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ORIGINAL ARTICLE

Use of guideline-recommended adjuvant therapies and survival outcomes for people with colorectal cancer at tertiary referral hospitals in South Australia

Pamela Adelson RN, BSc, MPH[1,8] | Kellie Fusco BHSc[2] | Christos Karapetis MB, BS, MMedSc, FRACP[3] | David Wattchow BM, BS, PhD, FRACS[4] | Rohit Joshi MB, BS, MD, FRACP FACP[5] | Timothy Price MB BS, DHlthSc[6] | Greg Sharplin BSc, BHS, MPsych[1] | David Roder BDS, MPH, DDSc (Epidemiology)[7]

[1] Research Officer, Manager, Research Unit, Cancer Council South Australia, Adelaide, South Australia, Australia

[2] Epidemiologist, South Australia Clinical Cancer Registry, University of South Australia, Adelaide, South Australia, Australia

[3] Associate Professor, Head Department of Medical Oncology, Flinders Centre for Innovation in Cancer, Flinders Medical Centre, Adelaide, South Australia, Australia

[4] Professor, Surgical Staff Specialist, Department of Surgery, Flinders Medical Centre, Adelaide, South Australia, Australia

[5] Director Cancer Research and Clinical Trials, Lyell McEwin Hospital, Adelaide, South Australia, Australia

[6] Professor, Medical Oncology Consultant, Medical Oncology, Queen Elizabeth Hospital, Adelaide, South Australia, Australia

[7] Professor, Chair, Cancer Epidemiology & Population Health, University of South Australia, Adelaide, South Australia, Australia

[8] Research Fellow, Rosemary Bryant Research Centre, School of Nursing and Midwifery, University of South Australia, Adelaide, Australia

Correspondence
Pamela Adelson, Research Fellow, Rosemary Bryant Research Centre, School of Nursing and Midwifery, University of South Australia, GPO Box 2471, Adelaide SA 5001, Australia.
Email: pam.adelson@unisa.edu.au

Abstract

Rationale, aims and objectives: Adjuvant care for colorectal cancer (CRC) has increased over the past 3 decades in South Australia (SA) in accordance with national treatment guidelines. This study explores the (1) receipt of adjuvant therapy for CRC in SA as related to national guideline recommendations, with a focus on stage C colon and stage B and C rectal cancer; (2) timing of these adjuvant therapies in relation to surgery; and (3) comparative survival outcomes.

Methods: Data from the SA Clinical Cancer Registry from 4 tertiary referral hospitals for 2000 to 2010 were examined. Patterns of care were compared with treatment guidelines using multivariable logistic regression. Disease-specific survivals were calculated by treatment pathway.

Results: Four hundred forty-three (60%) patients with stage C colon cancer and 363 (46%) with stage B and C rectal cancer received guideline-recommended care. While an overall increase in proportion receiving adjuvant care was not evident across the study period, the proportion having neoadjuvant care increased substantially. Older age was an independent predictor of not receiving adjuvant care. Patients with stage C colon cancer who received recommended adjuvant care had a higher 5-year survival than those not receiving this care, ie, 71.2% vs 53.2%. Similarly adjuvant therapy was associated with better outcomes for stage C rectal cancers. The median time for receiving adjuvant care was 8 weeks.

Conclusions: Survival was better for stage C CRC treated according to guidelines. Adjuvant care should be provided except where clear contraindications present. Other possible contributors to guideline adherence warranting additional investigation include co-morbidity status, multidisciplinary team involvement, and choice.

KEYWORDS

adjuvant therapy, clinical cancer registry, clinical guidelines, colorectal cancer, survival, treatment

1 | INTRODUCTION

Australia has one of the highest rates of colorectal cancer (CRC) in the world, with CRC recorded as the second most common cancer and cause of cancer death by Australian registries.[1] Following worldwide advances in diagnostic technology, surgical technique, and adjuvant therapy, CRC disease-specific survivals have increased steadily[1], with 5-year survivals increasing from 48% in the 1980s to 66% in 2006 to 2010. Similar survival increases have been reported in South Australia (SA), 1 of 8 Australian states and territories, which experience about

1240 new CRC diagnosed cases annually and approximately 450 CRC deaths.[2]

International studies have indicated that 70% to 80% of newly diagnosed CRC patients undergo curative resection, with 40% of them developing incurable recurrent disease.[3] Because patients with resected colon cancer TNM stage III (Dukes stage C) and rectal cancer stages II and III (Dukes stages B and C) are at increased risk of local and distant recurrence, adjuvant therapy has been advocated since the early 1990s.[3,4]

National treatment guidelines for CRC were first published in Australia in 1999 and updated in 2005. They recommend that resected stage C colon cancer receive adjuvant chemotherapy (postoperatively), and resected stages B and C rectal cancer have chemoradiotherapy although not specifying whether this adjuvant rectal cancer therapy should be administered preoperatively or postoperatively (Figure 1). Recommendations around the timing of adjuvant therapy were included in an updated clinical review of these guidelines published in 2014 by Cancer Council Australia (Figure 1).

The intention of guidelines is to guide, rather than enforce, and so the extent of their uptake varies. A range of patient characteristics has been previously described as possible contributors to variations in use of adjuvant therapy.[5,6] It is recognized that departures from guideline recommendations can be appropriate, as for example, to accommodate age-related frailty, co-morbidity, service access, and hospital factors. Australian studies have reported old age and rural residence to be negatively related to use of adjuvant therapies for CRC, after adjusting for co-morbidity.[5,7,8] Factors affecting guideline uptake would also include surgeon and patient choice.

In SA, information on CRC treatment is available through the South Australia clinical cancer registry (SACCR). SACCR data have shown a marked increase in use of adjuvant therapies since the 1980s. For stage C CRC cases, the proportion receiving this care increased from 5% in 1980 to 1986 to approximately 60% receiving this treatment for 2005 to 2010.[2] However, a recent SA population-based data-linkage study of CRC indicated that adjuvant therapy was less common than advised in guidelines, particularly for older patients.[9]

The present study aims to use SACCR data to explore guideline implementation for adjuvant chemotherapy and/or radiotherapy amongst patients with stage C colon and stages B and C rectal cancers. Comparisons are made of adjuvant therapy use by sociodemographic characteristics, the timing of adjuvant and neoadjuvant therapies in relation to surgery, and survival outcomes in relation to guideline-recommended adjuvant therapies. Conduct of the study was approved by the SA Health Human Research Ethics Committee (HREC/14/SAH/174).

