Outcomes of young patients diagnosed with locally advanced rectal cancer

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Background: The incidence of rectal cancer is higher in the older population. In developed nations, there has been a rise in incidence in young onset colorectal cancer (CRC). We examined the outcomes of locally advanced rectal cancer (LARC) in younger patients (yRC) compared with older patients, using a retrospective audit.

Methods: All cases of LARC referred to two tertiary referral cancer centres in Western Sydney were examined. Patient demographics, presenting symptoms, treatment, relapse free survival (RFS), overall survival (OS) and progression free survival (PFS) were obtained. Under 50 years old was used as the cut-off age for defining yRC.

Results: All 145 consecutive patients were treated for LARC, including 28 in the yRC and 117 in the older patient group. Median follow-up was 54 months. yRC were more likely to complete neoadjuvant therapy (100% *vs.* 86%; P=0.032) and to undergo more extensive surgical procedures (24% *vs.* 2%, P<0.0001). yRC were more likely to have microsatellite high (MSI) tumours (30% *vs.* 4.7%; P=0.003). yRC demonstrated significantly poorer RFS compared with the standard group (HR 2.79; median RFS 4.67 *vs.* 16.02 months; P=0.023). In the relapsed setting, yRC had poorer PFS compared with the standard group (median PFS 2.66 *vs.* 9.70, P=0.006, HR 3.04). A difference in OS was also seen between the two groups, with yRC demonstrating poorer OS (median OS 40.46 *vs.* 58.26 months, HR 3.48, P=0.036).

Conclusions: Patients under 50 years with LARC are more likely to have MSI tumours with a more aggressive disease course and poorer RFS, PFS and OS. Initiatives to improve early detection of these patients may improve outcomes. Further research is necessary to understand this disease and optimise its treatment.

Keywords: Rectal cancer; colorectal cancer (CRC); rectal bleeding; cancer; neoadjuvant treatment

Introduction

The incidence of colorectal cancer (CRC) remains high in Western countries despite the overall decline in incidence worldwide (1-3). It is the third most diagnosed cancer worldwide and the second leading cause of cancer-related deaths after lung cancer (4). According to the world health organisation (WHO), in 2018, the age-standardised incidence of CRC was highest in developed countries most notably Australia and New Zealand, followed by Europe and North America (5).

The last two decades have seen significant improvements in CRC early detection, therapies, and survival, owing to a rise in translational and clinical research in the field (6-11). Despite this, locally advanced and metastatic disease are still associated with high mortality, with a 5-year mortality rate of 30% for stage III CRC and 86.6% for stage IV disease. The majority of patients with stage IV CRC succumb to the disease over a median of 24 months (12,13).

Whilst the incidence of CRC is skewed towards an older patient population, a rise in incidence has been observed in patients younger than 50 years of age (14,15). One third of locally advanced rectal cancer (LARC) patients are younger than 50 (16,17). The prognosis of young onset rectal cancer (yRC) as a subgroup, however, is uncertain as results of retrospective audits to date have either been conflicting (18-20) or have not focussed specifically on rectal cancer (20-22). Another limiting factor is the use of different age limits for defining yRC (23), and often varies in the literature to cut-offs between 35 and 50 years of age. Whilst it is logical to assume a cut-off age of <50 given the fact that most screening programs begin from the age of 50, clear definitions of young onset CRC and very early onset CRC are yet to be formally established (24).

Against this background, our study examines the treatment-related outcomes of LARC (including relapse and mortality) in young versus older patients who receive neoadjuvant radiotherapy. We present the following study in accordance with the STROBE reporting checklist (available at http://dx.doi.org/10.21037/jgo-20-300).

