	
2	176 (5.3)	136 (3.8)	
3+	140 (4.3)	69 (1.9)	
Hospital type			-
Public	3,294 (100.0)	943 (26.2)	
Private	-	2,653 (73.8)	
Hospital location			<0.001
Metropolitan	2,637 (80.1)	2,101 (58.4)	
Rural/regional	657 (19.9)	1,495 (41.6)	

*Some data missing

Figure 2. Unadjusted rates of chemotherapy and radiotherapy receipt by age group



Predictors of chemotherapy and radiotherapy receipt

Table 2 presents the results of the multivariable models for treatment receipt. Increasing age was a significant independent predictor of decreasing chemotherapy use, both in the original and chemotherapy sensitivity models ($p < 0.001$). After adjustment, those aged 70-74 (OR=0.36), 75-79 (OR=0.18), 80-84 (OR=0.12) and 85+ (OR=0.04) were significantly less likely to receive chemotherapy than those aged less than 65. People with higher Charlson comorbidity score, emergency resection, those admitted to intensive care after their surgery, and people without a current partner were also significantly less likely to receive adjuvant chemotherapy. In the chemotherapy sensitivity model, socioeconomic status was an additional significant predictor of treatment receipt. This predictor may be partly explained by higher rates of private insurance among people with higher SES, given that the sensitivity model assumed that all those with private insurance received chemotherapy.

For radiotherapy, increasing age was also an independent predictor of underutilisation in both the original ($p = 0.003$) and radiotherapy sensitivity models ($p = 0.017$). Significant age differences only emerged for those over 75 years however. Other independent predictors of radiotherapy receipt included being discussed at a multidisciplinary team (MDT) meeting, being male, having higher T stage (T3/T4 vs. T2), and having an abdominoperineal resection or ultra-low anterior resection (both indications for low rectal cancer). These

predictors were the same in the radiotherapy sensitivity model, where radiotherapy was assumed for all those whose closest facility was private. Distance to nearest radiotherapy facility was not an independent predictor in either of the models.

In the health status sensitivity model that included ASA score, age remained an independent predictor of both chemotherapy ($p < 0.001$) and radiotherapy receipt ($p = 0.006$). People with poorer health status were significantly less likely to receive chemotherapy ($p = 0.015$) but not radiotherapy ($p = 0.096$) in these models.

Model statistics are displayed in Table 2. All models had good discrimination (area under ROC curve > 0.80). While rates of adjuvant therapy varied widely by surgeon, most of this variation was accounted for by adding the hospital where surgery was performed into the models. In the radiotherapy model, approximately 28% of the total variability in radiotherapy receipt was attributable to hospitals (ICC=0.28), 2% was attributable to surgeons and the remaining 70% to patient characteristics. For chemotherapy, most of the variability was attributable to patient characteristics ($\approx 84\%$), with hospital of surgery accounting for the remaining variability (ICC=0.16).

Comparison of rates of oral chemotherapy to a secondary data source

In the ClinCR cohort, 23.3% of those who had chemotherapy had capecitabine alone recorded. An additional 8.5% did not have any drug specified. Rates of capecitabine use were greatest for those aged 70-79 (38.3%). In the Biogrid cohort (mean age 66.9 years (SD=12.6), 55.8% male, 68.0% colon cancer), 104 of 146 people with stage III colon cancer had chemotherapy recorded (71.2%). Of these people, 24.0% received capecitabine as a single agent treatment. This rate was not significantly different from the rate of solitary capecitabine use recorded in the ClinCR cohort ($\chi^2[1]=0.02$, $p=0.896$).

Table 2. Results of multivariable models for receipt of adjuvant chemotherapy and radiotherapy

	Chemotherapy (node-positive colon)		Radiotherapy (high-risk rectal)	
	CTx recorded OR (95% CI)	Sensitivity ^a OR (95% CI)	RTx recorded OR (95% CI)	Sensitivity ^a OR (95% CI)
Age at diagnosis (ref=<65 years)	p<0.001	p<0.001	p=0.003	p=0.017
65-69	0.58 (0.28-1.21)	0.40 (0.19-0.87)	0.59 (0.30-1.18)	0.75 (0.37-1.51)
70-74	0.36 (0.18-0.74)	0.34 (0.16-0.73)	0.55 (0.27-1.12)	0.72 (0.35-1.48)
75-79	0.18 (0.09-0.35)	0.19 (0.09-0.39)	0.44 (0.21-0.93)	0.46 (0.22-0.95)
80-84	0.12 (0.06-0.24)	0.14 (0.07-0.29)	0.19 (0.07-0.47)	0.26 (0.11-0.61)
85+	0.04 (0.02-0.11)	0.09 (0.04-0.21)	0.24 (0.08-0.76)	0.34 (0.12-0.95)
Charlson comorbidity (ref=0)	p=0.008	p=0.071	p=0.373	p=0.223
1	0.34 (0.16-0.72)	0.52 (0.25-1.08)	0.93 (0.40-2.14)	0.97 (0.43-2.17)
2	0.75 (0.29-1.94)	1.01 (0.40-2.55)	0.75 (0.24-2.31)	1.39 (0.46-4.20)
3+	0.28 (0.09-0.89)	0.31 (0.10-0.94)	0.24 (0.05-1.21)	0.24 (0.06-1.00)
Marital status (ref=Partner)	p=0.023	p=0.004	-	-
No current partner	0.60 (0.39-0.93)	0.52 (0.34-0.81)		
Intensive care (ref=No)	p=0.024	p=0.007	-	-
Yes	0.51 (0.29-0.91)	0.47 (0.27-0.81)		
Emergency resection (ref=No)	p=0.047	p=0.773	-	-
Yes	0.60 (0.36-0.99)	0.93 (0.55-1.55)		
SEIFA (ref=1 Least disadvantaged)	p=0.338	p=0.049	-	-
2	1.06 (0.47-2.41)	0.94 (0.40-2.21)		
3	0.72 (0.30-1.72)	0.38 (0.16-0.90)		
4	1.58 (0.66-3.78)	0.77 (0.32-1.84)		
5 Most disadvantaged	0.97 (0.41-2.29)	0.47 (0.20-1.13)		
Sex (ref=Male)	-	-	p=0.002	p<0.001
Female			0.44 (0.26-0.73)	0.42 (0.25-0.69)
T stage (ref=T2)	-	-	p=0.003	p<0.001
T3			3.91 (1.75-8.75)	4.24 (2.02-8.86)
T4			2.75 (0.97-7.76)	1.87 (0.69-5.02)
Type of resection (ref=Other)	-	-	p<0.001	p=0.014
Abdominoperineal excision			3.77 (1.97-7.25)	2.51 (1.31-4.80)
Ultra-low anterior resection			1.82 (1.03-3.24)	1.64 (0.91-2.94)
Discussed at MDT (ref=No)	-	-	p<0.001	p=0.004
Yes			3.12 (1.78-5.47)	2.36 (1.33-4.20)
Model statistics				
Discrimination (area under curve)	0.85 (0.81-0.88)	0.82 (0.78-0.86)	0.86 (0.83-0.89)	0.86 (0.83-0.90)
Calibration (Hosmer-Lemeshow χ^2)	7.81, p=0.648	8.22, p=0.607	8.13, p=0.616	11.34, p=0.332
Surgeon variance (SE), [ICC] ^b	0	0	0.11(0.22),[0.02]	0.11(0.22),[0.02]
Hospital variance (SE), [ICC] ^b	0.61(0.29),[0.16]	0.41(0.22),[0.11]	1.32(0.59),[0.28]	2.46(1.14),[0.42]

^aReceipt assumed for all those with private insurance (for CTx) or whose nearest treatment centre was private (for RTx)

^bIntraclass correlation coefficient (ICC): estimated proportion of total variability attributable to surgeons or hospitals

3.5. Discussion

Chronological age was an independent predictor of receipt of stage-appropriate adjuvant therapy across all models. After adjusting for confounders, people aged over 70 years for chemotherapy and over 75 years for radiotherapy were significantly less likely to receive treatment than those aged less than 65. While much of the variation in adjuvant therapy utilisation was due to patient characteristics, the hospital where surgery was performed accounted for a considerable proportion of variation in these patterns of care. This indicates that there are opportunities to improve care at both a hospital and patient level.

Linked administrative health data may be more useful for routinely monitoring patterns of treatment than data collected through other methods, as it is less resource intensive, potentially timelier, and removes some of the bias that may occur through the self-selection of physicians into surveys or the use of single area data.²⁰ ClinCR data from local districts have been used previously to determine adjuvant therapy use.²¹ However, the quality of recording of treatment receipt across the combined registry requires validation. Potential undertreatment of older patients through reduced dose or early discontinuation could also not be explored as these data are incomplete in the ClinCR at present.¹⁰ While the current analysis was restricted to those who received surgery in a public hospital, the original models likely underestimate utilisation rates due to the collection of ClinCR data in public facilities only, and the sensitivity models likely overestimate rates by assuming everyone with private insurance or living near a private facility received adjuvant therapy. The present coverage of the ClinCR data also limits the ability to extrapolate the estimates to the whole state. Underestimates may result from the ClinCR subset being more disadvantaged than the state-wide cohort and so less likely to receive treatment,⁵ though the absence of data for two rural areas may mean state figures are overestimated, as travel distance has been reported to be a barrier to treatment.²² Nonetheless, the available data account for half of the treated cases in NSW, and may be useful for monitoring patterns of care in the public hospitals it is collected. The above issues are also more likely to increase age differences than reduce them.

Results from previous state-wide and other international population-based research suggest that our estimates of overall chemotherapy use (65-73%) and radiotherapy use (42-54%) are reliable. In a clinician survey conducted in NSW in 2000, 59% of node-positive colon cancer patients received chemotherapy and 33% of high-risk rectal cancer patients received radiotherapy.²³ The current results represent a considerable increase on these figures, consistent with reported trends for increasing utilisation over time. The results are also comparable to internationally reported rates of chemotherapy use for node-positive colon cancer of between 56% and 75%^{4,5,24,25} and rates of radiotherapy use for high-risk rectal cancer of between 45% and 63%.^{6,7,9,26} The accuracy of our estimates is additionally supported by the similar rates of oral capecitabine to the Biogrid dataset, a high proportion of younger patients receiving chemotherapy as in the previous NSW study,²³ and similar predictors of chemotherapy and radiotherapy receipt to other studies.^{3,4,7,27}

In our study, people over age 70 without significant comorbidity were less likely to receive adjuvant chemotherapy, despite having a life expectancy of up to 9 years.²⁸ The reason for the apparent underutilisation of adjuvant therapy among older adults is likely multifaceted. Previous research suggests that both surgeons and oncologists are less likely to recommend chemotherapy for older patients on the basis of age alone.^{29,30} The magnitude of these age differences increases for patients with comorbidities, where there is emerging but less definitive evidence for treatment tolerance and less potential survival benefit. The current study was unique in determining whether variation in treatment receipt occurred at the level of the surgeon or hospital. Lack of variation across surgeons in adjuvant chemotherapy rates when accounting for hospitals and patient characteristics indicates that surgeons may hold similar preferences against the referral of older patients and those with comorbidity. The unexplained hospital variation after accounting for patient predictors could point to differing practices of oncologists or MDTs, breakdowns in the care pathway, or unmeasured patient characteristics such as treatment refusal, which accounted for up to 10% of patients in a previous NSW study.²³ Routine recording of reasons for non-receipt is needed to further illuminate the continuing barriers to evidence-based care for all patients.

Determining whether patient age is an independent predictor of care requires adequate adjustment for factors that are associated with ageing and may impact treatment outcomes, such as poor functional status. Most population-based studies only include a measure of comorbidity. In the current study, older adults were significantly less likely to receive treatment after additionally adjusting for ASA physical health status, however more complete data or the inclusion of other measures of daily function or physiologic reserve could reduce the effect of age in the models. In addition, it is likely that some comorbidities were underascertained from the administrative data.²⁰ While a validated comorbidity index was used to increase the comparability of findings across studies, the non-linear association between Charlson score and chemotherapy receipt both in this study and elsewhere³¹ suggests that clinicians may weigh specific comorbidities differently in chemotherapy decision making than in the original mortality index.

Identifying factors that contribute to differences in the treatment of older patients also provides insight into ways to facilitate better care. Having a current partner was an independent predictor of chemotherapy receipt in our study, as in previous research.³² Increasing access to social support programs for older people, who are more likely to live alone, may improve their treatment and outcomes. Similarly, discussion at multidisciplinary team meeting was associated with increased radiotherapy use in the current study, as in previous research.³³ Greater implementation of MDTs would likely result in better care as well as survival.³⁴ Interestingly, those in the middle of the socioeconomic strata were the least likely to receive chemotherapy. This may reflect the access to care in major public tertiary institutions that is available to the most disadvantaged as part of Australia's universal healthcare system. Even with this safety net, however, it appears that many older patients are not receiving the recommended standard of care.

While it is clear that adjuvant chemotherapy for colon cancer substantially increases disease-free and overall survival,³⁵ the magnitude of survival benefit from radiotherapy in rectal cancer is reported to be relatively small.³⁶ Increases in local control due to the

introduction of improved rectal surgery techniques such as total mesorectal excision could mean that physicians decide the small additional survival benefits are not always worth the potential morbidity. The overall lower rates of radiotherapy use compared to chemotherapy use in the current study may reflect this uncertainty. The dependence of radiotherapy receipt on type of resection, and the variation attributed to rectal surgeons in our models, further indicate that surgery-related factors must be considered if the targets for optimal radiotherapy utilisation in rectal cancer³⁷ are to be met.

Despite increases on previous state-wide rates of adjuvant therapy utilisation and universal health care coverage, there are continuing age differences in this aspect of evidence-based care in NSW that are not explained by patients' comorbidities or health status. Further exploration and support for these complex treatment decisions is needed to improve the survival outcomes of older colorectal cancer patients. Though limitations exist, the routinely collected dataset used in this study provides a useful way to identify and monitor at-risk patient groups in the hospitals it is collected. Feedback on comparative performance to providers may be a starting point to reducing variation in care.

Acknowledgements

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Appendix 3.1. Additional information about the NSW ClinCR

Clinical cancer registries (ClinCR) were established in five Area Health Services (AHS) (North Coast, Northern Sydney Central Coast, South Eastern Sydney Illawarra, Sydney South West, and Sydney West AHS) in 2006, and in Hunter New England AHS in 2007. Clinical Cancer Registries were not established in Greater Southern AHS or Greater Western AHS. Each ClinCR is managed locally, with data collection, data entry, quality control and data governance the responsibility of the AHS. The ClinCR covers only patients treated within public facilities within the AHS. However, a major strength of this dataset is the depth of clinical information collected. Data items contained in the ClinCR include:

- Demographic details: sex, age, country of birth, postcode, indigenous status
- System details: AMO registration number, facility code
- Diagnostic and staging items: date of diagnosis, primary site of cancer, best basis for diagnosis, histopathological grade, morphology, degree of spread, TNM staging
- Clinical details: performance status at diagnosis, date of death, cause of death
- Treatment items: date of admission, date of discharge, ICD-10-AM procedure codes, date of radiotherapy start, date of radiotherapy end, radiotherapy type, dose and fractions, date of systemic therapy start, date of systemic therapy end, systemic protocol, number of cycles, date of referral to cancer specialist, date of consultation with specialist, date of decision to treat, date of clinical trial enrolment, date of MDT meeting, date of referral to palliative care, psycho-social referral to (type)

Creation of collated ClinCR dataset. Many data items were common across all ClinCRs, however some were unique to individual area datasets and many were recorded in different ways. Data were harmonised to best resemble the current data dictionary and to enable stacking (combining) of the datasets. This process included standardising data item names, cleaning erroneous data, standardising default codes, transforming data recorded as text strings to standard codes, determining meaning of area-specific coding not recorded in the minimum dataset dictionary and reassigning codes, standardising items where different coding systems had been used (e.g. systemic protocol).