Colon stage III: 1999, 2005 guidelines and 2014 updated clinical review	Recommendation
Colon, 1999 People with resected node-positive (stage III) should be offered adjuvant therapy	Strongly recommended
Colon, 2005 People with resected stage III i.e. node positive colon cancer should be recommended for adjuvant therapy.	Strongly recommended
Colon, 2014 clinical treatment review Adjuvant chemotherapy for resected stage III colon cancer has been the standard of care for the last two decades. Patients based on fitness and preference with completely resected stage III cancer should be offered 6 months of adjuvant chemotherapy which optimally should start within eight weeks of surgery.	Strongly recommended
Rectal stage II & III: 1999, 2005 guidelines and 2014 updated clinical review	
Rectal, 1999 Postoperative chemotherapy and radiotherapy is recommended for patients with high-risk rectal cancer (stage II or III)	Recommended (level II evidence)
Rectal, 2005 Adjuvant preoperative or postoperative radiotherapy should be considered for high-risk rectal cancer (stage II or III).	Strongly recommended
Rectal, 2014 clinical treatment review Patients with stage II/III current treatment include: (i) short course radiotherapy and immediate total mesorectal excision or (ii) neoadjuvant chemoradiotherapy followed by total mesorectal excision. Post-operative adjuvant chemotherapy should be offered to all medically fit patients. At present there are no markers to identify patients who may not require neoadjuvant chemoradiotherapy or who can avoid surgery.	Strongly recommended

[a] National Health and Medical Research Council. Guidelines for the prevention, early detection and management of Colorectal Cancer (rescinded). Commonwealth of Australia, 1999.
[b] Australian Cancer Network Colorectal Cancer Guidelines Revision Committee. Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. The Cancer Council Australia and Australian Cancer Network, Sydney 2005
[c] Michael M., Zalcberg JR. Adjuvant therapy for colorectal cancer. *Cancer Forum*, March 2014. Cancer Council Australia, Clinical Oncology Society of Australia.

FIGURE 1 Recommended national guidelines for adjuvant treatment of colon stage C (III) and rectal stages B (II) and C (III) cancer: 1999[a], 2005[b] guidelines, and updated clinical review recommendations 2014[c]

2 | METHODS

2.1 | Data source and coding

The SACCR has collected clinical cancer data from major teaching hospitals in SA since 1987. The data are compiled to monitor cancer stage at diagnosis, other prognostic features, and treatment. Colorectal cancer treatment data were extracted from the SACCR database for the 4 tertiary SA referral hospitals that have cancer centres for the 2000 to 2010 diagnoses, with follow-up to December 31, 2012. The data included stage, grade, and treatment information. Cases were classified, according to the ICD-O-3 international classification of diseases for oncology, in the C18-20 range for CRC: C18 colon, C19-20 for rectum. The Australian Clinico-Pathological Stage was recorded, which is an extension of the original Dukes' staging to include metastatic disease. Pretreatment-staging data are used in this study. For patients with synchronous CRCs, the lesion with the more advanced stage was used as the index cancer.

Radiotherapy, chemotherapy, and definitive CRC surgery dates are recorded by the SACCR. As only start dates were available for adjuvant therapies, it was not possible to determine whether radiotherapy was short or long course. Chemotherapy and/or radiotherapy were classified as adjuvant therapy if undertaken with curative intent and commenced within 6 months of surgical treatment. Such therapies, so close in time to the surgery and noted to be for curative intent on the database, were assumed to be for adjuvant purposes rather than a new event (eg, a recurrence or progression). Neoadjuvant therapy was indicated where chemoradiation commencement preceded surgical treatment for stages B and C rectal cancer. Chemotherapy agents used included 5FU and leucovorin, FOLFOX (with or without bevacizumab), and capecitabine (with or without oxaliplatin).

Residential postcodes at diagnosis were used to assign geographic socio-economic status and remoteness/accessibility to services, using the Australian Bureau of Statistics Socio-economic Indexes for Area and the Accessibility/Remoteness Index of Australia (ARIA), respectively.

Concordance with guideline recommendations were assessed for those Australian Clinico-Pathological stages where the 2005 national guidelines most strongly recommended use of adjuvant therapy, ie, chemotherapy for stage C colon cancer and chemotherapy/radiotherapy for stages B and C rectal cancers (Figure 1). The period between the start of neoadjuvant or adjuvant therapy and definitive CRC surgery was measured in days.

2.2 | Analysis

Patterns of care were compared with the 2005 Australian treatment guidelines, using binary analyses (χ^2) and crude and adjusted multivariable logistic regression. Candidate predictors of adjuvant therapies used in analyses, selected a priori, included available sociodemographic characteristics described above. Service site was examined for potential confounding and effect modification and was not found to differ significantly. As hospital was not a primary variable of interest, the data presented are unadjusted for service site. Any patient or sociodemographic variable potentially related to adjuvant therapy (as indicated by $P < 0.20$ in unadjusted analysis) were entered into regression models with backwards elimination to exclude non-significant predictors ($P < 0.05$) that did not improve model fit.

Disease-specific survivals were calculated by person in patient groups (colon or rectal) by receipt of adjuvant therapy, using Kaplan-Meier product-limit estimates, with censoring of follow-up on December 31, 2012. Cox proportional hazards regression analyses were also used to compare disease-specific survivals by stage and treatment, using the same censoring rules. Stata 13 (StataCorp) was used for all analyses.

3 | RESULTS

There were 4273 people treated for CRC at these hospitals in 2000 to 2010. Treatment and sociodemographic characteristics are shown in Appendix Table 1 (colon cancer, n = 2815) and Appendix Table 2 (rectal cancer, n = 1458). Adjuvant therapy was most common for stage C colon cancer (n = 738 patients) and stages B and C rectal cancer (n = 792 patients), as recommended in guidelines. These stages were the focus of further analysis (Figure 2). Residents of remote and very remote areas were combined in analyses due to small numbers.

