Rectal cancer treatment and outcomes in elderly patients treated with curative intent

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Abstract. The elderly population comprises a significant proportion of patients diagnosed with rectal cancer. However, there is a lack of evidence to guide treatment decisions in this group. Thus, this multicentre study compares the histopathology, treatment patterns and outcomes between the elderly and young populations with non-metastatic rectal cancer. The present study reported on the clinicopathological variables, treatment modalities and survival outcomes in 736 patients diagnosed with non-metastatic rectal cancer between 2006 and 2015. Patients were divided into the following two groups, <70 and ≥70 years of age, which were compared using Chi-square and survival outcome analysis using Kaplan-Meier. Elderly patients made up nearly half of the cohort and were less likely to undergo trimodality therapy or be discussed in a multidisciplinary meeting. Surgery in the elderly patients was associated with increased mortality. Elderly patients had worse cancer-specific survival (75 vs. 85%), which was particularly evident in stage III disease (hazard ratio, 2.1). Elderly patients in this subgroup treated with trimodality therapy had similar survival outcomes to younger patients. Elderly patients with locally advanced rectal cancer comprise a large proportion of the patient cohort. Consideration should be given for trimodality therapy in this group, taking into account biological age, especially in the context of increasing life expectancy and improvement in the management of age-related comorbidities.

Introduction

Colorectal cancer is the third and second most common cancer in males and females respectively (1). Rectal cancers comprise a third of colorectal cancer cases and more commonly affects the elderly with a peak incidence at 80-84 years (2).

Management of non-metastatic, locally advanced rectal cancer is challenging and requires multidisciplinary care. Elderly patients are at risk of aged-based disparities in cancer treatment, which may include being under-treated due to their chronological age, or over-treated for their degree of frailty (3). It is often challenging for the treating physician to find the optimal balance between attaining good disease control and limiting the toxicities of treatment for the elderly patient who may also have competing comorbidities. Data to guide treatment of elderly patients with rectal cancer is limited as the elderly patients are often under-represented in prospective clinical trials (4). The optimal treatment approach in this group will likely become even more nuanced with the gradual paradigm shift toward non-operative approaches in locally advanced rectal cancer (5).

The current standard surgical management of rectal cancer involves performing a total mesorectal excision (TME) for improved local control of disease and survival (6,7). Other operative approaches for selected patients with low risk early rectal cancers include transanal endoscopic microsurgery (TEM) and local excision (8,9). For locally advanced rectal cancer (clinical ≥T3 or node positive), trimodality therapy consisting of neoadjuvant chemoradiotherapy followed with surgery, with adjuvant post-operative chemotherapy, is the current standard of care (10). Trimodality therapy has been shown to have a survival benefit in elderly patients. Cancer specific survival

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was shown to be 70% in patients aged >75 who received neoadjuvant therapy, compared to 52% with surgery alone and 60% with adjuvant therapy (11). Multiple studies have found that older patients are less likely to receive neoadjuvant therapy, and that this is associated with poorer cancer-specific survival (12-14). One study found that each 5 years over the age of 70 was associated with a 37% increase in cancer-related mortality (13).

The reasons for a lower uptake of trimodality therapy in the older patients is multifactorial, including an increased incidence of treatment-related complications. The literature is divided on this, with some studies demonstrating an increase in complication rates (15-17), and some reporting a good tolerance of treatment (18-20).

Taking the evidence into account, the literature suggests that selected elderly patients should be treated in the same way, if comorbidity allows (21-23). The likelihood of initiation of therapy was found to be 22% lower in elderly patients, even after adjusting for comorbidities and other variables (24).

There is also data to suggest that elderly patients may have a different biology to younger patients. Patients over the age of 75 were found to have a lower likelihood of having distant metastases (12) and less advanced stage at presentation (13).

Given the lack of clarity in the literature, we aimed to examine the treatment patterns and outcomes of the elderly population with non-metastatic rectal cancer.

Materials and methods

Study population. The study received approval from the South Western Sydney Local Health District and the Illawarra Shoalhaven Local Health District ethics committees. The study was performed in accordance with the Declaration of Helsinki. The need for informed consent was waived due to the low and negligible risk, and retrospective nature, of the work.