4

The surgeon

In Chapter 3, increasing age was strongly associated with decreasing likelihood of receiving guideline-recommended adjuvant therapy. Multilevel modelling accounting for patient and hospital characteristics revealed that surgeons may hold similar preferences against the referral of older patients. This chapter outlines the findings of a self-administered survey of Australian and New Zealand colorectal surgeons. The survey aimed to determine surgeon's knowledge, opinions and self-reported practice regarding referral for, and use of, adjuvant therapy for older patients.

The study also contained a randomised comparison of postal and internet survey methods on surgeon response rates, survey completeness, and characteristics of responders. The findings of this study are reported in [Appendix 4.2](#), and an example screenshot of the online version of the survey is provided in [Appendix 4.3](#). A copy of the postal survey is available in [Appendix 4.4](#).

This chapter is presented as the following paper:

Jorgensen ML, Young JM, Solomon MJ. Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions, and practice. *Diseases of the Colon & Rectum* 2011; 54(3): 335-41.

Available: http://journals.lww.com/dcrjournal/Abstract/2011/03000/Older_Patients.13

CONTRIBUTION STATEMENT

Dear co-authors,

RE: *Jorgensen ML, Young JM, Solomon MJ. Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions, and practice. Diseases of the Colon & Rectum 2011; 54(3): 335-341.*

I would like to use the above paper as one of the chapters of my PhD thesis and request your permission to do so. As one of the requirements of the Academic Board of the University of Sydney, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author contributions

Jorgensen ML conceived and designed the study and survey, collected the data, analysed and interpreted the data, drafted the manuscript. **Young JM** designed the study, interpreted the data, critically revised the paper. **Solomon MJ** designed the study, interpreted the data, critically revised the paper. All authors read and approved the final draft of the manuscript.

If you agree with the contributions outlined above and give permission for this paper to be a part of my thesis, please sign next to your name below. Your support is greatly appreciated.

Kind regards,

Mikaela Jorgensen

Jane M Young



Michael J Solomon



Older patients and adjuvant therapy for colorectal cancer: surgeon knowledge, opinions, and practice

4.1. Abstract

BACKGROUND: Increasing patient age independently predicts non-referral and non-receipt of adjuvant therapy among patients with colorectal cancer. This study aimed to identify factors affecting surgeons' decisions to refer older patients for adjuvant therapy.

METHODS: A self-administered survey was sent to all Australian and New Zealand colorectal surgeons (n=146). The survey consisted of three sections: 1) knowledge of research evidence, 2) opinions on evidence and adjuvant therapy in older patients, and 3) self-reported practice, or likelihood of patient referral in different scenarios. Demographic information was also obtained.

RESULTS: Seventy percent of surgeons responded. Surgeons were significantly less likely to refer older patients than younger patients for adjuvant therapy in all scenarios ($p < 0.001$). The difference in referral recommendations was greatest when patients lived a long way from treatment, had a comorbid condition, or had little social support. There was greater variation in referral recommendations for older patients, and marked disagreement between surgeons in knowledge and opinion questions. Surgeon age was the only significant predictor of survey responses. Greater knowledge and more positive opinions predicted similar referral recommendations for older and younger patients ($p = 0.02$, $p = 0.01$).

CONCLUSIONS: Chronological age alone appears to impact colorectal surgeons' decisions to refer patients for adjuvant therapy. Sociodemographic and physiological factors further decrease the likelihood of referral of older patients. A lack of consensus among surgeons suggests that more research is needed both to predict how older patients with cancer will react to treatment, and to determine how information from emerging evidence can be best used to assist physicians' treatment decisions.

4.2. Introduction

More than half of all colorectal cancer (CRC) cases occur in those over 70 years of age.¹ However, older patients may be at risk for receiving suboptimal care. Patients over 70 years are significantly less likely to receive adjuvant therapy than younger patients, even after adjusting for age-related factors such as disease stage and comorbidity.²⁻⁴

Although receipt of adjuvant therapy may appear to rest in the hands of oncologists, surgeons play a critical gate-keeping role. Referral to medical oncology is one of the most important factors associated with receipt of chemotherapy among older patients with stage III colon cancer.⁵ Yet in an Australian patterns of care study, increasing patient age independently predicted nonconcordance with national clinical practice guidelines for the referral of patients with colorectal cancer for adjuvant therapy.⁶ Colorectal surgeons have also been found to hold significantly stronger preferences against all adjuvant options for rectal cancer compared with oncologists.⁷ Because physician opinion has a major impact on the treatment decisions of older patients,^{8,9} the views of surgeons regarding adjuvant therapy in older adults should be explored further.

Randomized trials of adjuvant chemotherapy typically find no significant interaction between age, efficacy of treatment, and incidence of toxicity.^{10,11} However, treatment decision making for older patients is inherently more complex. Individual physicians must balance factors such as physiological and psychosocial health, life expectancy, and the effects of cancer and cancer treatment on quality of life. Limitations of current evidence, in particular, because of the underrepresentation of older patients in clinical trials,¹² make these decisions all the more difficult.

Previous surveys have focused primarily on the impact of comorbidity or general health on physicians' adjuvant therapy recommendations.¹³⁻¹⁶ Where other factors are considered, differences by age are generally not compared.^{8,17} The association between knowledge of evidence, opinions, and practice in the treatment of older patients with adjuvant therapy has also not been explored. Therefore, the aim of this study was to identify factors affecting surgeons' decisions to refer older patients with colorectal cancer for adjuvant therapy by determining surgeon knowledge, opinions, and self-reported practice in a range of scenarios.

4.3. Method

Participants

The study sample comprised colorectal surgeons from Australia and New Zealand. Surgeons were identified through the Colorectal Surgical Society of Australia and New Zealand (CSSANZ). All members of CSSANZ were eligible for participation, unless they were no longer practicing medicine, were on extended leave of more than 6 weeks, or no longer resided in Australia or New Zealand.

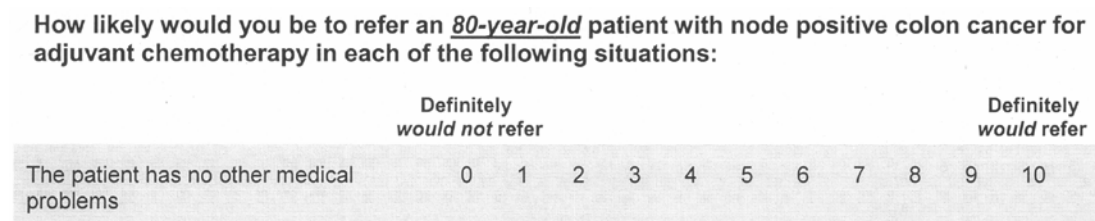
Surgeons were randomly allocated to receive either a hard-copy mailed survey, or an email with a link to an online survey with identical content. Three reminder letters/emails were sent to non-respondents at 2-week intervals. Further information and results by survey type will be presented elsewhere. The study was approved by CSSANZ and Sydney South West Area Health Service Ethics Review Committee.

Survey Instrument

A self-administered survey was developed to measure knowledge, opinions, and practice regarding referral of older patients by colorectal surgeons for adjuvant therapy. Survey questions were pilot tested by colorectal fellows for content, clarity, and ease of use.

Knowledge questions were based on recommendations of the current Australian clinical practice guidelines¹⁸ and current research evidence. Opinion questions were based on literature review. Level of agreement with statements in these sections were measured using a 5-point Likert scale (strongly disagree to strongly agree). For the self-reported practice section, surgeons were asked to indicate how likely they would be to refer 2 patients of different ages (60 years and 80 years) with node-positive colon cancer, given a number of patient-based and structural barriers to adjuvant chemotherapy. Self-reported practice was measured using 11-point visual analog scales (definitely would not refer to definitely would refer) (Figure 1).

Figure 1. Example of self-reported practice question



Data Analysis

Self-reported practice was analysed in 2 ways.

1. Absolute analysis: the likelihood of referral of patients in the different scenarios overall. That is, which factors had the greatest impact on the decision to refer in both patient groups. Mean scores for each scenario were calculated.
2. Relative analysis: the likelihood of referral of an older patient compared with a younger patient in the same scenario. That is, which factors (eg, comorbidity) produced the greatest differences on the decision to refer between the older and younger patient. Mean differences were analysed using paired t-tests. The total of the mean difference scores for each participant provided a total self-reported practice score.

Knowledge questions were dichotomized as either “consistent” or “inconsistent” with national guidelines and current research evidence. Responses were considered consistent if participants selected either “strongly agree/agree” or “strongly disagree/disagree” as appropriate to the question. The number of responses consistent with the evidence were tallied to provide a knowledge score for each participant. Correlation coefficients were obtained for the relationship between knowledge and self-reported practice scores.

Opinion questions were dichotomized in a similar manner to knowledge questions. Tally points were given to responses indicating similar opinions toward older and younger patients and belief in adequacy of current evidence. A summary score was calculated and correlation coefficients were obtained for the relationship between opinion and self-reported practice scores.

Multiple regression was used to test for independent associations between surgeon characteristics (eg, age, sex, practice location) and total scores for the knowledge, opinions, and self-reported practice sections. Any demographics that indicated a possible relationship to total scores ($p < 0.25$) were used as predictors in the models. Predictors with the least effect on total scores were dropped out of the models one at a time until all predictors were significant.¹⁹

4.4. Results

Of 146 eligible colorectal surgeons from Australia and New Zealand, 102 responded to the survey (70%). The mean age of responding surgeons was 49 years, and most surgeons were male (95%). The majority reported practicing in a capital city or other major urban area (94%) and 73% considered their major appointment as visiting medical officer/consultant. Eighty-one percent of surgeons reported attending multidisciplinary team meetings often (Table 1).

Table 1. Characteristics of colorectal surgeons responding to survey

		n	%
Responding surgeons (of 146)		102	69.9
Age in years (mean/SD)		48.9	8.7
Sex	Male	95	93.1
	Female	7	6.9
Practice location	Capital city	68	66.7
	Other major urban area	28	27.5
	Rural area	6	5.9
Hospital of majority work (not mutually exclusive)	Tertiary referral teaching hospital	60	58.8
	District general hospital	9	8.8
	Rural hospital	1	1.0
	Private hospital	47	46.1
Appointment (not mutually exclusive)	Conjoint staff/academic	22	21.6
	VMO/consultant	74	72.5
	Staff specialist	9	8.8
	Salaried university academic	10	9.8
Multidisciplinary team meeting attendance	Often	83	81.4
	Sometimes	13	12.7
	Never	4	3.9
	Not available	2	2.0
Chemotherapy services at hospital	Yes	93	91.2
	No	9	8.8
Radiotherapy services at hospital	Yes	69	68.3
	No	32	31.7

VMO = visiting medical officer

Self-Reported Practice (Relative)

Surgeons were significantly less likely to refer an older patient with node-positive colon cancer for adjuvant chemotherapy than a younger patient in all 8 self-reported practice questions ($p < 0.001$). The scenarios that produced the greatest difference in referral

recommendations between a younger and older patient were living a long distance from available treatment, having a comorbid condition, and having no close social supports (Table 2). For example, 93% of surgeons would likely refer a 60-year-old patient with node-positive colon cancer for adjuvant chemotherapy if they lived 300 km from the nearest treatment facility. However, only half as many surgeons (47%) would likely refer an 80-year-old patient in the same scenario. There was also much greater variation in referral recommendations for older patients (table 2).

Table 2. Likelihood of referring an older and younger patient for adjuvant chemotherapy*

	60-year-old, mean (SD)	80-year-old mean (SD)	Difference, mean (SD)	p
The patient lives 300km from the nearest treatment facility	10.2 (1.5)	6.6 (3.6)	3.6 (3.2)	<.001
The patient has an ASA status of III (e.g. controlled congestive heart failure)	9.5 (1.9)	6.2 (3.5)	3.3 (2.9)	<.001
The patient has no close family or friends to support them	10.2 (1.4)	7.0 (3.6)	3.3 (3.2)	<.001
The patient has some degree of cognitive impairment (i.e. needs some help with daily tasks)	8.0 (2.9)	5.2 (3.5)	2.8 (2.7)	<.001
The patient may have difficulty coping with additional medical costs or loss of income	9.9 (1.7)	7.3 (3.6)	2.6 (3.1)	<.001
The patient needs some assistance with personal care (e.g. bathing, dressing)	8.6 (2.7)	6.2 (3.5)	2.4 (2.6)	<.001
The patient refuses referral initially	8.0 (3.8)	5.6 (3.8)	2.4 (3.0)	<.001
The patient has no other medical problems	10.9 (0.5)	9.5 (2.5)	1.4 (2.4)	<.001

*11-point Likert scale used

Self-Reported Practice (Absolute)

The greatest barriers to referral for adjuvant chemotherapy overall were the same for both the younger and older patient. Cognitive impairment, initial patient refusal, and the need for assistance with personal care were the scenarios where patients were least likely to be referred (Table 2). For example, only 68% of surgeons would likely refer a 60-year-old patient if they had some degree of cognitive impairment, and 33% for an 80-year-old

patient in the same scenario. Not surprisingly, the scenario that produced the greatest referral rates for adjuvant chemotherapy, and the least difference in referral between the older and younger patient, was if there were no other medical problems. Nearly all surgeons (96%) would “definitely refer” an otherwise healthy younger patient with node-positive colon cancer, compared with 61% for the older patient in the same scenario.

Knowledge

The majority of surgeons “strongly agreed” or “agreed” with specific recommendations of the national clinical practice guidelines for the treatment of older patients with adjuvant chemotherapy (81%) and preoperative radiotherapy (97%). On the issues of toxicity, benefits, and quality of life, there was greater disagreement (Table 3). Interestingly, only 39% of surgeons agreed that adjuvant chemotherapy is underused in older patients. Surgeons with a greater knowledge score were significantly more likely to have similar referral recommendations for older and younger patients ($p=0.018$).

Table 3. Responses to knowledge questions

	Strongly agree / agree (%)	Neutral (%)	Strongly disagree / disagree (%)	Total % (n)
Older people derive similar benefits from adjuvant chemotherapy as younger people	72.5	14.7	12.7	100 (102)
Adjuvant chemotherapy is underutilised in elderly patients	39.2	43.1	17.6	100 (102)
The risk of toxicity from adjuvant chemotherapy increases with age	72.5	15.7	11.8	100 (102)
All patients with node positive colon cancer should be <u>considered</u> for adjuvant chemotherapy regardless of age	81.2	2.0	16.8	100 (101)
Adjuvant chemotherapy has a greater impact on the quality of life of older people than younger people	50.0	28.4	21.6	100 (102)
Elderly patients with high-risk rectal cancer should be <u>considered</u> for preoperative radiotherapy, either alone or as combined modality therapy	97.1	2.9	0	100 (102)

Opinions

Opinions were also significantly associated with self-reported practice, with higher opinion scores predicting similar referral of older and younger patients ($p=0.01$). Most surgeons believed that older patients preferred less aggressive treatment and that younger patients should have preference over elderly patients, but that the side effects of adjuvant chemotherapy were generally worth the benefits for older patients (Table 4). Thirty-nine percent of surgeons believed there is an upper age limit after which chemotherapy is no longer worthwhile (mean age, 82 y; range, 75-90 y). Yet the majority of responders reported that they believed there is adequate evidence to justify the use of adjuvant chemotherapy and radiotherapy in patients over 70 years.