3.1 | Colon cancer treatment, stage C

Overall, the proportion of stage C colon cases receiving guideline-recommended adjuvant (postoperative) chemotherapy was 60% (443/738). The other 40% (293/738) had surgery alone (Table 1). This did not vary significantly by hospital ($P = 0.522$) Cases from non-metropolitan areas were more likely to receive chemotherapy (66%) than those from metropolitan areas (57%). There was no significant difference in proportions receiving adjuvant therapy by hospital, socio-economic index, diagnostic epoch (2000-2004 vs 2005-2010), or sex ($P > 0.100$), but a decrease in receipt of adjuvant therapy applied for increasing age when examined by 10-year age groups from 40 to 80 + ($P < 0.000$). Cases aged 50 to 59 years were the age group most likely to receive adjuvant chemotherapy (90%), as compared with 70- to 79-year olds (63%) and 80+ year olds (14%), Table 1.

Multivariable logistic regression indicated that age groups 60 to 69, 70 to 79, and 80+ years were less likely to receive guideline-recommended adjuvant care than those under 60 years of age. (Table 2). Patients from areas classified as having moderate access to services were also more likely than those from highly accessible areas to receive this care ($P = 0.007$); however, the number of patients in this category was small (n = 22). Mean time to receipt of adjuvant chemotherapy was ≤8 weeks after surgery (mean 54 days, median 47 days). Seventy-five percent received adjuvant therapy within 59 days of surgery.

There was a survival benefit for cases receiving adjunctive chemotherapy ($P < 0.001$), with a 5-year survival of 71.2% (95% CI, 66.2-75.4) compared with 53.2% (95% CI, 46.6-59) for other stage C cases. The corresponding 10-year survivals were 61.6% (95% CI, 55.7-67.0) and 47.5% (95% CI, 40.0-54.5) (Figure 3). This was also

TABLE 1 CRC surgically treated & receipt of recommended adjuvant therapy per 2005 national guidelines

Potentially Eligible for Adjuvant Therapy (Strongly Recommended) Stage C Colon and Stage B & C Rectal Cancers	Treatment Colon *T* = 738 Stage C n = 738	Treatment Rectal *T* = 792		
		Stage B n = 351	Stage C n = 441	Total Rectal n = 792
Treatment	n (%)	n (%)	n (%)	n (%)
Surgery only	293 (39.7)	197 (56.1)	99 (22.4)	296 (37.4)
Surgery & chemo	430 (58.3)	23 (6.5)	110 (24.9)	133(16.8)
Surgery & radio	2 (0.3)	23 (6.5)	28 (6.3)	51 (6.4)
Surgery, radio, chemo	13 (1.8)	108 (30.8)	204 (46.3)	312 (39.4)
Total received adjuvant therapy per guidelines[a]	443 (60.0)	131 (37.3)	232 (52.6)	363 (45.8)
Proportion of guideline adjuvant that was *Neoadjuvant* chemo	12 (2.7)	79/131 (60.3)	113/232 (48.7)	192/363 (52.9)
Proportion of guideline adjuvant that was *Neoadjuvant* radio	n/a	101/131 (77.1)	130/232 (56.0)	231/363 (63.6)
Year group 2000-2004				
Adjuvant per guidelines	184 (61.3)	60 (36.1)	96 (54.5)	156 (45.6)
No adjuvant per guidelines	116(38.7)	106 (63.9)	80 (45.5)	186 (54.4)
Total years 2000-2004	300 (100)	166 (100)	176 (100)	342 (100)
Year group 2005-10				
Adjuvant tx per guidelines	259 (59.1)	71 (38.4)	136 (51.3)	207 (46.0)
No adjuvant tx per guidelines	179 (40.9)	114 (61.6)	129 (48.7)	243(54.0)
Total years 2005-2010	438 (100)	185 (100)	265 (100)	450 (100)
Gender received Adjuvant tx per guidelines				
Male	229/366 (62.6)	79/213 (37.1)	145/267 (54.3)	224/480(46.7)
Female	214/372 (57.5)	52/138 (37.7)	87/174 (50.0)	139/312(44.6)
Geographical				
Metro adjuvant treatment per guidelines	291/509 (57.2)	85 (35.9)	152 (52.6)	237/526 (45.1)
Non-metro adjuvant treatment per guidelines	152/229 (66.4)	46 (40.4)	80 (52.6)	126/266(47.4)
ARIA remoteness & adjuvant per guidelines				
1 highly accessible	345 (57.7)	103 (37.3)	174 (51.9)	277/611 (45.3)
2 accessible	63 (68.5)	22 (40.7)	34 (54.0)	56/117 (47.9)
3 moderate accessible	22 (75.9)	1 (8.3)	17 (53.1)	18/44 (40.9)
4 remote and very remote	13 (68.4)	5 (55.6)	7 (63.4)	12/20 (60.0)
Age & Adjuvant therapy per guidelines				
Adjuvant per guidelines <40	11 (78.6)	3 (100)	9 (64.3)	12/17 (70.6)
Adjuvant per guidelines 40-49	29 (82.9)	12 (66.7)	23 (76.7)	35/45 (72.9)
Adjuvant per guidelines 50-59	87 (89.7)	19 (43.2)	53 (60.2)	72/132 (54.6)
Adjuvant per guidelines 60-69	130 (76.5)	42 (43.8)	71 (58.7)	113/217 (52.1)
Adjuvant per guidelines 70-79	163 (63.2)	43 (36.1)	59 (47.0)	102/244 (41.8)
Adjuvant per guidelines 80+	23 (14.0)	12 (16.9)	17 (27.0)	29/134 (21.6)

[a]All stage C colon cancer cases should be considered for adjuvant chemotherapy (*strongly recommended*). All high-risk rectal cases (stage B or C) should be considered for adjuvant preoperative or postoperative radiotherapy (*strongly recommended*). Preoperative therapy may reduce the late morbidity compared with postoperative (level 2, recommended).

demonstrated in the Cox model with adjuvant chemotherapy independently associated with improved disease specific survival (HR 0.56; 95%CI, 0.42-0.75), Table 3.

3.2 | Rectal cancer treatment, stages B and C

Overall, 45.8% (363/792) of cases with rectal cancer received guideline-recommended adjuvant care; 39% (312/792) received combined chemoradiotherapy adjuvant therapy, with a further 6% (51/363) receiving adjuvant (n = 15) or neoadjuvant (n = 36) radiotherapy alone (Table 1). Approximately 17% had surgery and chemotherapy without radiotherapy, of which nearly half (47%) were rectosigmoid cases. As with colon cancer, the proportion receiving recommended adjuvant care did not differ significantly by hospital ($P = 0.522$).