Methods

Patient selection

We conducted a retrospective review of consecutive patients with LARC (defined as Tumour stage of 3 or 4 or Nodal stage of 1 plus any tumour stage) who received neoadjuvant radiotherapy in two tertiary institutions of the Western Sydney Local Health district (WSLHD), Sydney between January 1, 2009 and December 31, 2016. In this study, patients were separated into two groups according to their age at inclusion; the standard group was defined by the age cut-off of ≥50 years old and a yRC group (<50 years old). Patients were included if they had biopsy proven rectal adenocarcinoma and who were eligible for neoadjuvant chemoradiotherapy as determined by their pre-treatment staging on MRI or rigid endoscopy. Exclusion criteria included a histological diagnosis other than adenocarcinoma or mucinous adenocarcinoma, a prior history of CRC diagnosis, incomplete follow-up and if systemic treatment was delivered at other institutions. Patients who presented with *de novo* stage IV rectal cancer and those with an ECOG performance status of IV were also excluded from the analysis. Data were collected retrospectively and analysed anonymously. The study was performed in accordance with the standards of the Declaration of Helsinki (as revised in 2013) and was approved by the institutional ethics board of the Western Sydney Local Health District ethics committee (IBR: 1811-15 QA). No informed consent was required as this was a retrospective audit.

Measures of outcome

The diagnosis of LARC required a combination of tissue biopsy and imaging. All diagnoses were biopsy proven. The extent of disease was confirmed using computed tomography (CT) or magnetic resonance imaging (MRI). All diagnoses were biopsy proven rectal carcinomas including adenocarcinomas, mucinous or signet ring carcinomas. Squamous cell pathologies and sarcomas were excluded from the analysis.

Data was extracted for relapse free survival (RFS), progression free survival (PFS) and overall survival (OS). RFS was defined as the time from initial biopsy proven rectal carcinoma to the first event of local recurrence or metastatic recurrence. PFS was defined as the time from the diagnosis of a first recurrence to the time of progression on first line palliative chemotherapy or death from rectal carcinoma or other causes or censored to the last follow-up time. OS was defined as the time from initial biopsy proven rectal carcinoma to the time of death from rectal carcinoma or other causes or censored to the last follow-up time. RFS and OS were calculated for all patients in the study. PFS was calculated for patients who experienced disease progression.

Other data included in the analysis were patient demographics (age, sex, and comorbidities), clinical

presentation of symptoms, tumour stage at diagnosis, doses of neoadjuvant radiotherapy and duration and whether adjuvant treatment was offered subsequent to their surgery. Completion of neoadjuvant radiotherapy was considered if patients received the full dose of standard radiotherapy for either a planned short or long course treatment. Patients undergoing neoadjuvant long course radiation received 25 daily fractions of RT with or without radio-sensitising 5 fluorouracil (5-FU) based chemotherapy to a total dose of 45 Gy. An optional boost of 5.4 Gy in 3 fractions to a total of 50.4 Gy in 28 days was given as determined by the treating radiation oncologist. Alternatively, patients received a short course of radiotherapy with 5 daily fractions to a total of 25 Gy.

Data analysis included types of surgical procedures. Surgical margins were assessed as involved as follows: for upper rectal tumours, a positive margin was defined as a distal margin of transection of <5 cm; and for mid rectal tumours a distal margin of <1 cm (25). Rates of post-operative complications were also analysed, including infections, anastomotic leak, deconditioning leading to delay in initiation of adjuvant chemotherapy and death within 30 days post-operatively.

Histological features including postoperative stage (according to the AJCC classification, including tumour, node, metastasis), tumour grade and microsatellite instability were analysed. Pathological complete response (pCR) was defined as the absence of residual tumour cells on histopathologic examination of the rectal primary and resected lymph nodes. Other features including sites of recurrence, number of metastases and the types of palliative treatments (surgical, chemotherapy or radiotherapy) were also assessed.

Statistical analyses

Comparisons of the baseline characteristics between the two groups were performed using the χ^2 test for categorical variables and t-test for continuous variables. RFS, PS and OS curves were generated using the Kaplan-Meier method, and differences in the survival rates between the groups were compared by the log-rank test. The Cox proportional hazard model was used to estimate hazard ratios (HRs) and 95% confidence intervals (95% CI) of potential prognostic factors for RFS and OS.