Table 4. Responses to opinion questions

	Strongly agree / agree (%)	Neutral (%)	Strongly disagree / disagree (%)	Total % (n)
For the elderly, the side effects of adjuvant chemotherapy are generally not worth the benefits	9.8	20.6	69.6	100 (102)
Older people often prefer less aggressive treatment to younger people	66.7	13.7	19.6	100 (102)
Considering the limited resources of the health system, younger patients should have preference over the elderly for adjuvant chemotherapy	19.8	23.8	56.4	100 (101)
Older people generally prefer the physician to make treatment choices for them	38.2	26.5	35.3	100 (102)
There is adequate evidence to justify the use of adjuvant chemotherapy in the elderly	71.6	18.6	9.8	100 (102)
There is adequate evidence to justify the use of preoperative radiotherapy in the elderly with high-risk rectal cancer	78.4	8.8	12.7	100 (102)
Do you believe there is an upper age limit after which adjuvant chemotherapy is no longer worthwhile?	38.8 (yes)	82* (75-90)	61.2 (no)	98 (100)

*Mean age limit (range)

Physician Predictors

Surgeon age was the only significant independent predictor of survey responses. Younger surgeons were more likely to have a higher knowledge score ($p=0.006$) and a higher opinion score ($p=0.027$). However, surgeon age did not explain much of the variation in scores ($R^2=0.048$ and $R^2=0.074$). Surgeons who practiced in a capital city or other major urban area were more likely to have similar referral recommendations for older and younger patients than those who practiced in a rural location (mean total difference, 21 and 32), but this result was not significant. Referral recommendations did not vary by age, sex, hospital location, appointment, multidisciplinary team meeting attendance, or the availability of on-site chemotherapy or radiotherapy services at the surgeon's hospital.

4.5. Discussion

In this study, colorectal surgeons were significantly less likely to self-report referral of an older patient with node-positive colon cancer for adjuvant chemotherapy than a younger patient across a range of scenarios. Both knowledge of evidence and opinions about older patients and adequacy of evidence were strongly associated with referral recommendations. Surgeon age was the only factor that independently explained knowledge and opinion scores.

Older patients with colorectal cancer are less likely than younger patients to receive adjuvant therapy both in Australia^{3,20,21} and internationally.^{2,4} The results of this study may provide some insight into the underlying reasons for these differences. Although many consider that older patients with cancer are undertreated, there is also significant debate about the overtreatment of this population.²² This was reflected in physician disagreement in this survey. Only 39% of surgeons agreed that adjuvant therapy is underused in older patients, whereas 18% disagreed and 43% were neutral. Life expectancy is a function of age, comorbidity, disability, and cancer type and stage.²³ For some older patients, decisions to forgo adjuvant treatment may be appropriate, in particular where patient quality of life

might be significantly compromised. However, in this survey, an 80-year-old patient with no other medical problems was much less likely to be referred than a similar 60-year-old patient.

Patient age alone has also been reported to influence physicians' recommendations across other surveys.¹³⁻¹⁷ An otherwise healthy 80-year-old has a life expectancy of 9 years,²⁴ and there is evidence that adjuvant chemotherapy achieves significant 5-year survival for older patients²⁵ and may not have a significant negative impact on quality of life.²⁶ The differences in the treatment of older patients perhaps stem from a more delicate issue, that is, whether treatment is worth the cost (both for the patient and as a society) for potentially little long-term gain. Certainly 20% of surgeons reported that younger patients should have preference over older patients given the limited resources of the health system. These economic considerations deserve substantial research and debate given the expected rise in the number of older patients with cancer because of population ageing. Until this occurs, the question of benefit and burden is perhaps best answered by the well-informed patient, although too frequently adjuvant therapy is not discussed with patients.²⁷

Lack of consensus among surgeons about the treatment of older patients was a major feature of this survey. Although several surgeons noted that referral to medical oncology is mandatory, others reported not routinely referring patients over a certain age. Greater variation between referral recommendations was particularly evident where patients were older and sicker. Comorbidity is a major concern in the management of older patients, because it can have a substantial impact on treatment tolerance.²⁸ As a result, increasing comorbidity has been found to predict non-receipt of adjuvant chemotherapy in both population studies^{20,29} and other physician surveys.^{15,17} In this study, having a comorbid condition produced the second greatest difference in referral recommendations between an older and younger patient. Emerging evidence suggests that chemotherapy improves survival among patients with certain chronic conditions without increasing the probability

of hospitalization.³⁰ However, cohort studies do not account for inherent differences between treatment and nontreatment groups. Randomized control trials are needed to disentangle the effects of patient age, comorbidity, and other factors such as patient preference. Without this information, it is likely that physicians' views will continue to diverge,¹⁷ and the individual surgeon a patient sees will be an important variable in determining whether they are referred for, and perhaps in turn receive, adjuvant therapy.

The focus on comorbidity in other physician surveys is warranted given the frequency of chronic conditions in older patients. Yet this focus tends to ignore the possible impact of other factors on treatment decision making. In this study, an older patient was much less likely to be referred for adjuvant chemotherapy than a younger patient if they lived a long distance from available treatment. Travel has been reported to affect the treatment decisions of older patients and those who do not receive chemotherapy.⁸ Living in an urban area has also been found to independently predict chemotherapy use in patients 80 years and older.³¹ Population-based studies have not always found this association, however,^{32,33} and travel factors have not previously been reported to affect physicians' treatment decisions. Nevertheless, the role of structural barriers in the treatment of older patients should be further explored, in particular, in a local context.

In addition, patients with cognitive impairment, those who initially refused referral, and those who needed assistance with personal care, were the least likely to be referred for adjuvant chemotherapy overall. Krzyzanowska and colleagues¹⁷ similarly found that patient preference against therapy affected physicians' recommendations, and cognitive impairment has been reported to affect patient and physician decision making for older patients with cancer.²⁸ Although other factors such as life expectancy, social support, cost, and quality of life have been reported in previous surveys,^{8,17} this study was unique in allowing comparison between overall (absolute) barriers and age-comparative (relative) barriers. The differences between relative and absolute barriers to adjuvant therapy in this study, and the variety of factors that have been considered elsewhere, further demonstrate the complex nature of cancer treatment decisions for older patients.

The findings of this study should be interpreted in light of a number of limitations. Although necessary for the brevity of the survey, the self-reported practice section only contrasted two specific ages, and other factors that may influence referral were not included. Furthermore, any underuse of appropriate adjuvant therapy is most likely multifactorial. This study only assessed surgeons' perceived barriers to referral. If oncologists, for example, perceive fewer or different barriers to adjuvant therapy use in older patients, then variation in management could be reduced by increasing multidisciplinary planning.³⁴ The concordance between patient and physician views should also be explored further. Patient knowledge and beliefs about treatment, as well as medical mistrust, have been associated with underuse of adjuvant therapy in breast cancer.³⁵ Facilitating communication between physicians and patients, for example, through the use of decision aids,^{36,37} may help patients make the optimal treatment decision.

Nevertheless, older patients frequently cite physician judgment as the most important factor influencing their treatment decision making.⁸ Opinions and knowledge were highly associated with self-reported practice in this study. Because older patients are likely to follow physician advice, increasing awareness of evidence may therefore increase the rates of referral and ultimately the receipt of adjuvant therapy. Targeting specific physician groups for education is one possibility. In multivariate analysis, younger surgeons were more likely to have a greater knowledge of evidence and similar opinions toward older and younger patients. Physician age has also been reported to predict referral and receipt of adjuvant therapy in previous studies.^{15,35} However, targeting older physicians may not have a major impact on referral rates because physician characteristics explained so little of the results. Screening tools such as the Vulnerable Elders Survey (VES- 13),³⁸ a self-administered survey that is highly predictive of impaired functional status,³⁹ could be a useful alternative to aid treatment decision making.

Conclusion

Chronological age alone appears to impact colorectal surgeons' decisions to refer patients for adjuvant therapy. Sociodemographic and physiological factors further decrease the likelihood of referral of older patients. The lack of consensus among surgeons suggests that more research is needed both to predict how older patients with cancer will react to treatment, and to determine how information from emerging evidence can be best used to assist physicians' treatment decisions.

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Appendix 4.2. Comparison of postal and internet survey methods

Internet-based surveys have the potential to save time, effort and financial resources. With increasing professional usage of the internet by clinicians,ⁱ electronic surveys may no longer perform more poorly than traditional mailed surveys with regard to response rates and representativeness.ⁱⁱ Australian surgeons were randomly allocated to receive the survey described above either through the post (n=64) or through an email linked to an online survey with identical content (n=62). Both surveys included endorsements by a colorectal surgeon and the chairman of the research support committee of the CSSANZ. All New Zealand colorectal surgeons received an email invitation to the online survey (n=20), and were excluded from the present analysis. One surgeon allocated to online group requested a postal survey. Respondents were analysed as allocated.

While 77% of the postal group returned their surveys, only 65% of the internet group completed the online survey. However, these response rates were not statistically significantly different ($X^2[1]=1.6$, $p=0.19$). Survey completeness was nearly 100% for both groups. 25% of all online responders had completed the survey within 2 days of the initial invitation, but there were no differences between groups in median response time overall (median [IQR] = 15 [26] days vs 16 [25] days). The characteristics of responders in the online and postal group did not differ significantly by physician age, sex, qualification, type of hospital, or survey scores (all $p>0.05$), although more responders in the online group practiced outside of a capital city (32% vs 24%). Internet-based surveys may therefore be an effective tool for engaging surgeons in health services research, and could be a preferred option for regional or rural surgeons.

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Appendix 4.3. Example screenshot of online version of surgeon survey

Older patients and adjuvant therapy for colorectal cancer Exit this survey >>

Section I: Evidence

Please rate your level of agreement with each statement by selecting the most appropriate answer. Unless otherwise specified, each statement refers to people with colon cancer. For the purposes of this survey, 'older' or 'elderly' is defined as people over 70 years of age.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Older people derive similar benefits from adjuvant chemotherapy as younger people	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Adjuvant chemotherapy is underutilised in elderly patients	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
The risk of toxicity from adjuvant chemotherapy increases with age	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
All patients with node positive colon cancer should be <u>considered</u> for adjuvant chemotherapy regardless of age	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Adjuvant chemotherapy has a greater impact on the quality of life of older people than younger people	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Preoperative radiotherapy, either alone or as combined modality therapy, is appropriate for the treatment of high-risk (T3/4 or N1) rectal cancer	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
Elderly patients with high-risk (T3/4 or N1) rectal cancer should be <u>considered</u> for preoperative radiotherapy, either alone or as combined modality therapy	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Any other comments:

2 / 7 ██████████

Appendix 4.4. Postal version of surgeon survey

Older patients and adjuvant therapy for colorectal cancer

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This survey aims to gather information about the opinions of colorectal surgeons regarding referral for and use of adjuvant therapy for older patients with colorectal cancer.

The survey has 5 sections and should take about 10 minutes to complete.

Thank you for your time.

Section I: Evidence

Please rate your level of agreement with each statement by ticking the most appropriate box. Unless otherwise specified, each statement refers to people with colon cancer.

For the purposes of this survey, 'older' or 'elderly' is defined as people over 70 years of age.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
Older people derive similar benefits from adjuvant chemotherapy as younger people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Adjuvant chemotherapy is underutilised in elderly patients	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The risk of toxicity from adjuvant chemotherapy increases with age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
All patients with node positive colon cancer should be <u>considered</u> for adjuvant chemotherapy regardless of age	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Adjuvant chemotherapy has a greater impact on the quality of life of older people than younger people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Preoperative radiotherapy, either alone or as combined modality therapy, is appropriate for the treatment of high-risk (T3/4 or N1) rectal cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Elderly patients with high-risk (T3/4 or N1) rectal cancer should be <u>considered</u> for preoperative radiotherapy, either alone or as combined modality therapy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Any other comments:

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Section II: Opinions

Please rate your level of agreement with each statement by ticking the most appropriate box. Unless otherwise specified, each statement refers to people with colon cancer. For the purposes of this survey, 'older' or 'elderly' is defined as people over 70 years of age.

	Strongly agree	Agree	Neutral	Disagree	Strongly disagree
For the elderly, the side effects of adjuvant chemotherapy are generally not worth the benefits	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Older people often prefer less aggressive treatment to younger people	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
The recommendations for the management of elderly patients in the national Clinical Practice Guidelines for Colorectal Cancer should be more explicit	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Considering the limited resources of the health system, younger patients should have preference over the elderly for adjuvant chemotherapy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
There is adequate evidence to justify the use of adjuvant chemotherapy in the elderly	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Older people generally prefer the physician to make treatment choices for them	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
There is adequate evidence to justify the use of preoperative radiotherapy in the elderly with high-risk rectal cancer	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Do you believe there is an upper age limit after which adjuvant chemotherapy is no longer worthwhile?

No Yes

If yes, please specify this upper age limit: _____

Any other comments:

Section III: Scenarios

The following questions ask you to indicate how likely you would be to refer a patient for adjuvant chemotherapy in a number of scenarios. Please circle the number (0 – 10) that best describes how likely you would be to refer.

How likely would you be to refer a *60-year-old* patient with node positive colon cancer for adjuvant chemotherapy in each of the following situations:

	Definitely <i>would not</i> refer										Definitely <i>would</i> refer											
	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient has no other medical problems	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient refuses referral initially	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient has an ASA status of III (e.g. controlled congestive heart failure)	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient needs some assistance with personal care (e.g. bathing, dressing)	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient has no close family or friends to support them	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient lives 300km from the nearest available treatment facility	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient has some degree of cognitive impairment (i.e. needs some help with daily tasks)	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient may have difficulty coping with additional medical costs or loss of income	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10

Section IV: More scenarios

Please circle the number (0 – 10) that best describes how likely you would be to refer.

How likely would you be to refer an 80-year-old patient with node positive colon cancer for adjuvant chemotherapy in each of the following situations:

	Definitely <i>would not</i> refer										Definitely <i>would</i> refer											
	0	1	2	3	4	5	6	7	8	9	10	0	1	2	3	4	5	6	7	8	9	10
The patient has no other medical problems																						
The patient refuses referral initially																						
The patient has an ASA status of III (e.g. controlled congestive heart failure)																						
The patient needs some assistance with personal care (e.g. bathing, dressing)																						
The patient has no close family or friends to support them																						
The patient lives 300km from the nearest available treatment facility																						
The patient has some degree of cognitive impairment (i.e. needs some help with daily tasks)																						
The patient may have difficulty coping with additional medical costs or loss of income																						

Are there any other factors that you may take into consideration when deciding whether or not to refer a patient for adjuvant chemotherapy?

Section V: Demographic details

Finally, a few questions about you and your practice so that we can determine whether we have achieved a representative sample.

Your age: _____ years

Are you Male Female

Which of the following best describes the location in which you practice?

Capital city Other major urban area
Rural area Other, please specify _____

What type of appointment do you have?

Conjoint Staff/Academic Y / N VMO/Consultant Y / N
Staff specialist Y / N Salaried University Academic Y / N
Other, please specify _____

Where do you perform the majority of your hospital work?

Tertiary referral teaching hospital District general hospital
Rural hospital Private hospital
Other, please specify _____

Do you attend multidisciplinary team meetings for colorectal cancer patients?

Often Sometimes
Never Not available

Does your hospital have on-site chemotherapy or radiotherapy services?

Chemotherapy Y / N Radiotherapy Y / N

Any other comments:

**THANKYOU VERY MUCH FOR
COMPLETING THIS QUESTIONNAIRE**

Surgical Outcomes Research Centre (SOuRCe)
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5

The patient

In Chapter 4, factors affecting colorectal surgeons' decisions to refer older patients for adjuvant therapy were explored. Surgeons placed emphasis on practical barriers to treatment such as travel distance, as well as on patients' chronological age, social support and health status. This chapter investigates patient-based barriers to adjuvant chemotherapy use through a self-administered survey of colorectal cancer patients. Although the strength of patients' preferences has been explored previously, less is known about the processes that influence these preferences. The survey aimed to identify factors that uniquely affect older patients' decisions to undergo treatment, including preferences for information and involvement in treatment decision making. A copy of the patient survey is available in [Appendix 5.2](#).

This chapter is presented as the following paper:

Jorgensen ML, Young JM, Solomon MJ. Adjuvant chemotherapy for colorectal cancer: age differences in factors influencing patients' treatment decisions. *Patient Preference and Adherence* 2013; 7: 827-34.