Rectosigmoid cancers constituted approximately a quarter (n = 206, 26%) of rectal cases and were significantly less likely to receive recommended radiotherapy ($P < 0.001$) with only 16% (33/206) of them receiving radiotherapy as compared with 56% (330/586) of rectal cases that were not in the rectosigmoid area. The proportion of rectosigmoid cases that were stages B and C were similar in profile to non-rectosigmoid rectal cancers with 96/206 (47%) of rectosigmoid cases being stage B and 110/206 (53%) being stage C.

TABLE 2 Factors for receipt of guideline-recommended colorectal cancer adjuvant therapy, South Australia tertiary referral hospitals, 2000-2010

Characteristics (colon, stage C, n = 738)	Colon cancer (stage C) univariate logistic regression OR (95% CI)	*P* value	Colon cancer (stage C) adjusted logistic regression OR (95% CI)	*P* value
Gender: Male (ref)	1.0			
Female	1.03 (0.74-1.48)	0.852		
Age Group: (ref <60)	1.0			
60-69	0.47 (0.26-0.85)	0.013	0.47 (0.26-0.86)	0.014
70-79	0.25 (0.14-0.43)	<0.001	0.25 (0.14-0.43)	<0.001
80+	0.02 (0.01-0.04)	<0.001	0.02 (0.01-0.04)	<0.001
ARIA remoteness:				
Highly accessible (ref)	1.0			
Accessible	1.47 (0.72-3.01)	0.287	1.43 (0.83-2.46)	0.194
Moderately accessible	4.40 (1.39-13.89)	0.012	4.31 (1.50-12.38)	0.007
Remote	1.76 (0.49-6.30)	0.384		
Area:				
Metropolitan (ref)	1.0			
Non-metropolitan	0.99 (0.58-1.72)	1.000		
Year-group: (ref 2000-4)	1.0			
2005-2010	0.89 (0.62-1.27	0.515		
Characteristics (Rectal cancer, n = 792)	**Rectal Cancer (stage B & C) univariate logistic regression OR (95% CI)**		**Rectal Cancer (stage B & C) adjusted logistic regression OR (95% CI)**	
Gender: Male (ref)	1.0			
Female	0.98 (0.72-1.32)	0.902		
Age Group: (ref <60)	1.0			
60-69	0.77 (0.51-1.43)	0.194	0.76 (0.51-1.36)	0.183
70-79	0.51 (0.34-0.75)	0.001	0.50 (0.34-0.75)	0.001
80+	0.20 (0.12-0.33)	<0.001	0.19 (0.12-0.32)	<0.001
ARIA remoteness:				
Highly accessible (ref)	1.0			
Accessible	1.07 (0.60-1.93)	0.797		
Moderately accessible	0.68 (0.32-1.46)	0.325	0.64 (0.34-1.21)	0.174
Remote	1.64 (0.59-4.58)	0.342		
Area:				
Metropolitan (ref)	1.0			
Non-metropolitan	0.95 (0.58-1.53)	0.827		
Year-group: (ref 2000-4)	1.0			
2005-2010	0.99 (0.74-1.33)	0.980		
Stage (ref stage B)	1.0			
Stage C	1.73 (1.29-2.34)	<.001	1.73 (1.28-2.33)	<.001

Abbreviations: CI, confidence interval; OR, odds ratio.

Although rectosigmoid cases were less likely to receive radiotherapy, the results of the final logistic regression models were not affected by including or excluding rectosigmoid cases.

Overall, patients with stage C rectal cancer were more likely to receive guideline-recommended adjuvant therapy (53%) than cases with stage B (37%). As with colon cancer, there was no significant difference ($P > 0.050$) in the proportion who received adjuvant therapy by hospital, socio-economic index, sex, or diagnostic epoch. Cases from non-metropolitan areas were as likely to receive adjuvant therapy as those from metropolitan areas (45% vs 44%, respectively). The proportion treated by surgery alone was similar over time (39%, 135/342 for 2000-2004, and 36%, 161/450 for 2005-2010).

As was the case with colon cancer, there was a lower receipt of adjuvant therapy in older patients with rectal cancer ($P < 0.001$). When examined by 10-year age groups, the 40- to 49-year age group was the group most likely to receive adjuvant radiotherapy (73%, 35/45). These findings were confirmed in the adjusted logistic regression model, with the 2 oldest age groups, 70 to 79 and 80+, being significantly less likely to receive adjuvant therapy after controlling for other sociodemographic factors (Table 2).

Overall, most surgically treated cases received radiotherapy as neoadjuvant therapy (64%, 231/363 of adjuvant therapy was before surgery; Table 1). The proportion of adjuvant therapy that was neoadjuvant was higher for stage B patients both for chemotherapy (60%)

