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Original Research

The impact of driving time, distance, and socioeconomic factors on outcomes of patients with locally advanced rectal cancer

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ABSTRACT

Objectives: Cancer patients experience disparities due to socioeconomic status (SES) factors. We assessed the impact of SES factors on outcomes in patients with locally advanced rectal cancer (LARC) who received neo-adjuvant chemoradiation (nCRT) and surgery (Sx) in 3 Canadian provinces.
Study design: This study was a multi-institutional retrospective chart review.
Methods: Associations among community characteristics (2016 Canadian Census data), distance and time to the cancer center (mapping software), and outcomes were evaluated using the CHORD multi-institutional database.
Results: 1,064 patients were included. Median age 62, 68% male, 15% lived in a rural community, 19% with median community household income >$50,000 CAD, median community proportion with post-secondary education 66%, 12% lived >100km away, and 18% lived >1 h away.
Factors predictive of worse disease-free survival (DFS) and overall survival (OS) in univariate analysis included driving time >1 h, median community income ≤$50,000 CAD, driving distance >100km, and lower median community proportion with post-secondary education. Driving time >1 h remained significant in multivariate analysis for worse DFS (HR 1.47; 95% CI 1.14–1.90; p = 0.003) and OS (HR 1.60, 95% CI 1.19–2.16; p = 0.002).
Conclusion: Outcomes of patients with LARC undergoing nCRT are negatively associated with increased driving time to the cancer centre.

1. Introduction

Colorectal cancer accounted for 13% of all new cancer cases in Canada in 2017 and represented 12% of all cancer deaths. While rates are declining among older adults, they are increasing among adults younger than 50 years old [1]. Most colorectal cancers arise in the colon, while 30% arise in the rectum [2]. Whereas the stage distribution at diagnosis of colon cancer is relatively uniform, rectal cancers are most often diagnosed as stage III (34%) compared to other stages. Locally advanced rectal cancers (stage II and III) makeup 53% of all rectal cancers at diagnosis [1].

While often discussed together, rectal cancer and colon cancer are separate disease entities. Biologically, the rectum is distinct from the colon due to its distal location outside of the peritoneal cavity. While the proximal colon arises from the midgut embryologically, the rectum arises from the hindgut. Genetically, patients with mismatch repair gene alterations leading to the hereditary nonopolyposis colorectal cancer (HNPCC) syndrome are more likely to develop proximal colon cancers, whereas patients with familial adenomatous polyposis (FAP) are more likely to develop left sided colorectal cancers [3]. BRAF mutations are clearly more likely to occur in the proximal colon than the left colon or rectum, whereas studies of RAS mutation prevalence in the right vs left colon are incongruent, possibly because of differences in the prevalence of RAS mutation subtypes (ie: higher likelihood of KRAS exon 2 mutations in the right colon, and KRAS exon 3 mutations in the rectum) [4–6].

As such, the management of rectal cancers differs from that of colon cancers. Specifically, the treatment of locally advanced rectal cancer often involves the combination of radiotherapy, chemotherapy, and

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surgery [7–12], sometimes followed by further adjuvant chemotherapy [13,14]. In the 2004 landmark trial by Sauer et al. [12], it was demonstrated that chemoradiation given in the neoadjuvant setting prior to curative intent surgery improved local recurrence rates and reduced complication rates when compared with adjuvant chemoradiation. Specifically, 5-year local recurrence rates were 6% vs 13% ($p = 0.006$) and distant recurrence rates were similar at 38% vs 36% ($p = 0.84$). Despite this improvement in treatment, 5-year disease-free survival (DFS) and overall survival (OS) remained suboptimal at 68% and 76%, respectively [12].

As a result of the morbidity and mortality associated with rectal cancer recurrences, studies have investigated predictors of survival. Most studies have assessed pathologic variables and found that tumor stage, lymph node status, circumferential resection margin, and pathologic response to neoadjuvant chemoradiation were associated with survival [12,15–18].