Factors included in the univariate analyses for OS were the following: age, sex, Eastern Cooperative Oncology Group (ECOG) performance status (PS), pre-operative nodal stage, neoadjuvant therapy, histopathology, Lymphovascular invasion (LVI) and perineural invasion (PNI), immunohistochemistry for mismatch repair (MMR), post-operative nodal stage and adjuvant chemotherapy. For the relapsed patients, liver metastases and surgical treatment of metastases were additionally included in univariate analyses. Those cases with missing data relevant to the statistical analysis were excluded from the analysis. Variables with a P value ≤0.5 in the univariate analysis were subsequently included in the multivariate analysis. The cut-off value of continuous variables was determined based on the median value. A two-sided P<0.05 was considered statistically significant. All statistical analyses were performed using IBM SPSS® software platform version 26.

Results

Patient characteristics

Baseline patient characteristics are listed in *Table 1*. From January 1 2009 to December 31 2016, a total of 212 patients presented to our institution with a diagnosis of LARC or *de novo* stage IV rectal cancer. Twenty-three patients were excluded based on the aforementioned exclusion criteria. Of the 189 patients, 44 (23%) patients had *de novo* stage IV disease and were subsequently excluded from the analysis, while145 (77%) patients were treated for LARC. The median age of the study population was 62 (range, 27–91). Median follow-up was 54 months at data cut-off.

The locally advanced cohort comprised 28 (19.3%) yRC patients and 117 (80.7%) were in the standard group (*Table 1*). The median age in yRC group was 42 (range, 27–49), and 64 (range, 50–91 years), in the standard group.

yRC had an even proportion of males and females, whereas the older cohort had a predominantly male population, however this was not statistically significant. Most patients had an ECOG performance status of <2, however the older group were more likely to have a poorer ECOG status (≥2). There were no differences in symptoms at presentation with per rectal bleeding being the most common presenting symptom in both groups, followed by altered bowel habits (constipation or diarrhoea) and anaemia.

No differences were seen in the preoperative staging. Pre-operative MRI and PET scans were used at similar rates in both groups as additional means of assessing for local and distant metastatic disease. yRC were more likely to complete neoadjuvant radiotherapy (100% *vs.* 86%,

Table 1 Baseline demographics, pre-operative, and surgical data for the standard and yRC group

Variable	yRC (n=28)	Standard group (n=117)	P value
Median age, years (range)	42 (27 to 49)	64 (50 to 91)	–
Gender (male/female)	14 (50%)/14 (50%)	70 (60%)/47 (40%)	0.344
ECOG Performance status			0.018
0	25 (89%)	67 (57.3%)	
I	3 (11%)	38 (32.5%)	
II	0 (0%)	6 (5.1%)	
III	0 (0%)	5 (4.3%)	
Missing	0 (0%)	1 (0.85%)	
Symptoms at diagnosis			
Per rectal bleeding	23 (82%)	82 (70%)	0.200
Anaemia	3 (11%)	7 (6%)	0.375
Altered bowel habits	0 (0%)	1 (1%)	0.624
Pre-operative staging			
MRI	24 (86%)	91 (80%)	0.527
PET	27 (96%)	101 (89%)	0.248
Pre-operative stage			0.667
1	0 (0%)	2 (2%)	
2	10 (36%)	35 (30%)	
3	18 (64%)	62 (53%)	
Missing	0 (0%)	18 (15%)	
Completion of neoadjuvant radiotherapy	28 (100%)	100 (85.5%)	0.032
Radiotherapy dose			0.040
Long course	27 (96.4%)	94 (80%)	
Short course	1 (3.6%)	23 (20%)	
Surgical treatment			
No surgical treatment	3 (11%)	24 (21%)	0.232
Surgical treatment			<0.0001
APR	4 (16%)	24 (25.8%)	
LAR	6 (24%)	33 (35.4%)	
ULAR	8 (32%)	32 (34.4%)	
Colectomy/exenteration	6 (24%)	2 (2.2%)	
Other	1 (4%)	2 (2.2%)	
Postoperative complications	5 (20%)	14 (15%)	0.509