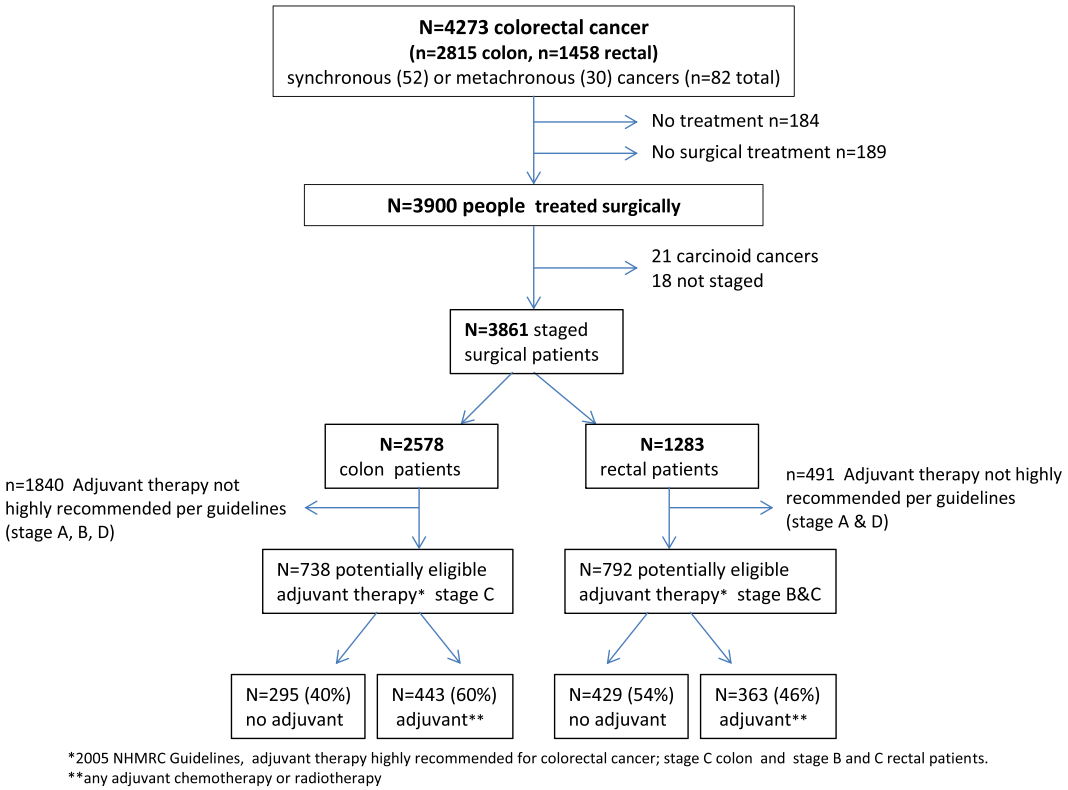

FIGURE 2 Colorectal cases 2000 to 2010, South Australia clinical cancer registry, and receipt of adjuvant therapy

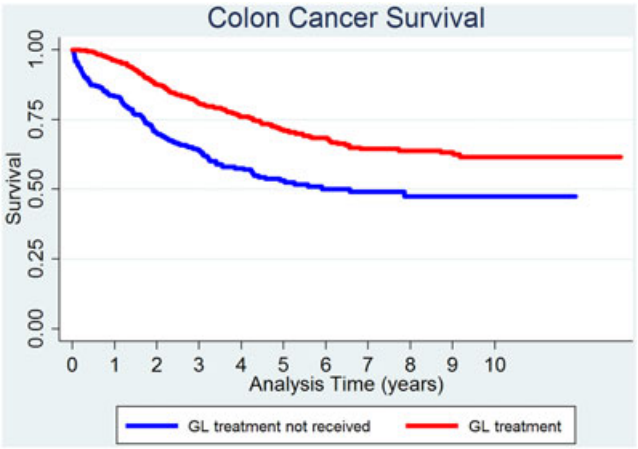

FIGURE 3 Colon cancer surgically treated stage C, receipt of GL recommended adjuvant care, South Australia tertiary referral hospitals, 2000 to 2010

TABLE 3 Hazard ratios (95% CI)* for death from colon cancer

Characteristics Colon, Stage C	Hazard Ratio (95% CI)	*P* value
Gender: Male (ref)	1.0	
Female	0.97 (0.75-1.24)	0.809
Age Group: (ref <60)	1.0	
60-69	1.05 (0.71-1.57)	0.790
70-79	1.08 (0.74-1.58)	0.669
80+	1.30 (0.84-2.03)	0.231
Year-group: (ref 2000-4)	1.0	
2005-2010	0.88 (0.68-1.14)	0.336
Treatment:		
Surgery only (ref)	1.0	
Surgery and chemo	0.56 (0.42-0.75)	<0.000

Abbreviation: CI, confidence interval.

*Adjusted for non-significant ($P > 0.05$) associations with ARIA remoteness and metropolitan area.

and radiotherapy (77%) when compared with stage C rectal cancers (chemotherapy 49% and radiotherapy 56%; X^2 4.5, $P < 0.020$ and X^2 16.1, $P < 0.001$), respectively. The proportion of adjuvant therapy that was neoadjuvant increased from 54%, 85/156, in 2000 to 2004 to 71.0%, 146/207, in 2005 to 2010 for radiotherapy, and for chemotherapy, from 43%, 67/156, to 60%, 124/207.

In a separate logistic model examining receipt of neoadjuvant therapy amongst those receiving adjuvant therapy, the 2005 to 2010 diagnostic epoch was a significant predictor of receiving neoadjuvant care and the age-groups 70 to 79 and 80+ were significantly less likely to receive neoadjuvant care than younger age groups (Table 4).

The median time to adjuvant therapy after surgery was 48 days for chemotherapy and 50 days for radiotherapy. Seventy-five percent of patients received adjuvant therapy within 67 days. For those receiving neoadjuvant chemoradiotherapy, the median time to surgery was 84 days. For those that were noted to have had only neoadjuvant radiotherapy (with no recorded chemotherapy) and rectal surgery (n = 36), the median time to surgery was 17 days. No distinction was made in the dataset between short- and long-course radiotherapy schedules. The length of time for receipt of any adjuvant therapy was similar for patients from metropolitan and non-metropolitan areas.

TABLE 4 Receipt of neoadjuvant therapy, rectal cancer, South Australia tertiary referral hospitals, 2000-2010

Characteristics (Rectal Cancer, n = 792)	Rectal Cancer (Stage B & C) Univariate Logistic Regression OR (95% CI)	*P* Value	Rectal Cancer (Stage B & C) Adjusted Logistic Regression OR (95% CI)	*P* value
Gender: Male (ref)	1.0			
Female	0.85 (0.62-1.17)	0.332		
Age Group: (ref <60)	1.0			
60-69	0.74 (0.49-1.11)	0.148	0.75 (0.49-1.12)	0.160
70-79	0.64 (0.43-0.96)	0.032	0.64 (0.43-0.95)	0.027
80+	0.28 (0.16-0.48)	<0.001	0.27 (0.16-0.47)	<0.001
ARIA remoteness:				
Highly accessible (ref)	1.0			
Accessible	0.66 (0.36-1.22)	0.189		
Moderately accessible	0.39 (0.17-0.94)	0.037	0.48 (0.22-1.03)	0.059
Remote	0.87 (0.31-2.47)	0.798		
Area:				
Metropolitan (ref)	1.0			
Non-metropolitan	1.18 (0.72-1.93)	0.499		
Year-group: (ref 2000-4)	1.0			
2005-2010	1.69 (1.22-2.32)	0.001	1.70 (1.24-2.34)	0.001
Stage (ref stage B)	1.0			
Stage C	0.95 (0.69-1.30)	0.747		

Abbreviations: CI, confidence interval; OR, odds ratio.