Other studies have investigated the impact of socioeconomic variables on outcomes in rectal cancer and have shown that education, income, marital status, rural status, race, and time/distance from the cancer centre were associated with disparities in outcomes. Specifically, studies have suggested that African- American race, living alone, having lower income, experiencing socioeconomic deprivation, and experiencing a long driving distance/time to the cancer centre were all associated with worse outcomes [19–26]. However, there is a paucity of data addressing the impact of socioeconomic status (SES) factors in rectal cancer in Canada. Canada has a variable climate with several months per year of cold and snowy weather. Canada also has a large geographical land area with great variations in climate across the country. It is unknown if the treatment of rectal cancer in Canada is impacted by SES factors or location of residence.

To determine the social influences on outcomes within our specific Canadian context, we assessed the impact of various SES factors on outcomes of patients with locally advanced rectal cancer (LARC) who received neoadjuvant chemoradiation and surgery in 3 Canadian provinces. We hypothesized that increased driving time and distance from the cancer centre would result in inferior outcomes for our population with LARC due to the nature and intensity of treatment necessitating frequent hospital visits.

2. Methods

2.1. Ethics and conduct

This study was approved by the Research Ethics Boards for all participating institutions. For all jurisdictions, informed consent was waived by the respective research ethics boards. This study was conducted and reported in accordance with the REMARK recommendations [27].

2.2. Setting and patients

This study utilized data from the CHORD Consortium [28], an academic outcomes database enrolling patients with rectal cancer in four Canadian provinces (British Columbia, Alberta, Ontario, and Newfoundland). The CHORD Consortium cohort consists of 1,527 consecutive patients from 2005 to 2013 with a diagnosis of LARC (defined as stage II or III rectal cancer [29]) who underwent curative intent treatment with neoadjuvant chemoradiation followed by surgery. It excludes patients who had a prior malignancy (except for non-melanoma skin cancer), who did not receive surgery, and who received neoadjuvant radiation without chemotherapy. All data in the database has been collected retrospectively from electronic and paper medical records.

CHORD Consortium data utilized in the present study encompassed 3 tertiary care centres: The Ottawa Hospital Cancer Centre in Ottawa, Ontario (ON), The Tom Baker Cancer Centre in Calgary, Alberta (AB), and the British Columbia Cancer Agency in Vancouver, British Columbia (BC). The full CHORD dataset was not utilized due to application of exclusion criteria as outlined below.

2.3. Data collection

Socioeconomic indicators were obtained and evaluated using the six-digit postal code of each patient's primary residence. Travel distance and time to the nearest cancer centre represent an estimate of the distance (in km) and time (in hours) between patients' residential postal code centroid (the central location within the postal code area) and the nearest cancer centres' specific and complete address, calculated using CDXZipStream mapping software [30] which utilizes Bing Maps. Time of day, weather conditions and traffic patterns were not taken into account in the time and distance calculations. Results from CDXZipStream were validated with the Google distance matrix Application Programming Interface (API) [31]. When a cancer centre encompassed multiple geographic sites, the site with the quickest driving time from the patients' primary residence was considered the nearest cancer centre.

Patients were excluded if their six-digit postal code was unavailable, if distance and time to the nearest cancer centre could not be computed by mapping software, or if patients lived more than 300 km or 3 h driving time from the cancer centre (because it was assumed that these patients relocated temporarily for cancer treatment, rendering driving distance and time from their residence inapplicable). The flow diagram in Fig. 1 shows the study exclusion criteria used to define the cohort.

Community socioeconomic information was obtained from the 2016 Canadian census data (Statistics Canada) through postal code linkage to census tracts using the postal code conversion files [32,33]. Socioeconomic information included: rural status, population centre size (small population centre: 1000–29000 people; medium population centre (30000–99999 people; large population centre: more than 100000 people) [28], population density (per square km), community household income (median total income of households for people older than 15 years), and community education (based on a 25% sample aged 25–64, differentiated by three categories: without a high school diploma, with a high school diploma, or with post-secondary education) [34,35]. We computed a derived variable called "community proportion with post-secondary education" based on the percent of people with a post-secondary education in the population sample within the geographic unit. Driving time and distance from the nearest cancer centre were dichotomized at 100km and 1 h respectively. This was based on methodology from previous literature [21,36–38].