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CONTRIBUTION STATEMENT

Dear co-authors,

RE: *Jorgensen ML, Young JM, Solomon MJ. Adjuvant chemotherapy for colorectal cancer: age differences in factors influencing patients' treatment decisions. Patient Preference and Adherence 2013; 7: 827-834.*

I would like to use the above paper as one of the chapters of my PhD thesis and request your permission to do so. As one of the requirements of the Academic Board of the University of Sydney, a signed written statement is required from all co-authors attesting to my contribution as evidence to satisfactorily identify the work for which I am responsible.

Author contributions

Jorgensen ML conceived and designed the study and survey, collected the data, analysed and interpreted the data, drafted the manuscript. **Young JM** designed the study, interpreted the data, critically revised the paper. **Solomon MJ** designed the study, interpreted the data, critically revised the paper. All authors read and approved the final draft of the manuscript.

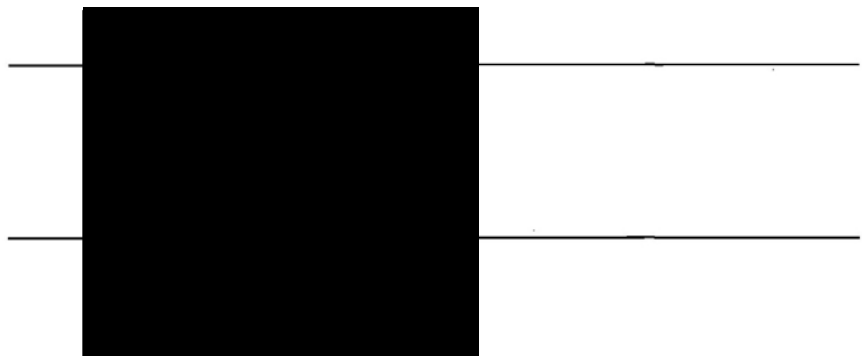
If you agree with the contributions outlined above and give permission for this paper to be a part of my thesis, please sign next to your name below. Your support is greatly appreciated.

Kind regards,

Mikaela Jorgensen

Jane M Young

Michael J Solomon



Adjuvant chemotherapy for colorectal cancer: age differences in factors influencing patients' treatment decisions

5.1. Abstract

PURPOSE: Older colorectal cancer patients are significantly less likely than younger patients to receive guideline-recommended adjuvant chemotherapy. Previous research has indicated that patient refusal of treatment is a contributing factor. This study aimed to identify potential barriers to adjuvant chemotherapy use in older patients by examining the associations between patient age, factors influencing chemotherapy treatment decisions, and preferences for information and decision-making involvement.

METHODS AND RESULTS: Sixty-eight patients who underwent surgery for colorectal cancer in Sydney, Australia, within the previous 24 months completed a self-administered survey. Fear of dying, health status, age, quality of life, and understanding treatment procedures and effects were significantly more important to older patients (aged ≥ 65 years) than younger patients in deciding whether to accept chemotherapy (all $p < 0.05$). Reducing the risk of cancer returning and physician trust were important factors for all patients. Practical barriers such as traveling for treatment and cost were rated lowest. Older patients preferred less information and involvement in treatment decision making than younger patients. However, 60% of the older group wanted detailed information about chemotherapy, and 83% wanted some involvement in decision making. Those preferring less information and involvement still rated many factors as important in their decision making, including understanding treatment procedures and effects.

CONCLUSION: A range of factors appears to influence patients' chemotherapy decision making, including, but not limited to, survival benefits and treatment toxicity. For older patients, balancing the risks and benefits of treatment may be made more complex by the impact of emotional motivators, greater health concerns, and conflicts between their need for understanding and their information and decision-making preferences. Through greater understanding of perceived barriers and motivators for treatment choice, physicians may be better able to support older patients to make informed decisions about their care.

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5.2. Introduction

Colorectal cancer (CRC) is the second most commonly diagnosed cancer in Australia, with those aged over 65 years accounting for two-thirds of all cases.¹ Current clinical practice guidelines for CRC state that advanced age alone should not be used to exclude patients from being offered effective treatment.² For fit older patients, adjuvant chemotherapy appears to achieve similar survival benefits with no greater toxicity than for younger patients.^{3,4} However, older patients are significantly less likely to be referred for and receive guideline-recommended adjuvant chemotherapy, even after adjusting for age-related factors such as comorbidity.⁵⁻⁷ While patient age is reported to be a strong influence of both surgeons' and oncologists' recommendations for chemotherapy,⁸⁻¹⁰ patient-based factors also appear to contribute to differences in treatment rates. A proportion of patients refuse adjuvant chemotherapy, and these patients are significantly more likely to be older than those who accept treatment.^{5,11,12}

Patients' preferences for chemotherapy in CRC have previously been examined by determining the amount of life cancer patients are willing to forgo to avoid treatment,¹³ the survival benefit needed to make chemotherapy worthwhile,¹⁴ and the recurrence rate at which patients will change their preference from surgery alone to surgery plus chemoradiation.¹⁵ Although the strength of patients' preferences has been explored, less is known about the processes that influence these preferences. Treatment-related determinants (eg, treatment benefits and toxicities) and patient characteristics appear to only partially explain cancer patients' preferences for adjuvant chemotherapy.¹⁶ Patient age is not a consistent predictor of preferences,^{16,17} yet the higher rate of treatment refusal in older cancer patients implies age differences in treatment decision making. As treatment

decisions are often made in the highly stressful period following cancer diagnosis, cognitive and affective determinants such as fear have been suggested as possible predictors.¹⁶

A range of other factors that may influence patients' chemotherapy decisions has also been proposed, for example, physician opinion, family support, and quality of life (QOL). Such factors have been explored in a qualitative study of older patients with breast cancer¹⁸ and a survey of older patients with colon cancer.¹⁹ However, these studies involved only patients aged 65 years and over, making it difficult to determine whether the reported factors actually distinguish the decision-making processes of older patients from younger patients. Other research involving cancer patients of all ages^{20,21} does not focus on determining age differences in treatment decision making. Greater understanding of factors that uniquely affect older patients' decisions to undergo treatment is needed to ensure optimal treatment and outcomes.

Preferences for information and decision making might also affect patients' decisions to accept treatment. Older patients appear to be at greater risk of being inadequately informed about their cancer and treatment, as they generally prefer to receive less information and to be less actively involved in making treatment decisions than younger patients.^{22,23} Physicians may also underestimate the absolute numbers of older patients who prefer to be fully informed and involved in decision making, as patient age is often reported solely as a predictor of preferences.^{21,24} In a study of CRC patients aged over 70 years, about half preferred an active or collaborative role in treatment decision making.²⁵ It has also been suggested that older people want specific information about treatment and side effects.²⁶ To create a more complete picture of older patients' decision making, age differences in specific chemotherapy preferences and their relationship to other influencing factors should be determined.

Thus, the aim of this study was to identify potential barriers to adjuvant chemotherapy use in older patients by examining the associations between patient age, factors influencing chemotherapy treatment decisions, and preferences for information and involvement in treatment decision making.

5.3. Materials and methods

Participants

Participants were recruited from a single tertiary referral hospital in Sydney, Australia. Patients aged over 18 years who had been admitted for CRC surgery within the previous 24 months were invited to participate either during their hospital stay or during a follow-up appointment with their surgeon. Eligible patients had sufficient English skills to participate, did not have cognitive impairment, and were not currently receiving chemotherapy. A surgical team member provided the researchers with the details of patients who gave their consent to be approached. Patients were given written information and the survey to complete in their own time. Those who received the survey during a follow-up appointment were provided with a reply-paid envelope, and non-responders were contacted at 2 weeks and 4 weeks. The study was approved by the Sydney South West Area Health Service Ethics Review Committee.

Survey instrument

A self-administered survey was developed to determine CRC patients' views on factors influencing chemotherapy treatment decisions, preferences for treatment information, and preferences for involvement in treatment decision making.

Using a 10 cm visual analog scale, participants were asked to rate how important various factors were (or would be) when deciding about chemotherapy treatment. The list of factors was based on a literature review and included items about survival, health impacts, opinion of others, practical barriers (eg, cost), and cognitive/affective aspects (eg, fear). Information preferences were measured using a modified version of the validated Cassileth Information Styles Questionnaire.²⁷ Participants were asked to choose a statement that best described their general attitude toward information regarding their illness, as well as specific preferences for chemotherapy information, such as side effects, treatment progress, and effectiveness in other patients. Decision-making preferences were measured

using the Degner and Sloan scale,²⁸ where participants can choose between five decision-making styles. Participant characteristics (eg, age, sex, education, and comorbidity) were also obtained.

Data analysis

For the purposes of this analysis, participants were divided into “younger” (<65 years) and “older” (≥65 years). The age of 65 years was selected to divide the sample because (1) the median age of the sample was 66 years, and (2) this cut-off is frequently used to define older age.²⁹

Factors influencing chemotherapy treatment decisions

A score for each factor was produced by measuring the distance from the lowest anchor point to the point that the participant marked on the scale, to the nearest half centimeter. To determine whether the importance of each factor differed significantly by age, mean scores for the older group were compared with mean scores for the younger group, using independent-samples t-tests. Mann-Whitney rank sum tests were also performed to determine whether any skewing to the high end of the scale affected these results. Because treatment preferences appear to become more favorable after the decision has been made to proceed with adjuvant chemotherapy,³⁰ multiple regression was used to assess whether any age differences in the importance of factors remained significant after adjusting for received or planned adjuvant chemotherapy.

Mean scores were also used to rank the overall importance of factors in chemotherapy decision making. Factors were tabulated by highest to lowest importance for the older age group. As a measure of complexity of decision making, the mean number of factors that participants rated as “important” was calculated. Factors with a rating over 5 were considered “important,” as this was the midpoint value of the visual analog scale (“not at all important” to “very important”).

Preferences for information and involvement in decision making

X² tests were used to examine age differences in information and decision-making preferences. Participants could select from four possible responses for their preferences for general information about illness. The proportions of older and younger participants who preferred as much information as possible about their illness were compared. Eight questions assessed specific preferences for chemotherapy information. The difference in the proportions of younger and older participants who reported that they “needed” or “wanted” all detailed chemotherapy information was examined. There were five options for preferred level of involvement in treatment decision making. The proportions of older and younger participants preferring active or collaborative decision-making roles were compared.²⁸

Associations between preferences and factors influencing decisions

Specific associations between information and decision-making preferences and factors influencing decisions were examined. To determine whether those who preferred minimal treatment information felt that understanding was still important in their decision making, the mean of the two factors about understanding (“understanding what is going to happen during treatment” and “understanding the benefits and side effects”) was calculated for all participants. A t-test was used to compare these mean scores between those who preferred not to have detailed information about chemotherapy and those who did.

To determine whether those who preferred less involvement in decision making still considered a range of factors when making treatment decisions, the mean number of factors rated as “important” (mean score >5 on a 10-point visual analog scale) was compared between those who preferred a passive role and those who preferred an active/collaborative role, using a t-test.

5.4. Results

Of 75 patients with CRC who consented to participate in the study, 68 returned the survey (91%). The participants ranged in age from 25 years to 82 years, with a mean age of 64 years. More participants were male and most spoke English at home (see Table 1 for further details). Nonparticipants did not differ significantly from participants for any of the characteristics listed in Table 1, though nonparticipants were slightly older (67 years versus 64 years).

Table 1. Characteristics of colorectal cancer patients responding to survey

Characteristic	Older group n (%)	Younger group n (%)	P-value ^a
Total participants	35 (51)	33 (49)	
Age in years (mean/SD)	73.9 (4.8)	53.6 (9.1)	
Male	22 (63)	17 (52)	0.34
English spoken at home	25 (71)	28 (85)	0.18
High school or tertiary	14 (40)	24 (73)	0.007
Employed full or part time	5 (14)	22 (67)	<0.001
Private health insurance	16 (46)	20 (61)	0.22
Lives alone	14 (40)	5 (15)	0.02
One or more comorbidities	27 (77)	14 (42)	
Site of cancer			0.32
Colon	20 (57)	14 (42)	
Rectum	13 (37)	17 (51)	
Dukes stage of cancer			0.79
A	5 (14)	4 (12)	
B	14 (40)	11 (33)	
C	11 (31)	12 (36)	
D	2 (6)	1 (3)	
Adjuvant chemotherapy (received or planned)	10 (29)	17 (51)	0.08

^aP-values based on χ^2 tests. *Abbreviation:* SD, standard deviation.

Factors influencing chemotherapy treatment decisions

Six factors were significantly more important to older patients than younger patients in deciding whether to have chemotherapy: “fear of dying from cancer” ($t[66]=7.07$; $p<0.001$), “how unwell I am to start with” ($t[66]=3.87$; $p<0.001$), “how old I am” ($t[63]=2.87$; $p=0.006$), “maintaining a good QOL during treatment” ($t[66]=2.94$; $p=0.005$), “understanding the benefits and side effects” ($t[66]=2.87$; $p=0.005$), and “understanding what is going to happen during treatment” ($t[66]=2.95$; $p=0.004$). After adjusting for received or planned chemotherapy, all of these factors remained significant except for “how old I am” ($p=0.07$).

“Reducing the risk of the cancer coming back” was the most highly rated item, on average, for both older and younger groups (see Table 2). “Having a doctor whose expertise I trust” and “having a doctor whom I feel comfortable asking questions of” both rated very highly. Another factor rated highly by both groups was “returning to my normal QOL after treatment.” Factors of lowest importance were also comparable between age groups. Traveling for treatment and treatment cost and duration were rated low by both older and younger patients, and “avoiding side effects” and “the opinion of my family” were also of low importance.

On average, both groups rated nearly all of the 22 factors as “important” in chemotherapy decision making (ie, mean score >5 on a 10-point visual analog scale). The older group rated more factors as “important” (mean [standard deviation {SD}] = 18.1 [3.1]) than the younger group (mean [SD] = 16.7 [3.6]) and had a slightly higher mean score for the importance of all factors (8.0 versus 7.4), but these differences were not significant.

Table 2. Factors of importance in chemotherapy decision making^a

Factor	Older group, mean (SD)	Younger group, mean (SD)	P-value ^b
Reducing the risk of the cancer coming back	9.3 (0.5)	9.3 (0.8)	0.44
Having a doctor whose expertise I trust	9.2 (0.5)	9.2 (0.6)	0.49
Understanding the benefits and side effects	9.2 (0.7)	8.5 (1.3)	0.02
Understanding what is going to happen during treatment	9.2 (0.6)	8.1 (2.2)	0.02
Returning to my normal QOL after treatment	9.1 (0.6)	9.3 (0.8)	0.10
Having a doctor who I feel comfortable asking questions	9.1 (0.6)	9.0 (1.0)	0.68
Maintaining a good QOL during treatment	9.1 (0.7)	8.1 (2.0)	0.04
The recommendation of the doctor	9.0 (0.9)	8.6 (1.2)	0.19
Increasing my chance of living longer	8.9 (1.3)	8.5 (1.6)	0.17
Doing everything possible to fight the cancer	8.9 (1.3)	8.4 (2.7)	0.71
Fear of dying from cancer	8.9 (1.3)	4.8 (3.2)	<0.001
How unwell I am to start with	8.5 (1.5)	6.0 (3.6)	0.03
Having someone to look after me during treatment	7.9 (2.5)	6.8 (2.8)	0.13
Maintaining my independence	7.8 (2.5)	8.4 (1.5)	0.70
Being able to look after significant others	7.5 (3.1)	7.5 (2.5)	0.97
How old I am	7.5 (3.1)	5.0 (3.8)	0.009
Having time to decide about treatment	7.3 (2.9)	7.7 (2.9)	0.28
Avoiding side effects	6.7 (3.2)	6.2 (3.3)	0.45
The opinion of my family	6.7 (3.6)	6.0 (3.0)	0.21
Total duration of the treatment	5.8 (3.3)	6.8 (3.5)	0.25
Cost of treatment	5.5 (3.6)	5.5 (3.6)	0.81
How far I would have to travel for treatment	3.8 (2.8)	5.5 (4.0)	0.05
Mean score of all factors	8.0 (1.0)	7.4 (1.4)	0.27

^aRanked highest to lowest for older group, based on 10-point visual analog scale;

^bP-values based on Mann-Whitney rank sum tests. *Abbreviation:* SD, standard deviation.