We utilised data from prospectively collated electronic records to identify patients with a histological diagnosis of rectal adenocarcinoma from 2006-2015, treated in the South Western Sydney and Illawarra Shoalhaven Local Health Districts, Australia. Patients with metastatic disease at diagnosis were excluded. Stage of disease was based on the 8th edition of the American Joint Committee on Cancer and College of American Joint Pathologists (AJCC) (25). Staging was based on clinical stage in patients undergoing neoadjuvant therapy, or pathological stage for patients who had surgery upfront. Clinicopathological variables, treatment modalities, recurrence and survival data were analysed.

Relapse-free survival was defined as the date of diagnosis to recurrence locally or distantly. Cancer specific survival was defined as date of diagnosis to death from rectal cancer. Overall survival was defined as the date of diagnosis to death from any cause. Patients who had not recurred and are still alive were censored at the date of last follow up.

Statistical analysis. Clinicopathological factors and treatment utilisation rates between patients <70 and ≥70 years were compared using Chi-Square. Median values for survival and corresponding 95% confidence intervals (CI) were calculated using Kaplan-Meier methods, and the log rank test was used to calculate P-values. Unadjusted and multivariable Cox proportional hazards regression analyses were used to estimate the association of age with survival outcomes, and to calculate corresponding hazard ratios (HRs) and 95% confidence intervals. The following variables were included in the multivariate model: Age, grade, lymphovascular invasion, perineural invasion, TNM stage, and receipt of adjuvant treatment. All statistical analyses were performed using SAS 9.2 software (SAS Institute, Inc.).

Results

Clinicopathological variables. We identified 736 patients with localized (stage I-III) rectal cancer, with median follow-up of 3.4 years. Of these, 326 (44.2%) were ≥70 years (median age at diagnosis 67 years, range 21-94). Elderly patients were more likely to present with earlier stage disease (stage III 47.6 vs. 57.1%, P=0.03), but there were no differences in other histopathological variables with age (Table I).

Treatment modalities. Elderly patients were more likely to be treated with a non-operative approach across all stages (7.4 vs. 2.0%, P=0.0014). In the management of stage I rectal cancer, a small percentage of elderly patients were treated non-operatively whilst all patients <70 years had curative intent surgery (8.8 vs. 0%, P=0.0079). In patients with stage III disease, elderly patients were more likely to be treated with surgery alone (25.2 vs. 4.3%, P<0.001), less likely to receive neoadjuvant (36.8 vs. 54.3%, P=0.007) or adjuvant therapy (47.1 vs. 79.1%, P<0.001). These results are shown in Table II. Two hundred and eight patients received neoadjuvant chemoradiotherapy and only 4 (2%) patients did not complete the entire radiotherapy course. Of these, 3 patients were <70 years and 1 patient was ≥70 years.

Surgical modality also differed with age, with the elderly patients less likely to undergo anterior resection and more likely to have a Hartmann's procedure (P<0.0001). The elderly cohort were also more likely to die within 30 days of surgery (P=0.0014) and less likely to be discussed at a multidisciplinary meeting (P=0.01), as depicted in Table I. The majority of post-operative deaths were from emergency surgeries for acute presentations such as bowel perforation.

Relapse and survival data. Overall survival was poorer in the elderly cohort (5 year overall survival 52 vs. 82%, P<0.0001), Fig. 1A. Univariate analyses for overall survival showed age, grade, presence of lymphovascular or perineural invasion, stage and adjuvant therapy to be significant predictors (Table III). Age, tumour grade, perineural invasion and adjuvant treatment remained significant in multivariate analyses.

Cancer specific survival was also poorer in the elderly cohort (5 year cancer specific survival 75 vs. 85%, P=0.008), Fig. 1B. For cancer-specific survival, age and histopathological variables were significant, but treatment modality did not impact outcomes in multivariate analysis (Table III).

Relapse-free survival was affected significantly by grade, lymphovascular and perineural invasion, as well as stage

Table I. Clinicopathological characteristics, surgical management and outcomes stratified by age.