Patient characteristics that were included as control variables were: province of residence (BC, AB, ON), age at diagnosis (continuous and dichotomized at 65 years), sex (female, male), body mass index (BMI) (categorized as underweight, normal weight, overweight, obese), distance of tumor to the anal verge, radiotherapy dose (continuous and dichotomized at 46 Gy), Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) [39] (0, 1, 2+), clinical stage (II or III) based on the American Joint Committee on Cancer AJCC) Staging Manual 7th edition [29], pathological stage, type of surgery (low anterior resection [LAR], abdominoperineal resection [APR], or pelvic exenteration [PE]), pathologic circumferential resection margin (CRM) (involved or not involved), and use of adjuvant chemotherapy.

2.4. Outcomes

The primary endpoints were overall and disease-free survival. Overall survival (OS) was calculated from the date of diagnosis until the date of death from any cause. Disease-free survival (DFS) was calculated from the date of diagnosis until the date of first recurrence (local or distant) or death from any cause. Patients were censored at the date of last contact when alive or at the date of event (recurrence or death).

Secondary endpoints included treatment-related outcomes.

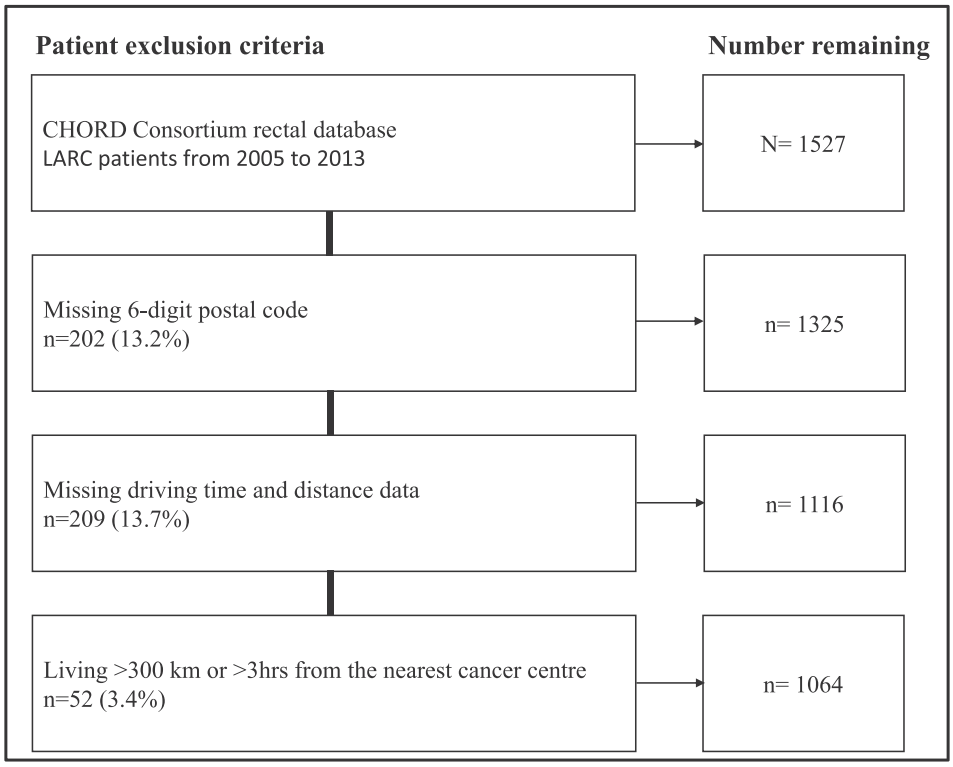

Fig. 1. Flow chart of study exclusion criteria from the CHORD database.