No significant survival benefit was demonstrated comparing those who did or did not receive recommended guideline treatment in the Kaplan-Meir survival curves for either stage B (P = 0.234) or C (P = 0.614) rectal cancer (Figure 4). For those with stage C, the 5-year survival was 69.4% (95% CI, 62.3-75.3) compared with 68.2% (95% CI, 60.6-74.6) for those who did not receive adjuvant therapy. In the adjusted Cox proportional hazard model and when compared with cases treated only by surgery, patients with stage C rectal cancer receiving (neo)adjuvant chemotherapy had significantly better survival outcomes than other stage C rectal cases (hazard ratios 0.27; 0.16, 0.47), and also better survival outcomes if they received chemotherapy and radiotherapy (hazard ratios 0.47; 0.30, 0.72), Table 5.

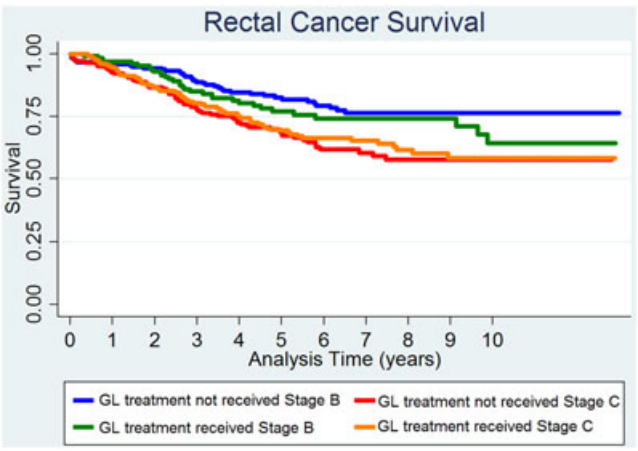

FIGURE 4 Rectal cancer surgically treated stages B and C, receipt of guideline (GL) recommended adjuvant care, South Australia tertiary referral hospitals, 2000 to 2010

4 | DISCUSSION

This study uses the SACCR data to investigate differences in profiles of patients according to whether they were receiving adjuvant therapy for stage C colon and stages B and C rectal cancer in accordance with the 2005 Australian CRC clinical practice guidelines.

Over the 10-year study period, older age was a significant independent predictor of not receiving adjuvant care. This was more apparent amongst colon cases where significantly less received adjuvant care after the age of 60, as compared with rectal cancer where the drop-off occurred in ages 70 and over. Differences by type of CRC cancer were also evident in the overall proportion of patients receiving stage-specific adjuvant care; the majority of surgically treated patients in SA teaching hospitals with colon cancer are receiving adjuvant therapy (60%), but less than half (46%) of rectal patients are receiving this treatment. However, with rectosigmoid cases excluded from the rectal group, this proportion increases to 56%.

For those who did receive guideline-recommended care, there were significant stage specific survival benefits when compared with those who did not receive this care. For stage C colon cases, receiving adjuvant therapy was associated with higher survivals, consistent with international and Australian literature.[10,11] The decreased hazard ratio for rectal cases receiving adjuvant therapy was also consistent with trial results, despite the nonexperimental routine-practice nature of the treatment environment.[12,13]

Although our analyses were limited to the major public teaching hospitals in SA, the proportion of patients receiving care is similar to that reported in a population-based linked SA study reporting CRC outcomes. In that study, for those diagnosed from 2003 to 2008, 61% of stage C colon cancer patients received chemotherapy and 35% of rectal stage B and 45% of rectal stage C cancer

TABLE 5 Hazard ratios* (95% CI) for death from rectal cancer

Characteristics Rectal Cancer	Stage B Hazard Ratio (95% CI)	*P* value	Stage C Hazard Ratio (95% CI)	*P* value
Gender: Male (ref)	1.0		1.0	
Female	0.76 (0.46-1.26)	0.288	0.69 (0.49-0.99)	0.043
Age Group: (ref <60)	1.0		1.0	
60-69	1.83 (0.82-4.04)	0.137	1.17 (0.73-1.90)	0.511
70-79	1.60 (0.71-3.59)	0.252	1.27 (0.79-2.03)	0.322
80+	7.13 (3.01-16.90)	<.001	2.00 (1.17-3.44)	0.011
Year-group: (ref 2000-4)	1.0		1.0	
2005-2010	0.65 (0.39-1.08)	0.096	0.72 (0.51-1.02)	0.069
Treatment:				
Surgery only (ref)	1.0		1.0	
Surgery & Radio	2.53 (1.09-5.80)	0.029	1.07 (0.58-1.97)	0.822
Surgery & Chemo	1.48 (0.50-4.38)	0.479	0.27 (0.16-0.47)	<0.001
Surgery, Radio & Chemo	1.99 (1.12-3.52)	0.018	0.47 (0.30-0.72)	0.001

Abbreviation: CI, confidence interval.

*Adjusted for non-significant ($P > 0.05$) associations with: ARIA remoteness and metropolitan area.

received radiotherapy.[9] These findings suggest that clinical cancer registry data are probably a good proxy for state-wide treatment data. While one might expect the alignment of treatment with guideline statements to be closer for major teaching institutions, it is also possible that as major referral centres, they manage more complex cases with higher levels of co-morbidity where adjuvant therapies may be contraindicated. Further, this could explain why the few patients with colon cancer from the more geographically remote areas were more likely to receive adjuvant care in the adjusted logistic regression model. That is, they could have been referred to the major referral centres, and as they lived >100 km away, they would have been eligible for subsidized travel and accommodation for the duration of their 5 to 6 weeks of adjuvant therapy. Alternatively, this could be a spurious finding based on low numbers in this category.

The proportion of patients receiving recommended adjuvant therapy in our study was also similar with reported rates from other retrospective studies for these stages in Australia, eg, in the national CRC concordance survey in 2000, recommended adjuvant therapy was 56% for colon cancer and 40% for postoperative chemoradiotherapy for rectal cancers.[14] In a 2006 to 2007 New South Wales study, 65% of patients with colon cancer received adjuvant chemotherapy and 42% of patients with rectal cancer received radiotherapy.[7] In a prospective study from Victoria, the proportion of patients with stage C colon cancer who received adjuvant therapy was 78%; however, all patients in the study were discussed with or referred to a medical oncologist.[15] It is not known in our study what proportion of patients was referred to oncologists.