P=0.032). yRC patients were more likely to receive long course neoadjuvant radiotherapy (P=0.040). Additionally, the average time to starting radiotherapy from diagnosis for yRC was shorter than that for the standard group (median 3.8 *vs.* 4.7 weeks; P=0.002). However, no differences were observed for time to surgery from completion of neoadjuvant therapy in both groups (median of 7.5 weeks for both, P=0.451).
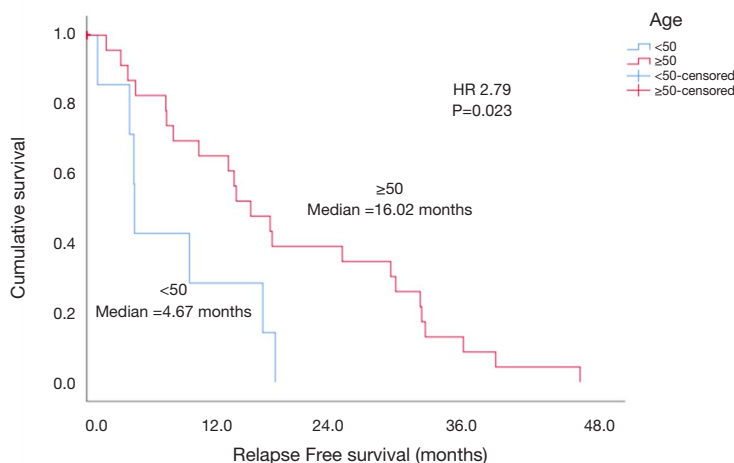
Figure 1 RFS by age. Red: standard group, blue: yRC (P=0.023). RFS, relapse free survival; yRC, younger patients.

Following completion of neoadjuvant radiotherapy, a combined total of 118 (81%) in both groups underwent surgical resection of the primary rectal cancer, including abdominal perineal resection in 24%, low anterior resection in 33% and ultralow anterior resection in 34%. yRC however, were more likely to undergo extensive surgical procedures, including total colectomies and exenterations (24% *vs.* 2%; P<0.0001). There were no differences in the rates of postoperative complications between the two cohorts.

Postoperatively, both groups had comparable histopathology results including overall stage, histology, lymphovascular and perineural invasion. Both achieved the same rates of pCR (8%). However, yRC were more likely to have microsatellite unstable tumours (30% *vs.* 4.7%; P=0.003). Both groups had similar rates of adjuvant chemotherapy use (Table S1).

Survival outcomes

yRC had poorer RFS post neoadjuvant radiotherapy and surgery

Overall, 30 patients relapsed with a median time to relapse of 14 months (range, 1.05–48.22 months). Rates (28% for yRC and 31% in the standard group; Table S1) and patterns of relapse were similar between the two groups. yRC had significantly poorer RFS compared with the standard group (HR 2.79; median RFS 4.67 *vs.* 16.02 months; P=0.023) (*Figure 1*).

Results of the univariate and multivariate analyses

relating to RFS are reported in *Table 2*. In the univariate analysis, factors associated with poorer RFS, other than age, included male gender (HR 2.592, median RFS 10.03 *vs.* 18.13 months; P=0.021) (*Table 2*) as well as lack of chemotherapy use in the adjuvant setting (HR 4.087; median RFS 4.77 *vs.* 18.42 months; P=0.001), whereas post-operative tumour grade, nodal stage and overall stage did not demonstrate a significant effect on RFS on univariate analysis (*Table 2*). Multivariate analysis results are reported in *Table 2*. Male gender and adjuvant chemotherapy use maintained their independent effect on RFS. Age did not remain an independent factor.

Age was not a significant prognostic factor for OS

Age was not a significant prognostic factor for OS (median 93.6 months *vs.* not reached for yRC, P=0.235) (*Figure 2*).