Clinicopathological characteristics	Age, years, n (%)		Total, n (%)	P-value
	<70	≥70		
Total	410 (66.0)	326 (44.0)	736 (100.0)	
Sex, male	269 (65.6)	202 (62.0)	471 (64.0)	0.3000
TNM stage				
I	77 (18.8)	80 (24.5)	157 (21.3)	0.0300
II	99 (24.1)	91 (27.9)	190 (25.8)	
III	234 (57.1)	155 (47.6)	389 (52.9)	
Lymphovascular invasion[a]	82 (20.8)	62 (21.3)	144 (21.1)	0.8700
Perineural invasion[b]	50 (13.2)	30 (10.8)	80 (12.2)	0.3700
Positive margin[c]	21 (5.3)	16 (5.5)	37 (5.4)	0.3900
Grade 3[d]	37 (9.2)	28 (9.2)	65 (9.2)	0.9800
Discussed at MDT	222 (59.5)	155 (50.2)	377 (55.3)	0.0100
Surgery[e]				
Anterior resection	271 (66.6)	175 (54.2)	446 (61.1)	<0.0001
APR	93 (23.9)	81 (25.1)	174 (23.8)	
Hartmann's procedure	6 (1.5)	19 (5.9)	25 (3.4)	
Local Resection	9 (2.2)	21 (6.5)	30 (4.1)	
Other, including palliative surgery	20 (4.9)	3 (0.9)	23 (3.1)	
No surgery	8 (2.0)	24 (7.4)	32 (4.4)	0.0014
Death within 30 days of surgery	0 (0.0)	8 (2.5)	8 (1.1)	0.0014

[a]52 patients missing; [b]80 patients missing; [c]52 patients missing; [d]32 patients missing; [e]six patients missing; APR, abdominoperineal resection; MDT, multidisciplinary meeting; TNM, tumour/node/metastasis staging.
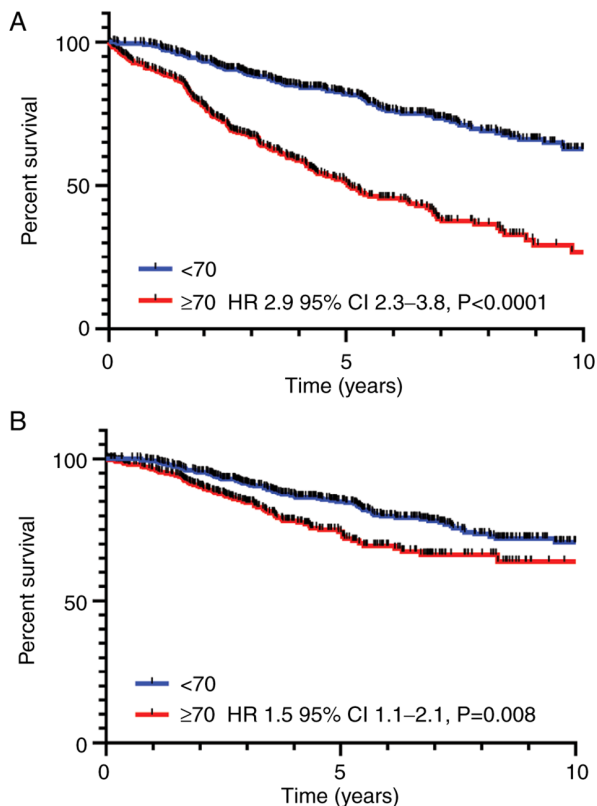

Figure 1. (A) Kaplan-Meier analysis for overall survival in patients ≥70 (n=326) vs. <70 years (n=410) of age. (B) Kaplan-Meier analysis for cancer-specific survival in patients ≥70 (n=326) vs. <70 years (n=410) of age. HR, hazard ratio; CI, confidence internal.

(Table IV). Use of neoadjuvant and adjuvant therapy predicted for worse survival in univariate analyses but were not significant in multivariate analyses.

Cancer-specific survival stratified by age. Elderly patients with stage III disease have worse outcomes compared to younger patients (Table V). However, elderly patients who received neoadjuvant +/- adjuvant therapy did not have significantly different outcomes compared to younger patients.

Summary of salient findings. Elderly patients composed almost half of the cohort, and presented with earlier stage disease. They were less likely to undergo trimodality therapy or discussed in a multidisciplinary meeting. Surgery in the elderly patients was more commonly a Hartmann's procedure, and surgery was associated with increased immediate post-operative mortality. Elderly patients had worse overall survival and cancer-specific survival, particularly evident in stage III disease. Elderly patients in this subgroup treated with trimodality therapy had similar survival outcomes to younger patients.

Discussion

Our study found that almost half of patients with non-metastatic rectal cancer undergoing treatment were over the age of 70. Although the majority (>90%) of elderly rectal cancer patients were treated with curative intent, this was significantly less than in younger patients. Elderly patients were

Table II. Treatment modalities stratified by stage.