In the most recent Australian survey of colorectal surgeons over the period 2007 to 2014, only half of all rectal cancer cases reportedly were discussed at multidisciplinary team (MDT) meetings, with specialist recommendations being an important predictor of treatment choice.[16] However, urgent presentations may preclude MDT opportunities. An New South Wales study suggests that surgeons (as compared with oncologists) acting as patient surrogates were less likely to recommend adjuvant therapy;[17]although with the increased use of MDTs, this is likely to be less of a factor. It is likely that increased use of MDT decision-making may be beneficial in supporting guideline-recommended care for rectal cancers.[6]

The reasons for proportionally fewer rectal cancer cases receiving adjuvant therapies are likely multiple, reflecting the greater case complexities and morbidities associated with treating these cancers. Combined modality treatment for rectal cancer increases both acute and late morbidity, and tri-modal treatment is often difficult for patients to endure. Various chemoradiotherapy regimes have been the standard of care for rectal cancer since the 1990s, and lower concordance is not surprising given conflicting information from trials and the large volumes of evidence that need to be incorporated into decision making.[6,18,19] Furthermore, many guideline recommendations for patients with high-risk stage B/C rectal cancers are to generally treat them alike. Many experts question whether these patients should be treated collectively as not all stage B and C cases are at high risk. In addition, the change from postoperative adjuvant to neoadjuvant chemoradiation often leads to down staging and complicates postoperative histopathology stage interpretation, which otherwise may have been more relevant than preoperative staging.[20] We were unable to determine from our database whether there was a complete clinical response following neoadjuvant chemoradiation therapy for rectal cancer, although it is possible that this may have applied for some of the patients who did not have surgery following this treatment regimen.

The classification and treatment of upper rectal and rectosigmoid cancers as a colon or rectal cancer can also affect interpretation of need for adjuvant therapy as was evident in our study with only 16% of these cancers receiving radiotherapy. In the 2010 national survey of Australasian colorectal surgeons, 53% of surgeons reported that they would not offer preoperative therapy for high-risk upper rectal cancer.[18] It was noted in the survey that treatment differences in Australasia may reflect varying radiological expertise in staging, patient preferences, access to resources, and oncology unit practices.[18] A study in New South Wales elected not to include rectosigmoid cancers when assessing receipt of adjuvant care due to controversies as to how they should be treated.[7]

Our data show a trend towards neoadjuvant therapy, reflecting the end of the postoperative era for rectal adjuvant therapy in the mid-2000s.[3] Adjuvant therapy recommendations are based on trial evidence, including evidence on whether preoperative radiation can be omitted for selected patients,[21] and non-surgical chemoradiation provided with an otherwise "wait and watch" approach for locally advanced rectal cancers.[22,23] The capacity of clinical registries to monitor these different radiotherapy regimes will be important in monitoring and assessing evidence-based clinical outcomes as they are put into practice.

Clinical practice guidelines are not prescriptive, and reasons for departing from guideline recommendations are multifaceted. Patient characteristics such as disease stage, co-morbidity status, sociodemographic factors, and age all need to be considered.[7,24] Undertreatment of older patients has been indicated in several Australian[7,14,25] and international studies,[24,25] with lower referrals and less receipt of adjuvant therapy. However, there is evidence of change with older patients now increasingly receiving adjuvant chemotherapy for higher risk disease.

In this study, we lacked data on the numbers of patients offered adjuvant therapy who refused it. Several studies have shown treatment discordance of 10% to 20% associated with factors such as increased age, co-morbidity, and patient refusal.[14,15,26,27] Capturing this information in clinical cancer registries would provide important insight into possible explanations around receipt of adjuvant care.

The optimal time interval from surgery to start of adjuvant therapy has been evaluated in trials, with conflicting results. Recent studies and a meta-analysis suggest worse outcomes when adjuvant therapy for stage C colon cancer is delayed for more than 8 to 12 weeks.[28,29] Delayed initiation of adjuvant therapy is now being used as a key quality measure of care in Australia.[30] In our study, most stage C colon cancer cases started adjuvant chemotherapy within the recommended 8 weeks of surgery.

For rectal cancers, the optimal interval to surgery with neoadjuvant chemoradiotherapy or adjuvant radiotherapy has not been established, although the Royal Marsden Hospital trial is evaluating results and the French Greccar 6 trial has recently reported on intervals ranging from 6 to 12 weeks.[31] In the Greccar trial, there was a significant increase in the overall morbidity rate in the 11-week group (as compared with the 7-week group) due to complications.[32] In our study, rectal cases received this therapy within 8 weeks, consistent with current practice evidence. Although we were not able to identify short-course radiotherapy within the historical SACCR registry system, it is likely that some who received only neoadjuvant radiotherapy and rectal surgery had short-course therapy as the median number of days to surgery following radiotherapy was 17 days. SACCR data from 2012 will be able to determine whether radiotherapy was short or long course and whether there was a pathological complete response to neoadjuvant therapy. These and other prognostic and treatment factors will be important in assessing outcomes of evolving rectal cancer treatment regimens.

It is notable that the percentage of CRC cases receiving adjuvant care remained fairly consistent over the 10-year period. Potentially closer guideline alignment could be achieved, with improved clinical outcomes. Adjuvant therapies may be underused for both colon and rectal cancers, and routine reporting and monitoring should be undertaken to address identified underuse. South Australia clinical cancer registry data from the year 2011 will include details of treatment regimens, reasons for receiving or not receiving surgical and adjuvant therapies, and information on whether MDT reviews were completed. With greater capacity to identify characteristics of those patients who are not receiving adjuvant therapies in line with guideline statements, efforts can be directed at exploring reasons and whether increased use of adjuvant treatment is warranted. Clinician input into improved data item collections including the additional information highlighted from this study will be important in assessing new national treatment guidelines for CRC currently being drafted.

Limitations of this study include a lack of information on patient co-morbidity and choice. Also, we did not have data regarding oncologist or surgeon recommendations for individual patients, and it could be that older patients and their families are more likely to reject multimodality treatment. This was a retrospective hospital-based study, and it could be that only the more complicated cases from non-metropolitan areas were seen at the major cancer centres and thus treatment patterns for those from non-metro areas are not representative.