Preferences for information and involvement in decision making

Fifty percent of older participants preferred to have as much information as possible about their illness, compared with 76% of younger participants ($\chi^2[1]=4.75$, $p=0.03$). However, the majority of the older group reported wanting or needing as much detailed information about chemotherapy as possible (60%), and this proportion was not significantly different from the younger group (76%) ($\chi^2[1]=1.93$, $p=0.17$). Most patients from both the older and younger groups had a preference for some degree of involvement in decision making (83% and 91%, respectively); no one expressed a preference for sole decision making. Although a greater proportion of younger participants preferred an active/collaborative role than older participants, this difference was not significant ($\chi^2[1]=2.37$, $p=0.12$). These results are summarized in Table 3.

Table 3. Patient preferences for information and involvement in decision making

	Older group, n (%)	Younger group, n (%)	P-value ^a
Preference for information about illness:			0.03
As much information as possible, good and bad ^b	17 (50)	25 (76)	
Only the information needed to care for self properly	4 (12)	6 (18)	
Additional information only if it is good news	3 (9)	0 (0)	
Leave it up to the doctor	10 (29)	2 (6)	
Preference for detailed information about chemotherapy:			0.17
Would like or needs to have all detailed information ^b	21 (60)	25 (76)	
Does not want all detailed information	14 (40)	8 (24)	
Preference for treatment decision making:			0.12
Shared responsibility with doctor for decisions ^b	13 (37)	14 (42)	
Select treatment by self after seriously considering doctor's opinion ^b	5 (14)	9 (27)	
Make final selection of treatment by self ^b	0 (0)	0 (0)	
Doctor makes final decision but considers their opinion	11 (31)	7 (21)	
Leave all decisions about treatment to doctor	6 (17)	3 (9)	

^aP-values based on χ^2 tests; ^bindicates grouping for significance testing of proportions.

Associations between preferences and factors influencing decisions

Participants who preferred to have detailed information about chemotherapy rated the understanding of treatment procedures and their effects as significantly more important in their decision making than those who preferred not to have detailed information (mean [SD] = 9.1 [0.9] versus 8.2 [1.7], $p=0.04$). However, the high mean score (8.2) for those preferring not to have detailed information indicates that understanding treatment procedures and effects was still important for these participants.

Those who expressed a preference for involvement in decision making rated significantly more factors as “important” than those who preferred to leave all decisions about treatment to the doctor (mean [SD] = 17.8 [3.2] versus 14.9 [3.4], $p=0.01$). Although a significant difference, participants preferring to leave all decisions to the doctor still rated a mean 15 of 22 factors as “important” in their decision making.

5.5. Discussion

In this study, fear of dying, health status, age, QOL, and understanding treatment and its benefits and side effects were significantly more important to older patients than younger patients in deciding whether to accept chemotherapy. Reducing cancer recurrence and physician trust were highly important to both age groups, and practical barriers such as travel and cost were of low importance. Older patients preferred less information and less involvement in treatment decision making than younger patients. However, 60% of the older group still wanted detailed information about chemotherapy, and 83% wanted some degree of involvement in treatment decision making. Those preferring less information and less involvement in decision making still rated many factors as important in their decision making, including understanding treatment procedures and effects.

Much of the literature that investigates patient preferences for chemotherapy focuses on weighing survival benefit against treatment toxicity.³¹ That these preferences are difficult to predict on the basis of patient or treatment characteristics implies that other factors

may influence patients' decisions to accept treatment.¹⁶ In our study, fear of dying was significantly more important to older patients than younger patients in deciding whether to have chemotherapy. Fear has been noted in other studies as both a barrier to adjuvant chemotherapy use²⁰ and a factor involved in decision making generally.³² Although fear of death is typically reported to decrease with age,³³ the greater fear of dying from cancer for older people in this study could stem from a historical belief that no treatment will work against cancer. This is a major concern, as those with higher levels of fear are more likely to avoid cancer information³⁴ that could actually help to dispel negative expectations about chemotherapy use and cancer survival.

Attitudes toward ageing may be another cognitive/affective factor influencing treatment decisions. In our study, age was significantly more important in chemotherapy decision making for older patients than younger patients. Older physicians also appear to place greater importance on patient age than younger physicians.^{8,10} Although age alone may be an important consideration for the oldest old, even those aged 80-84 years can experience treatment-associated survival benefit,³⁵ and current evidence supports the safety of adjuvant chemotherapy in fit older patients.⁴ Attitudes toward older age and treatment may change with the ageing of the "baby boomer" generation, as this group appears to have high expectations for their health, longevity, and care.³⁶ Until such a time, ensuring that both patients and physicians are aware of current research on the effectiveness of adjuvant chemotherapy for older adults could help to reduce the impact of attitudes on treatment receipt.

Practical barriers such as cost, duration, and traveling for treatment were factors of low importance for both older and younger participants in our study. Cost and travel were also factors that least influenced chemotherapy decisions in a previous survey of older patients with colon cancer.¹⁹ However, in a self-reported practice survey, traveling a long distance for adjuvant chemotherapy was the factor that most decreased the likelihood that surgeons would refer an older patient compared with a younger patient.⁸ Physician and

patient views frequently differ in many aspects of treatment decision making.^{13,19,25} As emotional motivators appear to play a large role in patient preferences, and practical considerations such as a small one, the question then arises whether patients are best placed to make difficult treatment decisions at such a highly stressful time. On the other hand, physicians may also make decisions based on their own attitudes, under the pressure of a finite health system where the benefits to older patients are much less clearly defined. Given the expected rise in the number of cancer cases due to population ageing, these motivational and economic considerations deserve substantial attention.

Many of the other findings in this study are comparable to those of previous research in treatment decision making. Trust in the physician and physician recommendation, rated highly by the participants in our study, are often reported as important factors influencing treatment decisions.^{19,21} Reducing recurrence and increasing survival are the benefits against which risks are commonly weighed in patient preference studies, and these were factors that both age groups rated highly in our study. Function preservation and maintenance of QOL represent major goals for an increasing proportion of older patients.³⁷ In our study, QOL and health status were indeed factors that older patients considered more important in their decision making than younger patients. Comorbid health status is similarly a key consideration in the treatment decisions of physicians.⁸⁻¹⁰ Although emerging evidence suggests that adjuvant chemotherapy does not substantially alter the QOL of older patients³⁸ and can provide a significant survival benefit in some chronic conditions,³⁹ further research is needed if QOL and comorbidity are to cease being barriers to treatment.

The preferences of older patients for information and involvement in decision making may also create a barrier to adjuvant chemotherapy use. Older patients are generally reported to prefer less information than younger patients and to prefer a more passive role in treatment decision making.^{22,23} This was the case in our study, with 40% not wanting detailed information about chemotherapy and 17% wanting to leave all treatment

decisions to the doctor. However, older patients were actually significantly more likely than younger patients to report that both understanding treatment procedures and understanding treatment benefits and side effects were important factors in decision making. In addition, those participants preferring not to be involved in decision making still rated 15 of 22 factors as important considerations. Similar paradoxes have been reported elsewhere,^{24,26} and may help to explain why physicians have difficulty predicting patient preferences.²⁵ It has been suggested that patients seek to understand the rationale behind doctors' recommendations rather than to make decisions themselves.⁴⁰ Given that older patients have greater difficulty understanding and remembering the information they receive^{24,41} and may not feel comfortable asking questions of their physicians,²³ the responsibility for ensuring that all patients are adequately informed and involved likely lies with physicians. Decision aids may be useful in increasing understanding, even where patients prefer a passive role in treatment decision making.⁴²

This was a relatively small single-site study, and the results should be interpreted with caution. None of the participants in our study refused chemotherapy, and therefore insights into actual barriers for this population could not be explored. Nevertheless, the results largely match previous findings about the decision-making processes of older adults and further illuminate specific age differences in CRC patients' treatment decisions.

Conclusion

A range of factors appears to influence patients' chemotherapy decision making, including, but not limited to, survival benefits and treatment toxicity. For older patients, balancing the risks and benefits of treatment may be made more complex by the impact of emotional motivators, greater health concerns, and conflicts between their need for understanding and their preferences for information and involvement in decision making. The variability in perceived barriers to treatment and preferences for information and involvement demonstrates the need for explicit and individualized assessment of both of these areas. Without formal assessment, physicians might assume that older patients would not travel

for adjuvant chemotherapy or that they do not want information on their prognosis and treatment. Through greater understanding of perceived barriers to treatment and unique motivators for treatment choice, older patients may be better supported to make fully informed decisions about their care.

Acknowledgments

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Appendix 5.2. Inpatient version of patient survey

Patients' chemotherapy decision-making

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This survey aims to gather information about the views of patients about chemotherapy. Please attempt the questions even if you think you will not be receiving chemotherapy. The survey has 3 sections and should take about 10 minutes to complete. **Thank you for your time.**

Section 1: Information and decision-making

Which statement best reflects your attitude towards information about your illness? Please circle the corresponding number.

- 1) I want only the information needed to care for myself properly
- 2) I want additional information only if it is good news
- 3) I want as much information as possible, good and bad
- 4) I prefer to leave it up to the doctor

How much information would you want about chemotherapy? Please tick one box per row.

	I absolutely need this information	I would like to have this information	I do not want this information
Information about all the possible side effects	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Information about what the treatment will accomplish	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Information about the likelihood of cure	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Information about what the treatment will do inside my body	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Information on the day-to-day (or week-to-week) progress	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
How effective the treatment has been for other patients	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Examples of cases where the treatment has been effective	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Examples of cases where the treatment has <u>not</u> been effective	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Which statement best describes your point of view? Please circle the corresponding number.

- 1) I prefer to make the final selection about which treatment I receive
- 2) I prefer to make the final selection of my treatment after seriously considering my doctors' opinion
- 3) I prefer that my doctor and I share responsibility for deciding which treatment is best for me
- 4) I prefer that my doctor makes the final decision about which treatment will be used, but seriously considers my opinion
- 5) I prefer to leave all decisions regarding my treatment to my doctor

Section 2:

Please indicate your views by putting a cross (X) on the line.

How important would the following factors be if you were deciding whether to have chemotherapy?

	Not at all important	Very important
Avoiding side effects (e.g. nausea, hair loss)	-----	-----
Maintaining a good quality of life during treatment	-----	-----
Maintaining my independence	-----	-----
How unwell I am to start with	-----	-----
Returning to my normal quality of life after treatment	-----	-----
How old I am	-----	-----
Reducing the risk of the cancer coming back	-----	-----
Increasing my chance of living longer	-----	-----
Doing everything possible to fight the cancer	-----	-----
Fear of dying from cancer	-----	-----
Being able to look after significant others (e.g. spouse, children)	-----	-----
Having someone to look after me during treatment	-----	-----

Section 2 cont'd:

How important would the following factors be if you were deciding whether to have chemotherapy?

	Not at all important	Very important
How far I would have to travel for treatment	-----	-----
The total duration of the treatment	-----	-----
The cost of treatment	-----	-----
The opinion of my family	-----	-----
The recommendation of the doctor	-----	-----
Having a doctor who I feel comfortable asking questions	-----	-----
Having a doctor whose expertise I trust	-----	-----
Having time to decide about treatment	-----	-----
Understanding what is going to happen during treatment	-----	-----
Understanding the benefits and side effects	-----	-----
Other (please specify below)	-----	-----

Any comments:

6

A risk model

In Chapter 3, continuing age differences in the receipt of guideline-recommended adjuvant therapy in NSW were identified. The results of Chapter 4 indicate that surgeon knowledge and views are a contributing factor to these differences. The variability in older patients' perceived barriers to treatment in Chapter 5 and their preferences for less information and decision-making involvement may also impact treatment receipt. Together, these findings suggest that more evidence-based tools should be developed to guide adjuvant therapy decisions and facilitate discussion of patient preferences and treatment benefits and risks.

This chapter presents a mortality risk prediction model that could be used by clinicians to assist the treatment decision-making process. The model identifies older lymph node-positive colon cancer patients who are unlikely to survive the first year after surgery and so would not benefit from adjuvant chemotherapy. The emphasis on a range of factors that predict mortality may help to reduce variation in guideline-recommended treatment that occurs on the basis of patient age alone.

This chapter is presented as the following paper:

Jorgensen ML, Young JM, Dobbins TA, Solomon MJ. A mortality risk prediction model for older adults with lymph node-positive colon cancer. [Submitted]

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Author contributions

Jorgensen ML conceived and designed the study, analysed and interpreted the data, drafted the manuscript. **Young JM** designed the study, data acquisition, interpreted the data, critically revised the paper. **Dobbins TA** designed the study, data cleaning and linkage, interpreted the data, critically revised the paper. **Solomon MJ** interpreted the data, critically revised the paper. All authors read and approved the final draft of the manuscript.

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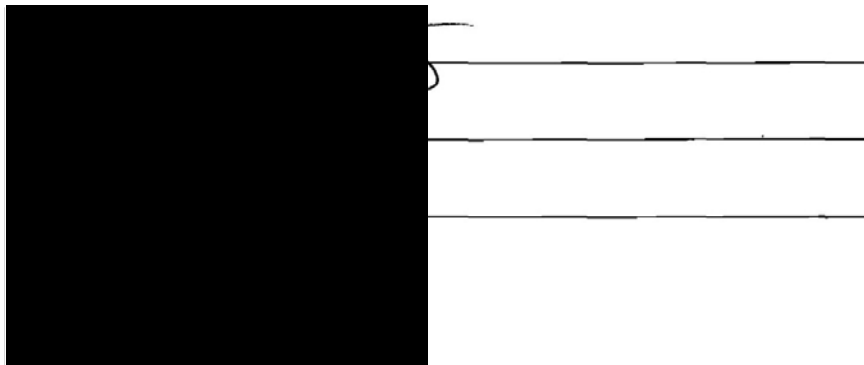
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6.1. Abstract

BACKGROUND: Surgeons and oncologists are less likely to recommend adjuvant chemotherapy for older adults based on their age alone. Physicians may rely on chronological age as a proxy for other age-related factors when making treatment recommendations. The aim of the study was to develop a mortality risk model to assist treatment decision making by identifying patients who are unlikely to survive the first year after surgery and thus will not benefit from adjuvant chemotherapy.

PATIENTS AND METHODS: All lymph node-positive patients aged ≥ 65 years receiving surgery for colon cancer in New South Wales, Australia in 2007/2008 were identified using a linked routinely collected population-based dataset ($n=1,550$). Multilevel logistic regression was used to build a model for predicting the risk of one-year all-cause mortality. Scores derived from each factor in the model were summed for each patient.

RESULTS: One-year mortality was 11.5% after excluding those who died within 30 days of surgery ($n=67$). The risk model consisted of fourteen factors, including patient comorbidities, hospital admission factors, and other markers of frailty or health status. Age was not an independent predictor of mortality in the adjusted model. People with a total risk score of 0, 1 or 2 were considered at low risk (predicted one-year mortality of 3.0%), those scoring 3 to 6 at medium risk (7.5% mortality), and those with a score of 7 or above were considered at high risk of mortality (25.8% mortality). The model had good discrimination (AUC=0.791, 95% CI: 0.754-0.828) and calibration ($p=0.46$).

CONCLUSION: The risk model developed in this study accurately predicts one-year mortality in older lymph node-positive cancer patients. The model may be useful in shifting the emphasis in treatment decision making from chronological age to the identification of those of any age who will live to benefit from these resources.