2.5. Statistical analysis

Descriptive statistical analysis was performed and tabulated as medians and interquartile ranges for continuous variables, and frequencies with percentages for categorical variables.

The Kaplan–Meier method was used to estimate OS and DFS. Univariate and multivariable Cox proportional hazard models were used to test for associations between patient characteristics and socioeconomic indicators with survival outcomes. Hazard ratios (HR) with 95% confidence intervals (CIs) were reported. The log-rank test was used to compare the survival distributions of two or more groups.

Proportional hazards assumptions were checked graphically and by Schoenfeld's residuals [40] for each variable individually prior to model fitting. Factors that show non-proportional hazards were set as strata.

When modeling continuous socioeconomic variables, linear effects on the log hazard were graphically explored using locally weighted scatterplot smoothing (LOWESS) of Martingale residuals. In case of non-linear effects, further investigation using categorization at cut-points, restricted cubic spline, piecewise regression, and visual assessment of plotted predicted hazard ratios from each approach were applied. By converting the continuous variables into categorical ones, we created clinically relevant risk groups.

For model building we started with all SES variables and the set of patient characteristics that showed significance at the 0.2 level in the univariate analysis. We reduced the model guided by a parameter estimate change of no greater than 15% and significance at the 0.05 (alpha) level in a process including deleting, refitting and verifying, to develop a model containing significant prognostic and confounding factors [41]. Difference in nested models were tested using the likelihood ratio test. Model performance was assessed by Akaike's information criterion and Bayesian information criterion.

Possible interactions were examined. Predictive performance and model fit for Cox proportional hazards models were estimated using Harrell's Concordance index (C). A value of 0.5 represents random prediction while a value of 1 represents perfect discrimination.

All analyses were done using Stata software version 15.0 (StataCorp, College Station, TX, USA). All statistical tests were 2-sided. A p-value <0.05 denoted statistical significance.

3. Results

3.1. Patient characteristics and socioeconomic indicators

In total, 1064 LARC patients were included. Median age was 62, 68% were male, and 82% had ECOG PS 0–1. Most lived in an urban

Table 1
Patient characteristics and socioeconomic indicators.

Characteristic N = 1,064	Result
Age years, median (IQR)	62 (53-70)
>65 years old	39%
Male	68%
ECOG PS 0-1	82%
Rural community	15%
Population density of community, median (IQR)	2,361/km^2 (766-4,042)
Community household income, median (IQR)	$40,064 CAD (32,224-47,648)
>$50,000 CAD	19%
Community proportion with post-secondary education, median (IQR)	66% (55–76)
Distance to the cancer centre, median (IQR)	15 km (8–42)
>100 km	12%
Driving time to the cancer centre, median (IQR)	20 min (13–39)
>1 h	18%

Abbreviations: IQR: interquartile range; ECOG PS: Eastern Cooperative Oncology Group Performance Status.

community, the median household community income was $40,064 CAD, 12% lived more than 100km from the cancer centre, and 18% lived more than 1 h from the cancer centre. Table 1 describes the clinical characteristics and community socioeconomic information of the cohort.

There was imperfect correlation between driving time >1 h and driving distance >100km. Of patients living <1 h from the cancer centre, 100% lived <100km driving distance away as well. Among all patients living >1 h from the cancer centre (n = 188), 30% lived <100km from the cancer centre and 70% lived >100km from the cancer centre.

3.2. Outcomes

The median follow-up time for the whole cohort was 72 months and the 5-year overall survival was 80%.

3.2.1. Treatment outcomes

Most patients (81%) completed neoadjuvant chemotherapy, and even more (94%) completed neoadjuvant radiation, while (81%) completed adjuvant chemotherapy. Overall, there was an 18% rate of pathologic complete response (Table 2).

3.2.2. Survival outcomes

The multivariate survival modelling started with predictors significant in univariate analysis at the 0.2 level including: age at diagnosis, ECOG PS, distance to the anal verge, type of surgery, radiotherapy dose and all socioeconomic factors. The proportional hazards assumption failed for variable indicators for province and adjuvant therapy so these were set as strata.