A, Stage I (n=157)

| Treatment modalities | Age, years | | P-value |
	<70	≥70	
Total	77	80	
Non-operative approach	0	7	
Curative resection	77	73	0.0079
Surgery only	74	70	0.0510
Neoadjuvant therapy	3	1	0.2900
Adjuvant therapy	2	2	0.9600

B, Stage II (n=190)

| Treatment modalities | Age, years | | P-value |
	<70	≥70	
Total	99	91	
Non-operative approach	5	7	
Curative resection	94	84	0.4500
Surgery only	29	59	<0.0001
Neoadjuvant therapy	52	22	<0.0001
Adjuvant therapy	34	10	0.0001

C, Stage III (n=389)

| Treatment modalities | Age, years | | P-value |
	<70	≥70	
Total	234	155	
Non-operative approach	5	16	
Curative resection	229	139	0.0005
Surgery only	10	39	<0.0010
Neoadjuvant therapy	127	57	0.0070
Adjuvant therapy	185	73	<0.0010

less likely to receive trimodality therapy or be discussed in a multidisciplinary meeting. The more conservative approach toward treatment in the elderly may be largely due to the uncertainty around clinical decision making in this group, as they are largely excluded from clinical trials. In addition, the elderly have competing comorbidities which may complicate treatment. The elderly group was also less likely to undergo an anterior resection, and more likely to undergo a Hartmann's procedure or abdominoperineal resection. Surgery was associated with a higher death rate within 30 days post-operatively, albeit rates are still low (2.5%) with most of these being emergency surgeries for acute presentations such as bowel perforation.

In this study, the overall survival and cancer specific survival for elderly patients with non-metastatic rectal cancer was significantly worse compared to younger patients. In stage III patients, we found that cancer-specific outcomes were more than two times poorer compared to younger patients. However, in the subgroup treated with trimodality therapy, outcomes were not inferior to the younger patients. These findings are consistent with previous studies in the literature which have reported lower utilisation of trimodality therapy in the elderly patients (12-14). The literature also reports inferior cancer specific outcomes in the older population (11,13). However we did not find significant differences in recurrence rates in the elderly patients, suggesting that cancer specific survival may potentially be impacted by variable treatment modalities at the time of recurrence, or alternatively differences in surveillance post curative intent therapy.

The elderly population in our study presented with earlier stage disease which may reflect a difference in tumour biology

Table III. Univariate and multivariate analyses for overall survival and cancer-specific survival.

A, Overall survival

Clinicopathological characteristics	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age <70, years	1.0			
Age ≥70, years	2.9 (2.3-3.8)	<0.0001	2.6 (2.0-3.5)	<0.0001
Grade 1-2	1.0			
Grade 3	1.8 (1.3-2.6)	0.0010	1.5 (1.0-2.2)	0.0420
Lymphovascular invasion	1.6 (1.2-2.1)	0.0040	1.3 (0.9-1.8)	0.1600
Perineural invasion	2.1 (1.5-2.8)	<0.0001	2.2 (1.6-3.2)	<0.0001
TNM stage				
I	1.0	0.0500	1.0	0.2800
II	1.5 (1.1-2.2)		1.4 (0.9-2.1)	
III	1.2 (0.9-1.7)		1.4 (0.9-2.2)	
Adjuvant treatment	0.6 (0.4-0.7)	<0.0001	0.6 (0.5-0.9)	0.0045
Neoadjuvant treatment	0.9 (0.7-1.1)	0.3600	1.0 (0.8-1.4)	0.9600

B, Cancer-specific survival

Clinicopathological characteristics	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age ≥70, years	1.5 (1.1-2.1)	0.0080	1.5 (1.0-2.1)	0.0400
Grade 3	2.8 (1.8-4.2)	<0.0001	2.1 (1.4-3.4)	0.0008
Lymphovascular invasion	2.1 (1.5-3.2)	<0.0001	1.5 (1.0-2.3)	0.0400
Perineural invasion	2.6 (1.7-3.9)	<0.0001	1.9 (1.2-2.9)	0.0040
TNM stage				
I	1.0	<0.0001	1.0	0.0020
II	7.3 (3.1-17.1)		6.2 (2.2-17.7)	
III	7.2 (3.1-16.3)		6.7 (2.3-19.6)	
Adjuvant treatment	1.04 (0.8-1.4)	0.8000	0.8 (0.5-1.2)	0.3400
Neoadjuvant treatment	1.3 (0.9-1.8)	0.1200	1.1 (0.8-1.6)	0.6000

HR, hazard ratio; CI, confidence interval; TNM, tumour/node/metastasis staging.