6.2. Introduction

The majority of colorectal cancer cases occur in those aged over 65 years.¹ For lymph node-positive colon cancer, surgical resection followed by adjuvant chemotherapy is the widely recommended standard of care.² Clinical practice guidelines explicitly state that age alone should not be used to exclude patients from being offered chemotherapy, as even those over 80 years can derive survival benefits.³ However, both surgeons and oncologists are less likely to recommend adjuvant chemotherapy for older adults on the basis of their age alone.^{4,5} Physicians may be relying on chronological age as a proxy for other age-related factors when making treatment recommendations.⁶

The heterogeneity of the ageing process means that chronological age is not a reliable way to estimate life expectancy or the risk of treatment complications. Better predictors of patient outcomes include comorbidity, functional status, and other specific markers of frailty.^{7,8} Determining how these factors contribute to mortality risk for this subset of node-positive patients is important, as survival is the primary benefit against which the risks of treatment are balanced. Results of randomised trials suggest that survival benefits from chemotherapy begin to emerge between one to two years after surgery.^{9,10} For those who are not likely to survive the first year, the potential impact of treatment on quality of life would make adjuvant chemotherapy untenable. Older patients who do survive this period may be as likely to benefit from treatment as younger patients, since mortality in the first postoperative year accounts for much of the age differences in survival following colorectal cancer surgery.¹¹

Prognostic indices appear to be a useful way to help move clinical decision making beyond arbitrary age cut-offs.¹² A number of models and tools exist for determining mortality risk in older cancer patients, but these tend to focus on postoperative mortality for surgical decision making¹³⁻¹⁵ or are developed on single area samples.¹⁶ Risk tools for chemotherapy are generally developed to predict treatment toxicity^{17,18} or only involve a limited evaluation of health status as they are not specifically designed for older patients.¹⁹

Thus, the aim of the current study was to use population-based data to develop a mortality risk model for older node-positive colon cancer patients, which could be used in treatment decision making to clarify which patients would not benefit from adjuvant chemotherapy.

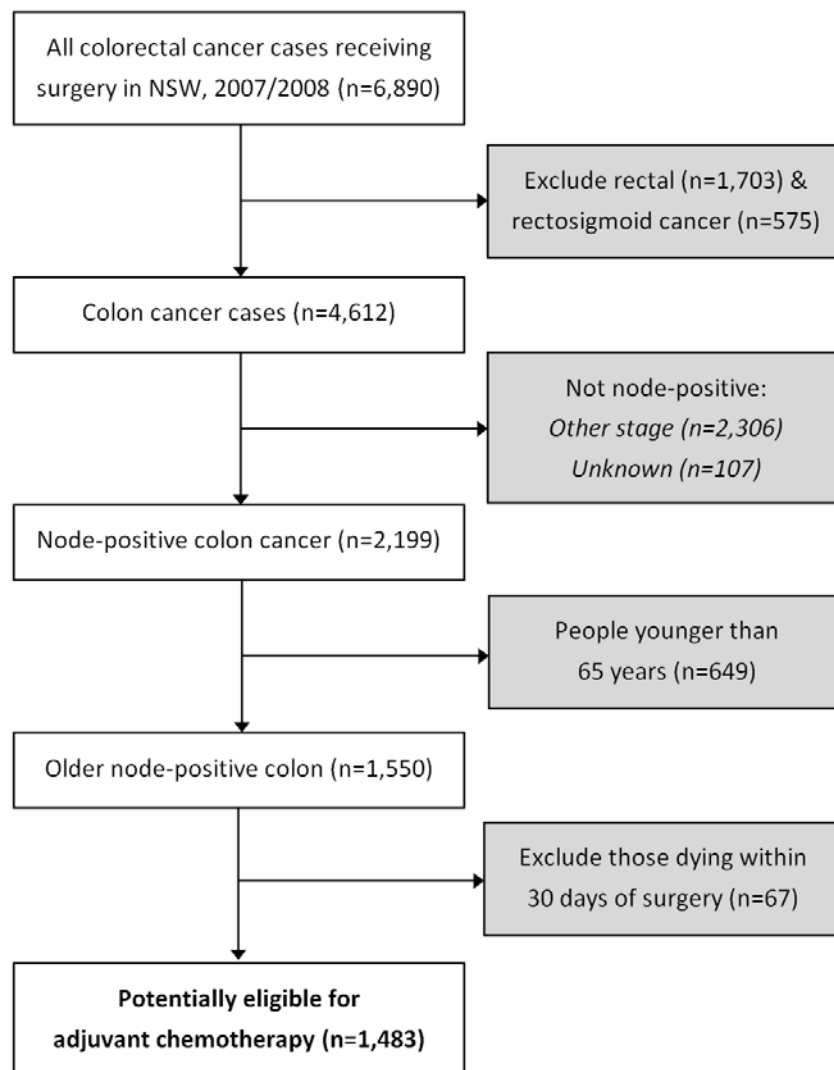
6.3. Methods

Data source

A linked dataset was used that consisted of the records of all people with a first unique cancer of the colon, rectosigmoid junction or rectum registered in 2007 or 2008 by the population-based NSW Central Cancer Registry (CCR). Data on all public and private hospital separations from the NSW Admitted Patients Data Collection (APDC) and death data from the NSW Registry of Births, Deaths and Marriages were linked to the CCR data by the Centre for Health Record Linkage (CHeReL). Ethics approval was provided by the NSW Population & Health Services Research Ethics Committee.

All people aged 65 years and over with lymph node-positive colon cancer that had an admission to a hospital for a surgical resection were identified from the dataset (see Figure 1). Those who died within 30 days of surgery were subsequently excluded, as initiation of adjuvant chemotherapy does not generally occur before this time.²⁰

Figure 1. Flowchart defining the denominator for the mortality risk model



Developing the risk model

Multilevel logistic regression was used to build a model for predicting the risk of one-year all-cause mortality. Multilevel models take into account the clustering of patients within hospitals (n=90 in the current study). Candidate predictors for the risk model were based on previously established prognostic risk factors for older cancer patients. These were patient age,^{7,13,21,22} marital status,^{22,23} emergency resection,^{13,21,24} long length of stay,^{16,24} comorbidities as outlined in the revised Charlson comorbidity index,²⁵ as well as depression, malnutrition, and falls risk, which are commonly assessed domains in geriatric

oncology.⁷ All of the candidate predictors were included in the final risk model. A full model approach using a small number of pre-established candidate variables attempts to avoid overfitting and selection bias that is known to occur when variables are included in a risk model based on significance testing in univariate analysis.²⁶ Age was categorised into five-year age intervals for ease of interpretation and usability of the risk model. Interactions between age group and all of the other variables in the final model were tested to determine whether there were any multiplicative effects of increasing age and other factors on mortality.

Comorbidities were identified from the APDC hospital separations data using ICD-10-AM diagnosis codes.²⁵ Malnutrition was similarly identified using diagnosis codes for mild, moderate or severe protein-energy malnutrition (E40-E46). Reduced mobility was defined from the codes for immobility (R26.3), other reduced or poor mobility (R26.8), difficulty in walking (R26.2), need for assistance due to reduced mobility (Z74.0), or presence of pressure ulcer (L89). The codes for falls (R29.81) and tendency to fall (R29.6) were used to identify those at high risk of falls. The accuracy of recording of comorbidities has been previously validated in NSW administrative data collections.²⁷ While a number of the other health markers have been used in previous Australian research,^{28,29} their validity has not been assessed.

The American Society of Anesthesiologists (ASA) physical health status score was available for 79.0% of the cohort. However, this variable couldn't be used in the main model as the characteristics of those with missing ASA score differed from the rest of the cohort, indicating potential systematic bias in its recording. Those with missing ASA score were more likely to be treated in a private hospital ($\chi^2[1]=54.4$, $p<0.001$), have no comorbidities ($\chi^2[1]=9.0$, $p=0.003$), and have low socioeconomic disadvantage ($\chi^2[4]=51.4$, $p<0.001$) than those with ASA recorded. Two separate sensitivity models were run using the subset with ASA recorded to determine whether the inclusion of this variable improved the accuracy of the risk model.

Determining model accuracy and validity

Model discrimination, or how well the model distinguishes between those who do and do not have the outcome, was assessed by calculating the area under the receiver operating characteristic curve (AUC or C-statistic). Model calibration, or how well the predicted outcome rates match the observed rates, was measured using the Hosmer-Lemeshow goodness-of-fit chi-square test. The internal validity of the risk model was assessed using bootstrap resampling.³⁰ This technique simulates the process of sample generation from an underlying population by taking a large number of random samples of the same size as the original dataset, with replacement. *With replacement* means that an observation can be included repeatedly within a bootstrap sample while others may not be included at all. An optimism-corrected AUC was obtained by fitting the model to the bootstrap samples (n=500) and subtracting the average difference between the AUC in the samples and the original prediction model from the AUC in the original model.³⁰ Because all data are used for model development, bootstrapping provides a more efficient and accurate estimation of internal validity than other techniques such as split-sample validation.³⁰

Developing risk scores

A score for each factor in the risk model was calculated by dividing the beta coefficient of each variable by the lowest beta coefficient in the model, and rounding to the nearest whole number.³¹ A total risk score was assigned to each person by summing the scores for each present risk factor e.g. a person with pulmonary disease (5 points) who was 70 years old (1 point) but who did not have long length of stay (0 points) would have a total of 6 points. Predicted outcome rates were calculated for each total score level using the model regression formula.

Categories of low, medium, and high risk were created by dividing the cohort into three equal sized groups, ordered by total risk score. This is the preferred method in the absence of an a priori clinical consensus on grouping cut-points.³² Rates of one-year mortality for each risk category were based on the predicted model estimates from the risk model.

6.4. Results

1,483 people aged ≥ 65 years were diagnosed with lymph node-positive colon cancer in 2007/2008 and survived longer than 30 days after surgery. Of these people, 170 (11.5%) had died within one year. Patient characteristics are presented in Table 1. Notably, 42.6% of the one-year mortality occurred within the first 30 days for those over 85 years, compared to 24.0% for the rest of the cohort.

Risk model predictors

Table 2 presents the adjusted odds ratios for the 14 factors included in the risk model. While increasing patient age was a significant predictor of one-year mortality in univariate regression ($\chi^2[5]=15.8$, $p=0.008$), this association was no longer evident after adjusting for other risk factors ($p=0.79$). Most of the other factors in the risk model were significant independent predictors of mortality, including hospital admission factors (emergency admission, long length of stay), comorbidities (dementia, pulmonary disease, kidney or liver disease, other cancer), and other markers of frailty or health status (previous emergency admissions, malnutrition, reduced mobility or falls risk). There were no significant interactions between age group and any other factor in the risk model.

One-year mortality following surgery varied between hospitals. Approximately 2.5% of the total variability in one-year mortality was attributable to hospitals in the risk model (hospital variance [SE] = 0.08 [0.10], intraclass correlation coefficient = 0.025). Adding hospital type and location to the patient characteristics in the model did not help to explain this variation (intraclass correlation coefficient = 0.023).

Table 1. Characteristics of older patients receiving surgery for node-positive colon cancer

	n (%)
Age at diagnosis (65-69)	319 (21.5)
70-74	344 (23.2)
75-79	338 (22.8)
80-84	293 (19.8)
85-89	157 (10.6)
90-95 (max)	32 (2.2)
Male	728 (49.1)
No current partner (single/divorced/widowed)	562 (38.4)
Socioeconomic status (SEIFA)	
1 Least disadvantaged	334 (22.5)
2	260 (17.5)
3	304 (20.5)
4	291 (19.6)
5 Most disadvantaged	293 (19.8)
ASA physical health status*	
1 Healthy	62 (4.2)
2 Mild systemic disease	523 (35.3)
3 Severe systemic disease	504 (34.0)
4 Severe systemic disease, constant threat to life	82 (5.5)
Hospital type – public (vs private)	924 (62.3)
Hospital location – metropolitan (vs rural/regional)	1,023 (69.0)
Emergency admission for resection	252 (17.0)
Length of stay > 21 days	247 (16.7)
<i>Comorbidities</i>	
Congestive heart failure	48 (3.2)
Dementia	15 (1.0)
Chronic pulmonary disease	50 (3.4)
Kidney or liver disease	66 (4.5)
Diabetes with chronic complications	38 (2.5)
Other malignancy (non-colorectal)	43 (2.9)
Depression	22 (1.5)
<i>Markers of frailty or health status</i>	
Previous emergency admissions (1 or more)	688 (46.4)
Malnutrition	21 (1.4)
Reduced mobility or high falls risk	56 (3.8)

*Some data missing; SEIFA = Socio-economic indexes for areas⁴³

Table 2. Risk factors for one-year mortality in multilevel logistic regression model

	Adjusted OR (95% CI)	P value
Age group (ref= 65-69)		0.79
70-74	1.3 (0.7-2.3)	
75-79	1.2 (0.7-2.2)	
80-84	1.5 (0.8-2.7)	
85-89	1.0 (0.5-2.1)	
90+	1.2 (0.4-3.7)	
No current partner	1.2 (0.8-1.8)	0.29
<i>Hospital admission factors</i>		
Emergency admission for resection	1.6 (1.1-2.5)	0.02
Length of stay > 21 days	2.1 (1.4-3.3)	<0.001
<i>Comorbidities</i>		
Congestive heart failure	1.5 (0.7-3.3)	0.27
Dementia	4.4 (1.4-14.0)	0.01
Chronic pulmonary disease	2.3 (1.1-4.8)	0.02
Kidney or liver disease	2.5 (1.3-4.7)	0.007
Diabetes with chronic complications	1.2 (0.6-2.4)	0.53
Other malignancy (non-colorectal)	2.8 (1.8-4.5)	<0.001
<i>Markers of frailty or health status</i>		
Depression	1.2 (0.3-5.6)	0.83
Previous emergency admissions	1.6 (1.1-2.4)	0.01
Malnutrition	4.1 (1.5-11.3)	0.007
Reduced mobility or high falls risk	2.7 (1.3-5.3)	0.006

Model accuracy and validity

The AUC for the risk model was 0.791 (95% CI: 0.754-0.828), indicating good to very good discrimination.¹² There was evidence that this model had considerably better discrimination than a model with age as the sole predictor of mortality (AUC=0.634, 95% CI: 0.589-0.678; p<0.001). The Hosmer-Lemeshow test for the risk model indicated no significant lack of fit ($\chi^2[10]=9.74$, p=0.46). No multicollinearity was apparent in the model, with all variance inflation factors less than 2.

The optimism-corrected AUC based on the bootstrap resampling was 0.736 (95% CI: 0.645-0.828). This measure of interval validity indicates that the model would still have good discriminatory power when applied to new patients with similar characteristics.

ASA health status was significantly associated with one-year mortality in univariate analysis ($\chi^2[3]=55.6$, $p<0.001$). However, the discriminatory ability of the risk model was not substantially increased by the inclusion of this variable in a subset sensitivity analysis for those with ASA recorded. Without ASA score in the model, the AUC for the risk model in this subset population was 0.805 (95% CI: 0.765-0.845). Adding ASA score to the model, the AUC was 0.811 (95% CI: 0.773-0.849). There was some evidence of multicollinearity between ASA score and the variable “previous emergency admission”. These factors were independent predictors of mortality when entered into the model separately, but when both factors were in the model neither was significant and their variation inflation factors were between 4 and 7. Indeed, ASA status was significantly associated with previous emergency admission in univariate regression ($\chi^2[3]=52.4$, $p<0.001$). Previous emergency admission may therefore be a useful proxy variable for ASA status.