The factors that were significant for poorer OS on univariate analysis were perineural invasion (P=0.003, HR 3.99), and lack of adjuvant chemotherapy (P=0.001) (*Table 3*). Post-operative N-stage and lack of adjuvant chemotherapy use significantly correlated with survival on multivariate analysis (*Table 3*).
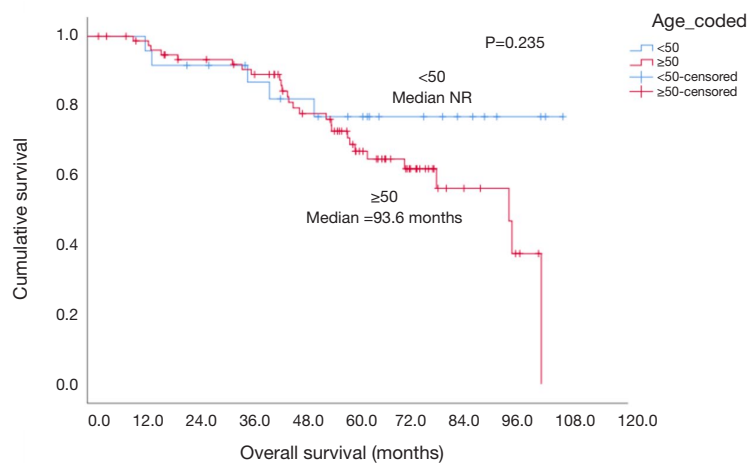
Relapsed disease

yRC with relapsed disease had poorer progression free and OS compared with the standard group

Of the 30 patients who relapsed, 23 patients received palliative chemotherapy, including 7 yRC and 16 in the standard group. There were no statistically significant

Table 2 Univariate and multivariate Cox proportional hazards for relapse free survival

Variable	Univariate analysis	Multivariate analysis
Age (ref: yRC)	P=0.029, HR 2.791, 95% CI: 1.113–6.999	P=0.062, HR 0.076, 95% CI: 0.005–1.139
Gender (ref: male)	P=0.021, HR 2.592, 95% CI: 1.152–5.830	P=0.05, HR 19.5, 95% CI: 2.43–156.34
Lack of adjuvant chemotherapy	P=0.001, HR 4.087, 95% CI: 1.723–9.693	P=0.021, HR 14.065, 95% CI: 1.495–132.33
ECOG	P=0.422	P=0.362
Histopathology (ref: adenocarcinoma)	P=0.141	P=0.072
LVI	P=0.123	P=0.870
PNI	P=0.146	P=0.138
MMR	P=0.118	P=0.941

Figure 2 OS for young onset rectal cancer compared with the standard group (P=0.235). OS, overall survival.

differences in the number or sites of recurrence of relapsed disease in yRC compared with the standard cohort.

A statistically significant difference in the median PFS following palliative chemotherapy was seen, with yRC demonstrating poorer PFS compared with the standard group (median PFS 2.66 *vs.* 9.70, P=0.006, HR 3.04). 26 patients (87%) died following relapse (7/7 in yRC and 19/23 in the standard group, P=0.236). A difference in OS was also seen between the two groups, with yRC demonstrating poorer OS (median OS 40.46 *vs.* 58.26 months, HR 3.48, P=0.036) (*Figure 3*).

Factors associated with OS are summarised in *Table 4*. Surgical resection of metastases improved OS (HR 4.18, median OS 94.2 *vs.* 50.36 months, P=0.016) (*Table 4*). Age, mucinous histology, and surgical treatment of metastases

remained significant on multivariate analysis (*Table 4*).

Discussion

Our study demonstrates that yRC with LARC have poorer survival outcomes compared with older patients despite having a better ECOG performance status, completing neoadjuvant radiotherapy at higher rates, and subsequently undergoing more extensive surgical resections. yRC demonstrated shorter RFS, and in the relapsed setting experienced shorter PFS and resultant shorter OS. yRC was also more likely to have microsatellite unstable tumours. Taken together, these data suggest a more aggressive tumour biology and potentially more resistance to palliative treatments.