Table IV. Univariate and multivariate analyses for relapse-free survival.

Clinicopathological characteristics	Univariate HR (95% CI)	P-value	Multivariate HR (95% CI)	P-value
Age ≥70	0.9 (0.7-1.2)	0.5000	1.0 (0.7-1.3)	0.9900
Grade 3	2.1 (1.5-3.2)	<0.0001	1.9 (1.2-2.8)	0.0030
Lymphovascular invasion	1.9 (1.4-2.5)	<0.0001	1.4 (1.0-2.0)	0.0400
Perineural invasion	2.2 (1.5-3.1)	<0.0001	1.7 (1.1-2.4)	0.0108
TNM stage				
I	1.0	<0.0001	1.0	0.0030
II	3.4 (2.0-5.8)		2.9 (1.6-5.5)	
III	3.8 (2.3-6.2)		2.7 (1.4-5.1)	
Adjuvant treatment	1.5 (1.2-2.0)	0.0030	1.1 (0.8-1.6)	0.6000
Neoadjuvant treatment	1.5 (1.2-2.0)	0.0030	1.2 (0.9-1.6)	0.4000

HR, hazard ratio; CI, confidence interval; TNM, tumour/node/metastasis staging.

Table V. Univariate analyses of cancer-specific survival stratified by age.

Stages	Univariate HR (95% CI)[a]	P-value
Stage I	0.8 (0.1-4.5)	0.8000
Stage II	1.1 (0.6-1.9)	0.8000
Stage III	2.1 (1.4-3.2)	0.0002
Stages II/III and received neoadjuvant therapy[b]	1.4 (0.8-2.4)	0.2600
Stages II/III and received neoadjuvant and adjuvant therapy[c]	1.4 (0.7-3.2)	0.3200

[a]≥70 vs. <70 years; [b]n=254 (176 vs. 78); [c]n=146 (112 vs. 34); HR, hazard ratio; CI, confidence interval.

or be attributed to incidental findings whilst screening for other conditions. This is consistent with some studies in the literature (12,13). A study exploring the genomic makeup of colorectal tumours found that older patients, defined as ≥70, had a greater index of genetic mutations, and a higher incidence of KRAS and BRAF mutations but less PTEN/PIK3CA mutations (26).

Limitations of this study include its retrospective nature, and the inability to assess the benefits of treatment due to selection bias. Fitter patients are expected to be selected to undergo adjuvant therapy thereby affecting overall survival, and patients with poor biology or very locally advanced disease are expected to undergo trimodality therapy hence translating to worse cancer specific outcomes. We recognise that we did not collect data on comorbidities and performance status which may impact on treatment pattern selection. Future research focused on the geriatric population will require information on comorbidities, nutritional status, cognitive status, and can employ the use of geriatric screening tools.

The toxicities and morbidity associated with trimodality therapy for locally advanced rectal cancer impact deliverability, especially in the elderly population. These patients are often excluded in clinical trial populations and hence the best management strategies and outcomes of treatment are unclear. There is also a shift towards a non-operative approach in the treatment of locally advanced rectal cancer (5), making treatment decision making in the older patients even more nuanced. Our study adds valuable insight into the treatment practices and outcomes in these patients, which comprise a large proportion of the patient population. Consideration should be given into deciding whether an 'elderly' patient should receive trimodality therapy, depending on their biological age and comorbidities, and not purely on chronological age alone. Elderly patients would benefit from being discussed in a multidisciplinary meeting. This is especially the case as life expectancy continues to rise, chronic illnesses are better managed, and definitions of the older patient are likely to shift upwards with time.

Acknowledgements

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

SK, KJW, DB and SHSL designed and conceived the present study. SK, KJW, DB, WC, WN, JC, EN, ML, KW, LB, RW, SP, CSL and SHSL were all responsible for the provision of patient materials and data collection. SK, KJW, DB and SHSL performed data analysis and interpretation. SK, KJW and DB confirm the authenticity of all the raw data. All authors wrote the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the South Western Sydney Local Health District (approval no. HREC/12/LPOOL/102) and the ethics committee of the Illawarra Shoalhaven Local Health District (approval no. LNR/15/WGONG/61). This study was performed in accordance with the Declaration of Helsinki. The need for informed consent was waived due to the low and negligible risk, and retrospective nature of the work.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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