Risk scores

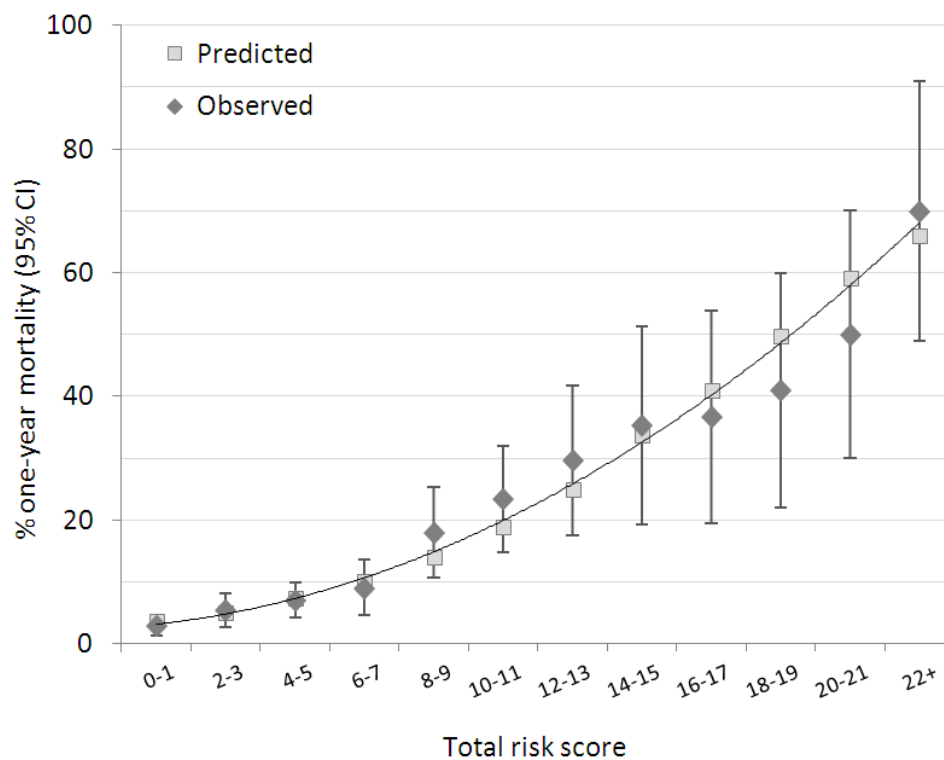
Scores for each factor in the risk model are presented in Table 3. A person with all of these risk factors (excluding age) would receive a total risk score of 54. In our cohort, total scores ranged from 0 to 31 (mean [SD] = 5.4 [5.1], median = 4.0). Figure 2 displays the observed and predicted rates of one-year mortality by total risk score. For this figure, the 14 people scoring over 22 (0.9% of the cohort) were grouped with those scoring 22 to create a more reliable point estimate.

Table 3. Scores for each factor in mortality risk model

	β coefficient (SE)	Score
Age group		
70-74	0.24 (0.30)	1
75-79	0.20 (0.30)	1
80-84	0.40 (0.30)	2
85-89	0.02 (0.36)	0
90+	0.18 (0.58)	1
Depression	0.17 (0.79)	1
No current partner	0.20 (0.19)	1
Diabetes with chronic complications	0.21 (0.34)	1
Congestive heart failure	0.43 (0.39)	2
Previous emergency admissions	0.48 (0.19)	3
Emergency admission for resection	0.50 (0.21)	3
Length of stay > 21 days	0.76 (0.22)	4
Chronic pulmonary disease	0.85 (0.36)	5
Kidney or liver disease	0.90 (0.33)	5
Reduced mobility or falls risk	0.98 (0.36)	6
Other malignancy	1.05 (0.23)	6
Malnutrition	1.40 (0.52)	8
Dementia	1.49 (0.59)	9

Predicted rates of one-year mortality for each risk category were calculated from the model estimates. Those with a total score of 0, 1 or 2 were considered at low risk (predicted one-year mortality of 3.0%), those scoring 3 to 6 at medium risk (7.5% mortality), and those with a score of 7 or above were considered at high risk of mortality (25.8% mortality). The proportion of people at high risk of one-year mortality increased with age ($\chi^2[5]=100.6$, $p<0.001$), from 15.0% of those aged 60-64 years to 46.9% of those aged ≥ 90 .

Figure 2. One-year mortality by total risk score



6.5. Discussion

This study used population-based data to develop a risk model that predicts one-year mortality in older node-positive colon cancer patients with considerably greater accuracy than a model based on patient age alone. While age was associated with mortality in univariate regression, it was not an independent predictor in the risk model after accounting for other factors such as comorbidities, hospital admission factors, and markers of frailty or health status. The model could be useful in clarifying which patients would not benefit from adjuvant chemotherapy.

There is evidence that older colon cancer patients experience similar survival benefits from adjuvant chemotherapy as younger patients, without substantial increases in toxicity.³ However, the diminishing returns of any curative treatment with increasing age may cause clinicians to apply an arbitrary age cut-off, if it is not clear which older patients will live to benefit from treatment. In our study, age was not associated with one-year mortality after

adjusting for comorbidities and other health-related factors. Similar findings have been reported in a number of studies of mortality in cancer patients.^{33,34} Patel and colleagues (2013) suggest that higher rates of 30-day mortality in older patients account for much of the overall age differences in survival.³⁵ This was also a likely contributing factor to our finding for age, as the large proportion of people over 85 who died within 30 days were necessarily excluded. Those elders who survive this period and do not have significant health problems may therefore represent a group who could benefit from adjuvant chemotherapy well into their 80s and beyond. While older age was not an independent risk factor in our study, a greater proportion of the older groups were deemed at high risk of one-year mortality due to increasing prevalence of health conditions, and these people clearly have less to benefit from chemotherapy. Nonetheless, the risk model may be useful in helping to shift the emphasis in treatment decision making from chronological age alone to the identification of those of any age who will live to benefit from these resources.

Our risk model may also be useful for identifying older adults who require more comprehensive assessment and ongoing management to better cope with treatment. While routine screening to identify vulnerable and frail elderly is widely recommended,³⁶ there is no consensus on the definition of frailty,³⁷ and current screening tools have insufficient discriminative power to select cancer patients for further evaluation.³⁸ However, consistent predictors of risk across the literature imply that programs known to improve outcomes should be more regularly employed. Targeting malnutrition and physical mobility or function in cancer prehabilitation can decrease treatment-related morbidity and improve health outcomes.³⁹ Length of stay can be reduced through the incorporation of Enhanced Recovery After Surgery (ERAS) protocols to ease surgical stress and minimise complications,⁴⁰ and improved screening of older people can help to lessen the risks associated with emergency resection.⁴¹ Poorer survival for those without a current partner suggests that social support remains a key target area. In addition, the variability in mortality that was attributable to the hospital where surgery was performed indicates the need to further explore and address potential differences in the provision of care.

Markers of patient frailty or health status are frequently unavailable in routinely collected administrative datasets and are not often incorporated in prognostic models, though they can add important information about mortality risk⁸ and would readily form part of clinician judgement in practice. In the current study, ASA physical status could not be used as the characteristics of those with missing ASA score differed from the rest of the cohort. The variable 'previous emergency admissions' could be a potential substitute for ASA status in research or peer comparisons that rely on administrative data, as there was a strong association between these variables, and model performance was similar whether one or other of these variables was used. The discrimination and calibration results for our risk model were also as good or better than many other mortality models.¹² Nonetheless, more complete data for ASA status or the incorporation of other health measures such as ECOG performance status or activities of daily living could further increase the accuracy of the risk model and therefore its usefulness.

Although routinely collected population data can lack breadth, one advantage that it has over other methods of data collection is a reduction in the potential for sampling bias. The risk model developed in this study may be more clinically acceptable than similar models in that it uses population-based data as well as incorporates markers of frailty and health status. The optimism-corrected AUC also indicated that the model should perform well when applied to other patients that are similar to the development sample. However, external validation is required if the risk model is to be used outside of NSW, particularly as colorectal cancer mortality in this state is relatively low compared to many other areas.⁴² Another limitation of this study is the high likelihood of underascertainment of comorbidities and other health status markers through the use of hospital separations data.²⁷ While many of these factors have been reported to have high specificity,²⁷ some comorbidities may not have been recorded where they were not perceived to directly impact on the patient's cancer or treatment. Finally, any prognostic model will ultimately only be useful if there is evidence of its clinical effectiveness. The proposed risk model is currently being developed into an online tool where its ability to impact treatment decision making and improve patient assessment and management will be evaluated.

For older cancer patients, treatment decisions involve careful consideration of the potential risks and benefits of treatment. Major gaps in evidence from clinical trials about the optimal treatment of older patients,³ and the significant financial costs associated with chemotherapy within a finite health system, make these decisions all the more difficult. Despite limitations of the data, the current study creates a greater understanding of how pre-existing patient factors influence outcomes for a specific population who are potentially at risk of suboptimal care. A tool developed from the risk model may be useful in helping to supplement clinicians' judgements about prognosis and the utility of adjuvant chemotherapy, and could be incorporated into shared decision-making discussions alongside quality of life considerations, patient preferences, and the potential for treatment toxicity. By shifting the emphasis from chronological age to better predictors of survival, the variation that occurs on the basis of age alone may be reduced and the care and outcomes of older cancer patients may improve.

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7

Conclusions

This thesis has presented a series of studies exploring the barriers to evidence-based care for older people with colorectal cancer, with a focus on the receipt of guideline-recommended adjuvant chemotherapy and radiotherapy. While differences in the treatment of older patients continue to exist in NSW (Chapter 3), decision making for this population is inherently complex. Issues in the measurement of outcomes (Chapter 2), surgeon knowledge and views (Chapter 4), and patient preferences (Chapter 5) appear to contribute to age differences in treatment. A risk model that could be used by clinicians to assist treatment decision making was developed (Chapter 6). This final chapter outlines the unique contributions of this thesis to the literature, addresses limitations, and discusses implications for clinical practice and future research that will be needed to ensure greater understanding and improved outcomes for this growing and potentially vulnerable group.

7.1. Summary of unique research findings

7.1.1. Measurement

Chapter 2 examined potential issues in the measurement of patient-reported outcomes (PROs) that may affect the treatment and care that older patients receive. In Study 1, the supportive care needs of older and younger patients were compared at one month and three months after hospital discharge for colorectal cancer surgery. As in prior research,

younger age was an independent predictor of unmet need for nearly all domains at both time points. However, this study was unique in exploring whether this counterintuitive finding resulted from older patients being more likely to have their needs met ('satisfied'). In this study, older patients were actually *less* likely than younger patients to report 'satisfied' needs, instead being more likely to report that they had 'no need' ('not applicable'). These results may indicate that older patients are less likely to express their needs for help, or that their needs are not being adequately captured.

The study also adds to the literature by clarifying the absolute prevalence of unmet needs for older patients across the cancer trajectory. More than half of all older patients had unmet needs at one month (56%), and this figure had increased to 65% by three months. While expressing relatively fewer unmet needs than their younger counterparts, older patients may have less capacity to cope with *any* level of unmet need due to poorer health and less social support.

In Study 2, age differences in item non-response were explored in quality of life (QOL) assessments that had been completed at baseline, one month and three months after hospital discharge. As in previous research for other patient groups, older age was associated with non-response to a number of 'sensitive' questionnaire items (e.g. sex life, diarrhoea), as well as greater levels of missing data overall. This study was unique in further examining the effects of this missing data on QOL estimates. QOL in one domain was significantly overestimated when the suggested 'simple mean imputation' method was used to manage missing data, and item non-response was associated with poorer QOL overall. Where studies exclude patients with missing data, the QOL of older cancer patients may be inadequately or inaccurately represented.

7.1.2. Local context

In Chapter 3, linked population-based administrative and clinical data was used to determine whether patient age alone remains a predictor of adjuvant therapy receipt for colorectal cancer in NSW. Other local factors that may hinder or facilitate adjuvant therapy

use were also identified. While previous state-based estimates of adjuvant treatment receipt have relied on resource-intensive clinician surveys, routinely collected clinical registry data was used for the first time in this study to monitor patterns of care.

The analysis revealed that increasing age remains an independent predictor of non-receipt of chemotherapy for lymph node-positive colon cancer and radiotherapy for high-risk rectal cancer. However, the overall levels of chemotherapy and radiotherapy use represent a considerable increase on treatment rates from a previous NSW study conducted in 2000, consistent with international trends. The current study accounted for both comorbidities and physical status (ASA score), which is rare in population-based health inequality studies. Determining the sources of variation in treatment through the use of three-level data modelling to account for the clustering of patients by surgeon and the clustering of surgeons within hospitals was another unique contribution of the study. Though much of the variation in adjuvant therapy receipt was found to be due to patient characteristics, the hospital where surgery was performed accounted for a considerable proportion of treatment variation. Other predictors of treatment receipt in this study, such as discussion of the case at a multidisciplinary meeting, indicate further opportunities to improve care.

7.1.3. The surgeon

Surgeons act as important gatekeepers to the care of patients after their cancer surgery. Chapter 4 outlined the findings of a self-administered survey of Australian and New Zealand colorectal surgeons. The study aimed to identify factors affecting surgeons' decisions to refer older patients with colorectal cancer for adjuvant therapy by investigating surgeon knowledge, opinions, and self-reported practice across a range of scenarios.

Colorectal surgeons were significantly less likely to refer older patients with node-positive colon cancer for adjuvant chemotherapy than younger patients, based on chronological age alone. While previous physician surveys have tended to focus on patient age and comorbidity, this study found that other factors such as distance to treatment and social

support had considerable effects on surgeons' recommendations for referral of older patients. Lack of consensus among surgeons about the treatment of older patients was another major feature of the survey. Both knowledge and opinions about current research evidence and adjuvant therapy receipt were strongly associated with referral recommendations. In particular, older surgeons were less likely to report views that were consistent with national guidelines and less likely to hold similar opinions toward older and younger patients. Overall, 39% of colorectal surgeons indicated that there is an upper age limit after which chemotherapy is no longer worthwhile. These findings indicate that variation in surgeon opinions and practices may contribute to differences in the treatment of older patients.

7.1.4. The patient

It has been reported that older cancer patients are more likely to refuse recommended adjuvant therapy than younger patients. In Chapter 5, patient-based barriers to adjuvant chemotherapy use were investigated through a self-administered survey of patients who had undergone colorectal cancer surgery within the previous 24 months. The survey aimed to identify factors that distinguish the decision-making processes of older patients from younger patients, including preferences for information and involvement in treatment decisions.

Previous research in this area has tended to focus on the balance of toxicity and survival benefits, or the strength of preferences for adjuvant therapy, or has not specifically investigated age differences in barriers. This survey found that a range of factors were uniquely important to older patients' treatment decision making. Fear of dying, health status, age, quality of life, and understanding treatment procedures and effects were more important to older patients than younger patients in deciding whether to accept chemotherapy. While older patients preferred less information and less involvement in treatment decisions, the majority of the older group did want detailed information about chemotherapy and some level of involvement in decision making. A novel finding of this

study was that patients who preferred less information and involvement still rated many factors as important in their decision making, including understanding treatment procedures and their effects. The results imply that treatment decisions for older patients may be more complex because of the impact of emotional motivators such as fear and perceptions about ageing, their greater health concerns, and conflicts between their need for understanding and their preferences for information.

This study also revealed that surgeons' and patients' perceived barriers to adjuvant chemotherapy use may differ. Practical barriers such as distance to treatment were important to the colorectal surgeons surveyed in Chapter 4, but were not important to the older patients in this study.

7.1.5. A risk model

A mortality risk prediction model was presented in Chapter 6 that could be used to identify older patients who will not benefit from adjuvant chemotherapy. Physicians may use chronological age as a proxy for survival, though this is not a reliable way to estimate an individual patient's prognosis. Previous risk models for chemotherapy in older patients have been developed to predict treatment toxicity only. Where risk models have focused on survival, they are not specifically designed for older patients, or are only based on small single-centre samples.

Age was not a significant predictor of one-year mortality after excluding those who died within 30 days and accounting for other age-related factors. Instead, a range of factors including patient comorbidities, hospital admission factors, and other markers of health or frailty were used to build a model that predicted mortality risk with greater discrimination than age alone. This model was unique in being developed on a large population-based dataset, while also incorporating markers important to the assessment of older patients such as reduced mobility and malnutrition. The model may be useful in shifting the emphasis in chemotherapy decision making from chronological age alone to the identification of those of any age who may live to benefit from these resources.

7.2. Practical implications of findings

7.2.1. For future research

PROs such as quality of life and supportive care needs are increasingly being seen as central to cancer treatment decision making.¹ In Chapter 5, older patients rated QOL as more important to their decision making than younger patients, consistent with previous literature.² However, recent research suggests that many oncologists do not feel comfortable using PRO data to inform clinical practice and their discussions with patients.³ One cause may be a lack of methodological rigour in analysis and reporting.⁴ Findings from Chapter 2 highlight the need for transparency of reporting of PROs for older patients particularly. Without noting the reasons why older patients are less likely to report unmet needs, clinicians may assume that older patients are simply more likely to have their needs 'met'. Where missing data or methods for handling missing data are not reported in QOL studies,⁵ clinicians cannot determine whether accurate conclusions have been drawn about the QOL of those at greater risk of non-response.