Table 3 Univariate and multivariate analyses for overall survival

Variable	Univariate analysis	Multivariate analysis
Age (ref: yRC)	P=0.235	P=0.267
Gender (ref: male)	P=0.606	P=0.354
Post-operative N stage	P=0.020, HR 1.53, 95% CI: 1.07–2.18	P=0.001, HR 2.85, 95% CI: 1.56–5.21
Histopathology (ref: mucinous)	P=0.103	P=0.363
LVI	P=0.082	P=0.672
PNI	P=0.006, HR 2.82, 95% CI: 1.35–5.88	P=0.373
Lack of adjuvant chemotherapy	P=0.001, HR 2.72, 95% CI: 1.51–4.90	P<0.0001, HR 6.45, 95% CI: 2.59–16.08
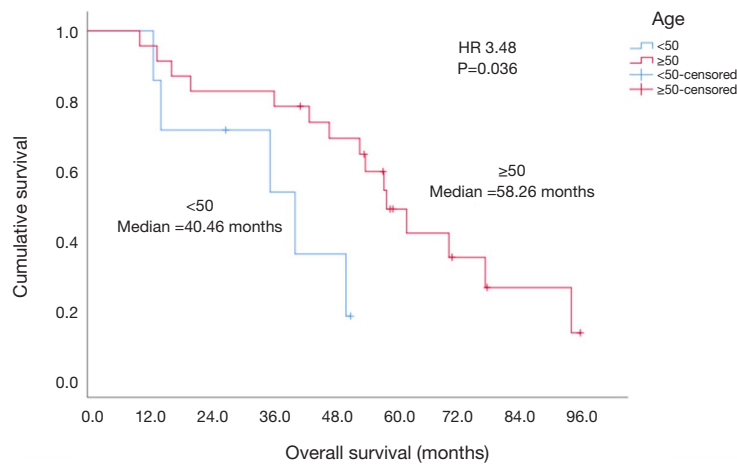
Figure 3 OS for relapsed disease for yRC compared with the standard group. Red: standard group, blue: yRC (P=0.036).

Table 4 Prognostic factors for overall survival in relapsed disease identified by the univariate and multivariate analyses

Variable	Univariate analysis	Multivariate analysis
Age (ref: yRC)	P=0.036, HR 3.96, 95% CI: 1.087–11.151	P=0.030, HR 3.91, 95% CI: 1.14–13.43
Gender (ref: male)	P=0.098	P=0.512
Histopathology (ref: mucinous)	P=0.125	P=0.029, HR 5.69, 95% CI: 1.20–26.52
Liver metastases	P=0.380	P=0.763
Surgical treatment (ref: lack of surgical treatment)	P=0.029, HR 4.113, 95% CI: 1.174–14.414	P=0.030, HR 4.58, 95% CI: 1.16–18.09

Our findings are in keeping with work by Lieu *et al.* who analysed pooled data from 24 different clinical trials of early CRC and demonstrated poorer RFS for younger patients (26). We also corroborate some of the findings by You *et al.* who compared outcomes of both locally advanced and stage IV rectal cancer in patients <50 years to those older than 65 years, who were treated with multimodality therapy. In their study, yRC also had poorer RFS on univariate analysis (19).

Our large dataset of colonoscopies in young patients confirmed the low overall incidence of sporadic CRC in this age group. Young patients were more likely to present

with left sided disease (data not shown). An analysis from the Mayo Clinic registry demonstrated a similar tendency for yCRC to develop left sided tumours (17). All of the young patients diagnosed with rectal cancer in our study were symptomatic and a large proportion had per rectal bleeding as their predominant complaint, a finding also supported by others (27,28). Another study by Kaplan *et al.* also demonstrated similarities in presenting symptoms in adolescents and young adults (AYA) (using a cut-off age of 25 years old) compared with older patients (2). This highlights that young patients do develop CRC without predisposing high risk syndromes and present with similar complaints as older patients.

In our study, significantly more yRC had MSI-high tumours compared with older patients and this may lend an explanation for the poorer outcomes seen in yRC. Lynch-like tumours have a higher preponderance in MSI high rectal primaries (29). Recent retrospective studies have demonstrated that MSI-high patients do not derive benefit from 5-FU based chemotherapy (29-31) possibly due to a lack of DNA mismatch repair enzymes that are required for cell cycle arrest and apoptosis following exposure to 5-FU therapy (32).

Given that we focussed on LARC, our study was not powered to detect significant differences in mucinous and non-mucinous histopathology between the two groups, however, in the relapsed cohort, mucinous histology and yRC were associated with shorter OS on multivariate analysis. Other studies have demonstrated a greater tendency for yCRC to present with mucinous and signet ring adenocarcinomas (2,33,34). These tumours tend to present at later stages, are inherently resistant to standard of care therapies and carry a poorer prognosis (35).