Distance to the nearest cancer centre, driving time to the nearest cancer centre, and community household income were found to have nonlinear effects on the log hazard function, so we utilized the following categorical predictors: distance greater vs. less than 100 km to the cancer centre, time greater vs. less than 1 h from the cancer centre, and community household income greater vs less than $50,000 CAD. Population density and community proportion with post-secondary education were utilized as continuous variables.

After adjustment for age at diagnosis and ECOG PS, in the final model (stratified by province and adjuvant chemotherapy use), driving time to the nearest cancer centre was the only SES factor significant for OS. No interaction term contributed to model performance. The OS model achieved goodness-of-fit with a Harrell's C concordance statistic of 0.61 (Table 3).

Predictors significant at the 0.2 level for DFS in univariate analysis included ECOG PS, distance to the anal verge, type of surgery and radiotherapy dose. Age at diagnosis, province, and adjuvant therapy failed the proportional hazards assumption and were set as strata. Socioeconomic factors used were: distance (greater vs less than 100 km to the cancer centre), time (greater vs less than 1 h to the cancer centre), community household income (greater vs less than $50 000 CAD), population density, proportion with post-secondary education, and population centre size.

Factors that remained significant in the multivariate analysis included only driving time >1 h to the nearest cancer centre. The discrimination ability of the DFS model using Harrell's C concordance statistic was 0.57 (Table 4).

Table 2

Outcome	Result
Median follow-up time, months	72.3 (95% CI 68.8–76.7)
5-year overall survival rate	80% (95% CI 77–82)
Completed neoadjuvant chemotherapy	81%
Completed neoadjuvant radiation	94%
Completed adjuvant chemotherapy	81%
CRM not involved	87%
Complete pathologic response	18%

Abbreviations: CRM: Circumferential resection margin.

Table 3
Predictors of overall survival.

Factors	Overall Survival					
	Univariate Analysis			Multivariate Analysis[a,b]		
	HR	95% CI	p-value	HR	95% CI	p-value
Distance >100 km	1.59	1.14-2.23	0.006			
Driving time >1 hr	1.57	1.17-2.10	0.003	1.60	1.19–2.16	0.002
Income >$50,000 CAD	0.62	0.43-0.89	0.009			
Population density	1.00	0.99–1.00	0.74			
% PSE	0.98	0.98-0.99	0.001			
Urban vs rural						
Rural	ref					
Small population centre	1.48	0.91-2.43	0.23			
Medium population centre	1.74	0.99-3.06				
Large population centre	1.31	0.89-1.94				

Abbreviations: Hr hour, PSE post-secondary education.
[a] Adjusted for Age, ECOG PS.
[b] Stratified by province, and adjuvant chemotherapy.

Table 4
Predictors of disease-free survival.

Factors	Disease-free Survival					
	Univariate Analysis			Multivariate Analysis[a,b]		
	HR	95% CI	p-value	HR	95% CI	p-value
Distance >100 km	1.16	1.09-1.96	0.01			
Time >1 hr	1.50	1.17-1.93	0.002	1.47	1.14–1.90	0.003
Income >$50,000 CAD	0.64	0.47-0.87	0.004			
Population density	1.00	0.99–1.00	0.56			
% PSE	0.99	0.98-0.99	0.01			
Urban vs rural						
Rural	ref					
Small population centre	1.13	0.76-1.67	0.61			
Medium population centre	1.26	0.79-2.01				
Large population centre	1.00	0.73-1.34				

Abbreviations: Hr hour, PSE post-secondary education.
[a] Adjusted for ECOG PS.
[b] Stratified by age, province, and adjuvant chemotherapy.