A focus on relative age differences in many studies may also affect perceptions of older patients' needs, well-being, and treatment preferences. While older patients expressed relatively fewer unmet needs than younger patients in Chapter 2, over half reported unmet needs at both one and three months after surgery. Reporting solely that older patients have fewer unmet needs or better QOL may create the impression that their needs and well-being are being adequately addressed. Similarly, studies that report older patients prefer less treatment information and involvement in decision making should also document whether, as in Chapter 5, the majority of older patients actually would prefer to be involved and fully informed.

Much of the literature approaches issues in cancer and ageing from a disease-based perspective, with a particular emphasis on comorbidity. Consideration of comorbidity is certainly essential, in that chronic conditions can increase the risks of treatment and

decrease the potential for benefit.⁶ However, greater understanding of the reasons for age differences in adjuvant therapy receipt likely requires a more 'holistic' approach, including consideration of psychological, social ageing, and lifespan aspects. In Chapters 4 and 5, the multifactorial nature of physicians' and patients' decision making was highlighted. Perceptions about the importance of social support, QOL, logistical barriers, and cognitive or affective factors appear to inform how both patients and physicians balance the potential risks and benefits of treatment. An individual's personal experiences and their own age will influence their views about ageing and disease, as well their beliefs about whether and for whom treatment is worthwhile. A number of surgeons specifically commented that all patients should be equally considered for treatment. However, 20% of surgeons reported that younger patients should have preference over older patients given the limited resources of the Australian health system. The rationality of patients' decision making at such a highly stressful time has also been questioned.⁷ Older patients may be more vulnerable to forgoing worthwhile treatment because of a fear that cancer is a death sentence, or differences in their preferences for risk taking and certainty.⁸ More research is therefore required to understand how these psychosocial factors underlie decision-making processes and preferences for both physicians and patients.

A 'holistic' approach also appears to be important in examining how variation in practice occurs within the health care system. Variation was a hallmark of surgeon opinions and practice recommendations for older patients in Chapter 4. However, a multilevel modelling approach using a population-based dataset in Chapter 3 indicated that the hospital of surgery was a far greater source of variation in treatment receipt than the surgeon, suggesting that these clinicians may actually hold similar preferences against the referral of older patients. The effects of the hospital and clinician are generally neither entirely independent nor synonymous.⁹ Highly-trained clinicians may be attracted to hospitals where there is greater access to a range of specialist colleagues, a factor that is associated with adjuvant treatment receipt.¹⁰ Further exploration of these complex interactions and patient care pathways is needed, and are important considerations for future research that aims to determine sources of treatment variation.

Understanding the reasons for differential treatment of older patients requires good quality data. Chapter 3 demonstrated that linkage of existing health datasets is a promising way to monitor at-risk patient groups in NSW. With greater coverage and access to data collected in the private sector, these resources could provide a timelier and more cost-effective way of conducting patterns of care studies in NSW. Routine recording of factors such as patient refusal of treatment, or greater completeness of important health measures such as performance status or ASA physical status, would allow greater insight into the causes and magnitude of health inequalities. However, increasing the use of existing data in research is also feasible. In Chapter 6, a number of health measures were able to be extracted from hospital data and used to build a risk model that accurately predicts mortality for older colon cancer patients. While further validation of these variables and greater collection of physical performance measures is required, the results also indicated that potential proxy health measures, such as previous emergency admissions, could be useful in the interim.

7.2.2. For clinical practice

The concept of unmet needs appears to have originated in the gerontology literature.¹¹ It has evolved from an objective assessment of existing support for any functional deficits to increasingly focus on patient-perceived needs.¹¹ However, relying on patient-reported assessments may actually be detrimental to the outcomes of older patients. The results of Chapter 2 support previous findings that older patients are less likely to report their health needs. This could result from a number of factors including stoic attitudes towards coping,¹² lower expectations of care,¹³ or being less willing to disclose 'sensitive' health issues, as in Chapter 2. When coupled with a tendency for physicians to be less communicative with older patients and to underestimate their needs,^{14,15} older adults may be less likely to receive the care that would enable them to better cope with their cancer and cancer treatment, including adjuvant therapy. Increasing physicians' awareness of their communication behaviours and their use of specific communication techniques could

facilitate older patients to express their concerns.¹⁶ Involving family or caregivers can also provide critical information, though the patient should always have the final word.¹⁷

More explicit and individualised assessment of patient preferences may also be necessary to ensure older patients are fully informed and supported throughout the decision-making process. In Chapter 5, a range of factors were important to older patients' treatment decisions, and there was considerable variability in patient preferences for information and involvement in decision making. Without formal assessment, physicians might assume that travelling for treatment is an important factor for older patients (as in Chapter 4), where patients themselves may not actually perceive this as a barrier to adjuvant therapy use (as in Chapter 5). An additional consideration is the apparent clash between older patients wanting less information and involvement in treatment decisions than younger patients, but being more likely to rate understanding of treatment as an important factor. Decision aids can be useful for all patients, including those who seek to understand the reasoning behind doctor's recommendations without wanting to make treatment decisions themselves.¹⁸ Nonetheless, the majority of older patients in Chapter 5 did want to be fully informed and involved in their treatment decisions. Greater tailoring of information and awareness of the factors that individual patients perceive as important may help to improve patient satisfaction with decision making and ultimately patient outcomes.

The weight of the evidence suggests that non-receipt of adjuvant therapy rests predominantly in the hands of physicians. Physician recommendation and trust in the physician were rated highly by patients in Chapter 5, as in previous research.¹⁹ The vast majority of older patients are willing to accept chemotherapy if it is offered.^{20,21} In a patterns of care study conducted in NSW in 2000, the proportion of patients with node-positive colon cancer refusing referral for adjuvant chemotherapy was 8.5%.²² Too often, older patients report that adjuvant therapy was not discussed.^{23,24} Variation in surgeon opinions and knowledge in Chapter 4 suggests that the individual surgeon a patient sees may determine whether they are referred for adjuvant therapy. The variation between

hospitals in rates of adjuvant therapy receipt in Chapter 3, and rates of one-year mortality in Chapter 6, demonstrate that the care a patient receives can depend on the hospital they attend for surgery.

However, variation also indicates that there is potential for improvements in care and outcomes. Multidisciplinary team meetings, a predictor of adjuvant therapy receipt in Chapter 3, can be effective in decreasing variation in management and survival.^{25,26} Certainly, surgeons who work closely with oncologists have been found to have higher oncology consultation rates, which is a crucial factor in adjuvant therapy receipt.²⁷ The involvement of other disciplines such as the geriatrician and general practitioner are often advocated as part of shared care models or clinical care pathways for older patients.^{28,29} Decreases in unmet need over time were less apparent for older patients in Chapter 2, suggesting a more prolonged assault of surgery and a need for greater ongoing monitoring, possibly through general practitioners in primary care. Other factors associated with adjuvant therapy use in Chapter 3, such as having a current partner, and the high importance that older patients placed on maintaining independence in Chapter 4, further indicate that greater social support and access to care may be necessary to facilitate adjuvant therapy use.

Chen and colleagues suggest that underutilisation of treatment for older cancer patients may be reduced if physicians had better tools to select patients who would benefit from and tolerate treatment.³⁰ It is now widely legislated that chronological age must not be used as a proxy for the proper assessment of individual need.³¹ Indeed, age was not an accurate way of determining who will live to benefit from health resources in Chapter 6. Clinicians' estimates of life expectancy can be imprecise.³² Risk stratification through the use of a simplified tool, such as that proposed in Chapter 6, may be a useful way to supplement physician judgements in the absence of the considerable resources that may be needed to complete the 'gold standard' comprehensive geriatric assessment for all patients.³³ Such tools can also be useful for identifying patients who may benefit from

prehabilitation strategies to optimise their health before starting treatment.³⁴ In Chapter 6, the mortality risk model that was developed indicated that factors such as malnutrition, length of stay, and emergency resection are potential targets for improving the outcomes of older patients.

7.3. Limitations

7.3.1. Adjusting for confounders

Determining whether age alone is a predictor of care or outcomes requires that factors associated with age, such as comorbidity and functional status, are both collected and used in analyses. The incorporation of health markers in clinical trials and population-based databases has been identified as a major gap in geriatric oncology research.³⁵ In Chapter 3, measures of both comorbidity and ASA physical status were able to be extracted from existing hospital data collections to examine age differences in adjuvant therapy receipt. A number of other health markers were able to be utilised to develop a mortality risk model for node-positive colon cancer patients in Chapter 6. However, it is likely that comorbidities and health markers are underascertained in the health datasets used for both of these studies.

There is also no gold standard approach to measuring comorbidity in cancer.³⁶ The use of a summary score may miss the impact of specific comorbidities, or the potential multiplicative effect of two or more chronic conditions in combination.³⁷ A standard validated summary score (Charlson index) was used in Chapter 3, while individual comorbidities were used in Chapter 6 to develop a more user-friendly risk model. Physical function is perhaps of greater importance for treatment decision making in older patients, and will not be adequately captured by a single physical status score. Indexes that predict physical function could therefore have greater usefulness for this population.³⁸ Increasing the completeness and collection of health status measures is vital for ensuring that the rich information provided by population-based datasets can be better utilised to generate evidence for underresearched groups such as older cancer patients.

Another major challenge when comparing older and younger populations is separating the effects of age, cohort and period.³⁹ That is, determining whether observed age differences are intrinsically due to the process of ageing, or can be attributed to the time in which a cohort grew up in, or are living in at present. These factors cannot be separated in the studies conducted as part of this thesis, as they are all cross-sectional (or short-term longitudinal) in nature. Older patients and physicians may have views about treatment and the medical encounter stemming from the poorer medical outcomes of the past, or from previous paternalistic models of care. Concerns about functional suitability for treatment could also be the result of cohort attitudes about the effect of functional dependence on family, or about present-day technology that is available to facilitate independence. As the baby boomer generation approaches old age, barriers and facilitators of treatment will likely change in response to the growing demand for services, views on how to allocate resources, and the high expectations of this generation for their health, longevity, and care.⁴⁰ Ongoing monitoring of vulnerable groups is therefore necessary.

Social desirability bias in self-report questionnaires can confound results.⁴¹ The potential for older patients to underreport their symptoms was discussed in Chapter 2. Physicians have also been found to overestimate their adherence to treatment guidelines.⁴² The finding that surgeon age was a predictor of survey responses in Chapter 4 could be biased if younger surgeons were more likely to inaccurately portray themselves as treating older and younger patients similarly. Nonetheless, considerable differences remained in referral recommendations for older and younger patients in this survey.

7.3.2. Internal and external validity

While the surgeon survey in Chapter 4 achieved a good response rate (70%) and had a relatively large sample size (n=102), the studies of patients' needs and QOL in Chapter 2 and the patient survey in Chapter 5 consisted of relatively small samples (n<70) recruited from a single tertiary referral hospital. There is the potential that these studies were underpowered to detect age differences in unmet needs, missing data, or factors of

importance for patients' decision making. The patients recruited for these smaller studies were broadly representative of CRC patients in terms of sex, cancer stage, and country of birth, however the median age of both of these populations was 4-5 years lower than would be expected. These factors may affect the generalisability of the findings, particularly for the older age groups. In the patient survey of barriers to chemotherapy use, none of the participants had refused adjuvant therapy. Insights into actual barriers could therefore not be deduced. While the findings of these small studies should be treated with caution, it is encouraging that the results are largely consistent with previous findings and a priori hypotheses.

The trade-off between the cost and quality of data is an ongoing issue in monitoring the quality of care at a population level.⁴³ Issues in the coverage and completeness of the ClinCR dataset used to determine rates of adjuvant therapy uptake were extensively discussed in Chapter 3. However, the findings of Chapter 3 are likely to have high validity in the Australian context, as one third of the country's population resides in NSW. Developing cancer-specific geriatric tools is frequently cited as a priority area for improving the care and outcomes of older patients.^{44,45} The use of local data to develop a risk model that included markers of frailty and health status in Chapter 6 may increase the clinical credibility and therefore the usefulness of this model, though it requires further development and testing.

7.3.3. Specific research gaps

This thesis did not explore the potential for the impact of the oncologist on the treatment of older patients. While surgeons have previously been found to act as important gatekeepers in the receipt of adjuvant therapy, oncologists also appear to hold preferences against the treatment of older patients⁴⁶ and are less likely to recommend adjuvant therapy even in the absence of comorbidity.⁴⁷ In Chapter 3, the hospital variation in adjuvant therapy receipt that was present after accounting for surgeons could point to differing practices of oncologists, or breakdowns in the care pathway. An important

consideration for research examining surgeon treatment patterns in isolation is that surgeons generally happen to fall before oncologists in the treatment pathway. That is, the surgeon may select out those who the oncologist would deem unfit for adjuvant therapy anyway. Where hospital variation in adjuvant therapy receipt is large, a system-based approach to intervention may therefore be necessary.

This thesis also focused primarily on issues in adjuvant chemotherapy for colon cancer, rather than adjuvant or neoadjuvant radiotherapy for rectal cancer. While having similar aims in terms of prevention of recurrence and survival, these treatments differ significantly in their effects on the body and in surgical issues dictated by the tumour location. Overall rates of radiotherapy for rectal cancer were lower than rates of chemotherapy for colon cancer in Chapter 3, consistent with previous research. However, age differences in radiotherapy receipt were less significant. This finding was reflected in Chapter 4 where there was greater consensus between surgeons that age alone should not be a barrier to radiotherapy use. Greater exploration of the decision-making issues unique to radiotherapy in rectal cancer is needed, including the smaller potential benefits resulting from improved surgery techniques, additional local concerns around out-of-pocket costs and travel,⁴⁸ and the investment needed in new facilities to keep pace with the demand for services.⁴⁹

7.4. Future directions and priorities

Though cancer and ageing would appear to be obvious bedfellows, geriatric oncology is a relatively new field. The first programs dedicated to geriatric oncology only appeared in the mid 1990s,⁵⁰ and the first Australian program was created less than five years ago.⁵¹ With the realisation that this group is rapidly becoming the vast majority of cancer patients, issues in geriatric oncology have been receiving increasing attention.⁵² Treatment guidelines for adjuvant therapy in colorectal cancer have existed since 1990.⁵³ However, older cancer patients present a unique set of challenges for physicians, not least of which is their notorious under-examination in all aspects of health research.

What is needed to increase the evidence-based care of older colorectal cancer patients?

The lack of consensus among surgeons in Chapter 4 suggests that more research is needed both to predict the benefits and risks of treatment for older patients, and to determine how information from emerging evidence can best be used to assist physicians' treatment decisions. Both of these are needed in tandem; more high-quality and specialised geriatric trials will not be of benefit unless this research can be translated into practice. Evidence is sparse on the best ways to affect change in physician treatment practices. Routine monitoring of performance and peer-comparison feedback is one potential avenue.⁵⁴ It is also promising to note that rates of guideline-recommended treatment are already on the rise, suggesting that further improvements are possible.

Recent trends towards personalised medicine based on an individual's genetic profile will certainly be of benefit for older cancer patients. Strides in identifying biomarkers that predict physiological age may help to shift the emphasis in treatment decision making from arbitrary age cut-offs to better predictors of treatment complications and life expectancy. In the meantime, the care and outcomes of older patients may be improved by routine assessment to identify fitness and vulnerability, greater use of tools to help patients and physicians balance the benefits and risks of treatment, investment in geriatrics training and service infrastructure, and more rigorous and valid PRO research. Additional informed debate is also required around the social and economic considerations in ageing and cancer, as no assessment tool on its own will be able to change attitudes about the value of treating cancer in older patients.

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