Notwithstanding the limitations of this study, there were several important strengths. This included 10 years of clinical treatment information from major referral centres, with little missing data. It provides a benchmark on the timing and receipt of adjuvant therapy for CRC against which future practices can be compared especially for older age groups. With greater capacity to identify characteristics of those patients who are not receiving adjuvant therapies in line with guideline statements, efforts can be directed at exploring reasons and whether increased use of adjuvant therapy is warranted. Future research should include measures of morbidity and address any unwarranted disparities in cancer management.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1. Australian Institute of Health and Welfare. *Cancer Survival and Prevelance in Australia: Period Estimates from 1982 to 2010*. Canberra: AIHW; 2012.
2. Roder D, Karapetis CS, Wattchow D, et al. Colorectal cancer treatment and survival: the experience of major public hospitals in South Australia over three decades. *Asian Pac J Cancer Prev*. 2015;16(6):2431-2440.
3. Michael M, Zalcberg JR. Adjuvant Therapy for Colorectal Cancer. *Cancer Forum*. 2014;38(1):44-52.
4. Adjuvant Therapy for Patients with Colon and Rectum Cancer. *National Institutes of Health Consensus Statement 1990*. Vol 8. Washington, DC: U.S. Government Printing Office; 1990:1-25.

5. Jorgensen ML, Young JM, Dobbins TA, Solomon MJ. Predictors of variation in colorectal cancer care and outcomes in New South Wales: a population-based health data linkage study. *Med J Aust*. 2014;200(7):403-407.
6. Hong JS, Young CJ, Solomon MJ. Observational study of decision making concerning radiotherapy in rectal cancer. *Int J Surg*. 2014;12(5):390-393.
7. 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? *J Geriatr Oncol*. 2014;5(3):323-330.
8. Coory MD, Ho T, Jordan SJ. Australia is continuing to make progress against cancer, but the regional and remote disadvantage remains. *Med J Aust*. 2013;199(9):605-608.
9. Beckmann KR, Bennett A, Young GP, Roder DM. Treatment patterns among colorectal cancer patients in South Australia: a demonstration of the utility of population-based data linkage. *J Eval Clin Pract*. 2014;20(4):467-477.
10. Morris MPC, Fritschi L, Iacopetta B. Failure to complete adjuvant chemotherapy is associated with adverse survival in stage III colon cancer patients. *Br J Cancer*. 2007;96:701-707.
11. Marshall JLHD, de Gramont A, Hochester HS, Lenz H, Ajani JA, Goldberg RM. Adjuvant therapy for stage II and III colon cancer: consensus report of the International Society of Gastrointestional Oncology. *Gastrointest Cancer Res*. 2007;1(4):146-154.
12. van Gijn W, Marijnen CA, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12(6):575-582.
13. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol*. 2005;23(24):5644-5650.
14. The National Colorectal Cancer Care Survey. In: CGU, ed. *Australian Clinical Practice in 2000*. Melbourne: Commonwealth of Australia; 2002:1-124.
15. Heong VJM, Wong HL, McKendrick J, et al. Delivery and effectiveness of adjuvant therapy for stage III colonic cancer in routine clinical practice. *J Clin Oncol*. 2014;32(15):e14540
16. Heriot A, Hunter A, Platell C, et al. The bi-national colorectal cancer audit report. Hawthorn, VIC. 2015.
17. Harrison JD, Solomon MJ, Young JM, et al. Patient and physician preferences for surgical and adjuvant treatment options for rectal cancer. *Arch Surg*. 2008;143(4):389-394.
18. Ooi K, Frizelle F, Ong E, et al. Current Management in preoperative therapy and surgical management of locally advanced rectal cancer: a bi-national survey. *Colorectal Dis*. 2011;14:814-820.
19. Gerard JP, Andre T, Bibeau F, et al. Rectal cancer: French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). *Digestive and liver disease: official journal of the Italian Society of Gastroenterology and the Italian Association for the Study of the Liver*. Jan 20 2017.
20. Maas MNPJ, Valentini V, Crane CH, et al. Adjuvant chemotherapy in rectal cancer: defining subgroups who may benefit after neoadjuvant chemoradiation and resection. *Int J Cancer*. 2015;137:212-220.
21. Weiser MRFA, Schrag D, Boughey JC, You N. Progress in the PROSPECT trial: precision treatment for rectal cancer? *Bull Am Coll Surg*. 2015;100(4):51-52.
22. Maas MB-TRGH, Lambregts DMJ, Nelemans PJ, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol*. 2011;29:4633-4640.
23. Habr-Gama AJGPS, Perez RO. Nonoperative management of rectal cancer: identifying the ideal patients. *Hematol Oncol Clin N Am*. 2015;29:135-151.
24. Chagpar R, Xing Y, Chiang YJ, et al. Adherence to stage-specific treatment guidelines for patients with colon cancer. *J Clin Oncol*. 2012;30(9):972-979.
25. Young JM, Leong DC, Armstrong K, et al. Concordance with national guidelines for colorectal cancer care in New South Wales: a population-based patterns of care study. *Med J Aust*. 2007;186(6):292-295.
26. Becerra AZ, Probst CP, Tejani MA, et al. Opportunity lost: adjuvant chemotherapy in patients with stage III colon cancer remains underused. *Surgery*. 2015;158(3):692-699.
27. van Erning FNJ-HM, Creemers GJ, Pruijt HFM, et al. Deciding on adjuvant chemotherapy for elderly patients with stage III colon cancer: A qualitative insight into the perspectives of surgeons and medical oncologists. *J Geriatr Oncol*. 2015;6(3):219-224.
28. Biagi JJ, Raphael MJ, Mackillop WJ, Kong W, King WD, Booth CM. Association between time to initiation of adjuvant chemotherapy and survival in colorectal cancer: a systematic review and meta-analysis. *JAMA*. 2011;305(22):2335-2342.
29. Klein M, Azaquoun N, Jensen BV, Gogenur I. Improved survival with early adjuvant chemotherapy after colonic resection for stage III colonic cancer: A nationwide study. *J Surg Oncol*. 2015;112(5):538-543.
30. Victoria State Government. Guidelines for timely initiation of chemotherapy. In: Services DoHH, ed. *A Proposed Framework for Access to Medical Oncology and Haematology Cancer Clinics and Chemotherapy Services in Victoria*. Melbourne: Victorian Government; 2015.
31. Chadi SA, Berho M, Wexner SD. Surgeon perspectives on the use and effects of neoadjuvant chemoradiation in the treatment of rectal cancer: a comprehensive review of the literature. *Langenbecks Arch Surg*. 2015;400(6):661-673.
32. Lefevre JH, Mineur L, Kotti S, et al. Effect of Interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: a multicenter, randomized, controlled trial (GRECCAR-6). *J Clin Oncol*. 2016.

SUPPORTING INFORMATION

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