3.3. Exploratory analysis

In the exploratory analysis, patients living >1 h or >100km from the cancer centre were more likely to be diagnosed at a lower stage (stage II) compared to those living closer to the cancer centre. Living >1 h from the cancer centre was associated with an increased rate of the composite endpoint of local or distant recurrence, and living >100km from the cancer centre was associated with both distant recurrence and the composite endpoint of local or distant recurrence. There were no differences in the rates of completion of neoadjuvant radiation therapy or neoadjuvant chemotherapy among patients living ≤100km or ≤1 h from the cancer centre compared to their counterparts living further away (Table 5).

4. Discussion

In our retrospective analysis of consecutive patients seen for LARC receiving neoadjuvant chemoradiation and surgery at 3 tertiary

Table 5
Exploratory analysis.

	Distance from cancer centre			Time to cancer centre		
	≤100km	>100km	p-value	≤1hr	>1hr	p-value
Stage II at diagnosis	26%	38%	0.006	26%	34%	0.035
Local pelvic recurrence	8%	11%	0.28	8%	11%	0.11
Distant recurrence	21%	28%	0.03	24%	31%	0.08
Local or distant Recurrence	22%	31%	0.02	22%	31%	0.007
Completion of neoadjuvant chemotherapy	81%	79%	0.44	82%	79%	0.36
Completion of neoadjuvant radiation	94%	95%	0.91	94%	96%	0.23

Abbreviations: Hr hour.

Canadian cancer centres, we found that living more than 1 h driving time to the nearest cancer centre was associated with worse OS and DFS. Our exploratory analysis revealed that long driving time was associated with increased rates of recurrence but there was no association with completion of therapy. This suggests that other factors beyond completion of therapy may be contributing to increased recurrence and worse outcomes among patients living further away. Given that patients living further from the cancer centre had increased likelihood of being diagnosed with lower stage cancer (stage II as opposed to stage III), it is clear that stage distribution did not contribute to the worsened outcomes seen in patients living further from the cancer centre in our cohort. Other factors previously shown to be associated with reduced survival in patients with colorectal cancer that may have impacted our cohort include diet (more red meat and/or fat), reduced physical activity, increased BMI, smoking, and presence of co-morbid conditions [42]. It is possible that the prevalence of these risk factors differs by geography, which could explain the survival disparities of those living more remotely. Similarly, increased sitting time due to longer driving time may predispose to lower rates of physical activity or higher BMI, which are associated with lower colorectal cancer survival.

Our results are similar to those seen in a retrospective cohort analysis in Alberta which assessed the impact of driving time from the nearest specialist on outcomes in all stages of biliary cancer. In this analysis, it was shown that living more than 2 h from the nearest hepatobiliary surgeon and from the nearest cancer centre was associated with decreased survival, possibly because those living further away were less likely to receive chemotherapy. The inverse association of driving time and survival was especially pronounced among those receiving only best supportive care and those who received biliary drains [43]. Similarly, in Scotland, it has been shown that living further from the nearest cancer centre was associated with increased mortality in an assortment of malignancies. Parodoxically, it was also clear that patients living further from the cancer centre accessed referral and treatment faster than those living closer. Reasons for the paradoxical association of faster access with worsened outcomes among patients living further away are unclear, but may relate to more limited treatment choices once a diagnosis is made, or reduced engagement with post-treatment follow-up among patients with a long driving time [36]. It is also possible that patients living further from the cancer centre who experience treatment-related toxicities access closer emergency rooms with lesser experience in the management of cancer-related health problems. That said, this paradox may be location-specific, as patients living further from the nearest treatment centre in British Columbia, Canada had longer waits for oncologic consultation and resultant worsened outcomes [38]. Further evidence of the association between longer driving distance and worsened outcomes comes from Australia where it was shown that patients living more than 100km from the nearest radiotherapy facility were more likely to die from rectal cancer than those living within 50km of the nearest facility, and each 100km increment in distance was associated with a 6% increase in mortality. Similar to our results, these facts suggest that centralization of cancer care services may be a disservice to patients living remotely [21], as increased travel time to the cancer centre may be a barrier to follow-up and may reduce access to clinical trials [44]. In addition to worsened outcomes for patients living >1 h driving time from the cancer centre, previous research has also revealed increased healthcare costs and hospitalization rates (resource use) for older patients with cancer living more than 1 h driving time from a cancer centre in the United States [45].