Forecasting by Bailey *et al.* predict a continued rise in CRC incidence for patients younger than 50. By 2023, a diagnosis of 1 in 4 rectal cancers and 1 in 10 colon cancers in this age group is likely to be made (36,37). Whilst microsatellite instability and mucinous pathology lend an explanation for the poorer outcomes seen in this group, they may serve only as surrogate markers. Future retrospective and prospective translational and clinical research in this field should explore biological reasons for the disparities in outcomes in this age group (26,33,38).

Early relapse and poorer PFS secondary to the development of distant metastases were seen in yRC in our study, demonstrating poor response to standard of care therapies. To improve RFS in LARC, recent clinical trials have assessed the use of neoadjuvant systemic chemotherapy with FOLFOX monotherapy or in combination with radiotherapy. Unfortunately, despite an improvement in local disease control, these trials did not translate into improved RFS (39,40). There is preclinical evidence to support the beneficial role of checkpoint inhibitors either administered concomitantly with, or at the end of, radiotherapy in mouse models of colorectal carcinoma (41). This has been taken to clinical trials exploring the addition of immunotherapy to determine whether it augments clinical response to standard pre-operative therapy (ClinicalTrials.gov registry: NCT04293419, NCT03299660, NCT03854799).

The advantage of our population-based study is that it did not rely upon a database for information, rather, detailed data about treatment, morbidity, performance status and other information was obtained. We reviewed data from multiple sites, including two of the largest tertiary referral centres in Sydney, as well as from a larger dataset of colonoscopies, which enabled us to capture all colonoscopies performed and rectal cancers detected. Further, we focussed on LARC as a specific subgroup, the risk of which is rising significantly in incidence in yCRC and remains an area of unmet need.

Due to the study design several limitations exist. Given the retrospective nature of this study, unmeasured confounders may exist, which were not accounted for in this study design. Further, given the small sample size, there may be limitations in detecting small differences in survival between the two cohorts.

Conclusions

Our study provides preliminary data to suggest that young patients with LARC have poorer treatment outcomes compared with older patients. Patients under 50 years with LARC are more likely to have MSI tumours with a more aggressive disease course and in our study demonstrated poorer RFS. Further, yRC with relapsed disease demonstrated poorer PFS and OS. Initiatives to improve early detection of these patients may improve outcomes.

Given the rising incidence of left sided yCRC, which is dominated by rectal primaries, our study highlights the need for further research to understand the biology of the disease and correlate that with measurable outcomes and to identify novel neoadjuvant and adjuvant treatments for locally advanced yRC.

Acknowledgments

Footnote

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Table S1 Postoperative clinicopathologic characteristics for yRC (n=25) compared with standard group (n=74)

Variable	yRC (n=25)	Standard group (n=74)	P value
Histopathology			0.320
Adenocarcinoma	20 (80%)	64 (87%)	
Mucinous adenocarcinoma	5 (20%)	10 (13%)	
Pathological complete response	2 (8%)	7 (8%)	0.937
Lymphovascular invasion	6 (24%)	20 (29%)	0.197
Perineural invasion	4 (14%)	15 (22%)	0.382
MMR deficiency	4/13 (30%)	3/63 (4.7%)	0.003
Nodal stage			0.814
0	11 (44%)	45 (60.8%)	
1	4 (16%)	13 (17.6%)	
2	5 (20%)	14 (18.9%)	
Unknown	5 (20%)	2 (2.7%)	
Overall stage			0.790
I	0 (0%)	1 (1%)	
II	10 (40%)	39 (53%)	
III	9 (36%)	28 (38%)	
Incomplete	6 (24%)	6 (8%)	
Received adjuvant chemotherapy	17 (68%)	49 (66%)	0.595
Relapse	7 (28%)	23 (31%)	0.996
Number of sites of metastases			0.369
1	5 (71.4%)	16 (70%)	
2	0 (0%)	4 (17%)	
≥3	2 (28.6%)	3 (13%)	
Recurrence			0.419
Local	0 (0%)	2 (8.7%)	
Distant	7 (100%)	21 (91.3%)	