Our results demonstrated worsened survival outcomes for patients living >1 h driving time from the cancer centre but not those living >100km driving distance. Reasons for this discrepancy are unknown, as increased driving time would generally be assumed to correlate with increased driving distance, resulting in similar outcomes. That said, in our analysis, while those living <1 h from the cancer centre all lived <100km driving distance, many who lived >1 h away also lived <100km from the cancer centre, potentially explaining the discrepancy. Other potential explanations include the possibility that traffic conditions, weather patterns, or the availability of public transportation diminished the impact of driving distance on outcomes in our cohort. Similarly, postal code areas may encompass a large diameter, so estimating patients' primary residence by postal code may have introduced some imprecision leading to the discrepant impact of driving time and distance on survival.

Aside from driving time to the nearest cancer centre, other individual SES factors analyzed in our cohort (rural status, community household income, community proportion with post-secondary education, population density) did not meaningfully influence survival in multivariate analysis. Interestingly, such factors have previously been shown to impact outcomes in a variety of cancer types and stages, in Canada and abroad [19–26,46–48]. For example, in an American retrospective cohort study in the early 2000s, it was seen that patients with rectal cancer living in suburban areas had increased odds of receiving radiotherapy, whereas having lower SES based on census tract was associated with reduced odds of receiving surgery; rural residents with colorectal cancer had an increased risk of dying, which was partially explained by treatment differences and fully explained by census-tract level SES [20]. Further, it has been shown that socioeconomic deprivation (deprivation in income, employment, health, education/training, housing and services, living environment, and crime) in England is associated with lower rates of surgical resection for rectal cancer as well as lower OS. These negative outcomes may be related to multiple associated factors including unhealthy lifestyles, increased smoking, worse dietary habits, lower levels of physical activity, higher levels of obesity, lower likelihood of attending screening opportunities, delay to referral for oncologic treatment, and reduced access to oncologic services, to name a few [24]. Regarding education and colorectal cancer outcomes, it was shown in a study of women that higher education (college or greater) was inversely associated with developing colon cancer. Similarly, higher neighbourhood SES was inversely related to developing rectal cancer. This suggests that behavioural differences related to SES may impact the risk of colorectal cancer [23]. In our cohort, we did not assess the risk of developing cancer, however this raises the possibility that behavioural differences related to SES may also impact the outcomes of rectal cancer treatment seen in our cohort.

The fact that we did not demonstrate an association between many of the individual SES factors analyzed and outcomes in rectal cancer suggests that there is a complex interplay between cancer type, stage, location of residence and socioeconomic factors This also highlights the importance of defining SES, which may be described differently in various studies. In our study, we defined SES using several individual variables, but it may be more accurate and descriptive to use an SES index encompassing a multitude of factors [48].

Strengths of our analysis include its large sample size and its multicentre population spanning several Canadian provinces. Limitations

include its retrospective nature and limited ability to generalize outside of our specific Canadian context. Traveling distance, time, and community SES factors were estimated from the centroid of patients' residential postal codes (which may have spanned a large area) and not their full address, rendering estimates of distance, time and SES descriptors less reliable.

In summary, patients living more than 1 h driving time from the nearest cancer centre experienced meaningfully worse OS and DFS from LARC treated with neoadjuvant chemoradiation and surgery despite similar treatment completion rates. Based on our results, future allocation of oncology resources and infrastructure should consider barriers to access. Travel time should be a consideration when choosing the location of facilities. Further efforts to understand and reduce socioeconomic disparities are warranted.

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Ethics approval

This study was approved by the Research Ethics Boards for all participating institutions. For all jurisdictions, informed consent was waived by the respective research ethics boards.

Competing interests

None.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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