SCIENTIFIC ARTICLE

Quality improvement in colorectal cancer care; marching towards homegrown data.

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Keywords: colorectal cancer, South Asia, Sri Lanka, quality improvement, data collection, survival.

Background

Colorectal cancer (CRC) is currently the 3rd commonest cancer and the 2nd commonest cause of cancer deaths globally (1). Low and middle-income earning countries have experienced a recent surge in the incidence of CRC while there is a drop in incidence in the west (2)(3)(4). Sri Lanka has seen a steady increase in the incidence of CRC over the last two decades and it is currently the 3rd commonest cancer amongst Sri Lankans of both sexes (5). Currently 1.9 million new CRCs are diagnosed annually worldwide which is expected to increase up to 3.2 million new cases and 1.6 million deaths per year (6). The management of CRC has evolved significantly during the last century from a disease with almost 100% mortality in the early 20th century to a disease treated with curative intent for stage IV in the 21st century.

There is ample data on survival predictors and surgical quality parameters in colorectal cancer that were generated in the western populations (7–9). The human developmental index, genetics, social and environmental factors play a significant role in survival and the quality of surgical care (10–13). Therefore, direct application of available evidence on local populations is debatable. Hence there is a need for locally adopted data. Data on survival from CRC in Sri Lanka is scars owing to the absence of a national programme forprospective data collection (14). Several authors have highlighted the he lack of survival data and the possible inaccuracies of the existing incidence data in the Sri Lankan cancer registry (15). (14)

The North Colombo CRC database was established in the year 1995. Prospective data collection was done on all patients undergoing curative resections for CRC. The prospective data collection was initiated with printed proforma and has currently developed to a point of care real time data entry into a cloud based data storage using the RedCap platform.

This oration presents the attempts of the North Colombo University Unit to develop locally applicable evidence in the improvement of patient care. Whilst each of the studies is presented and analysed separately, the discussion will focus on the value of data from Sri Lankan patients, including the ability to compare our results with international studies and will focus on the value of scientifically informed adoption of clinical treatment pathways for CRC in Sri Lankan patients.

Methodology

Data is extracted from the North Colombo CRC database, from patients who underwent surgery with curative intent for CRC. Preoperative work up and management was standardized by protocol described in detail elsewhere (16). Neoadjuvant chemoradiotherapy (NCRT) was adopted for rectal cancers from the early 2000s and principles of enhanced recovery have been gradually incorporated to be a standard protocol. The same team at the university units performed surgery and histopathological assessment of the specimens. All postoperative complications were recorded and updated up to 30 days and at subsequent clinic visits. Anastomotic leakage was diagnosed with clinical evidence of intra-abdominal sepsis and ultrasound or CT evidence of intra peritoneal fluid.

Post operative surveillance is carried out with clinical examination coupled with carcino-embryonic antigen (CEA) levels three monthly for the first 2 years and biannually for 3 years. A colonoscopy and computer tomographic evaluation of the abdomen and pelvis at 1, 3 and 5 years post operative is undertaken.

Four areas pertaining to CRC management were assessed throughout this period. Namely, development of a locally feasible prognostic marker, response of the local population to NCRT, optimal nodal harvest in the local population with a survival advantage and improvement in patient outcomes over time.

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https://orcid.org/0000-0002-3485-961X
Received: 15-11-2023 Accepted: 29-11-2023
DOI: http://doi.org/10.4038/sljs.v41i03.9099

The ethics review committee at the University of Kelaniya medical school, Sri Lanka, approved the data base maintenance.

In selecting a cut-off value for serum preoperative albumin and optimum nodal harvest, serial increments were used instead of arbitrary values. Serially ascending values of 5 g/L of serum albumin were compared to define a finite cut-off value while serially ascending values of lymph nodes starting from a minimum of 5 were used. (17,18). Survival analysis was performed using Kaplan Meier curves whileKaplan-Meier analysis and Cox proportional hazard model were used for univariable analysis of confounding factors. For the significant confounders identified in the cohort for serum albumin, a type III analysis with a Weibull hazard model and two-way interaction terms were used for multifactorial analysis while Cox-proportional hazard model was used for the group for optimum nodal harvest. Patients with both stage II and III with a minimum of 3 year follow up were included in the lymph node harvest analysis to mnimise biases.

Only patients with mid and lower rectal cancer receiving NCRT were analysed to assess tumour response and its implications for survival (16). NCRT regime comprised radiotherapy (5040 cGy) to the true pelvis, which was delivered in 25 fractions combined with cyclical 5-fluorouracil. Patients underwent low or extended low anterior resection with TME of rectal cancer, abdomino perineal excision (APR), transanal resection of residual tumour at a median of 10 weeks (range 8–11 weeks) post NCR. Tumour regression grading (TRG) was done as described by Mandard et al. TRG 1 was a complete response with the absence of residual cancer and fibrosis extending through the wall; TRG 2 was the presence of residual tumour cells scattered through the fibrosis; TRG 3 was an increase in the number of residual cancer cells compared with TRG 1, in which fibrosis was predominant; TRG 4 was residual cancer outgrowing fibrosis and TRG 5 was the absence of regressive changes. Degree of TRG was grouped into subgroups; good regression – TRG 1 + 2; moderate regression – TRG 3; no regression – TRG 4 + 5, for the ease of analysis.

For survival assessment across time periods, Kaplan-Meir survival curves were used to compare survival pre and post 2010. The year 2010 was considered as a half-way point for the survival analysis as the authors believe it is an appropriate time point to mark the improvement in technical and adjunct treatment in the management of CRC. Also this enabled sufficient patient numbers for comparison in each group with

Table 1. Survival comparison using Kaplan-Meier method for serially ascending serum albumin levels. Reproduced from Chandrasinghe et al. 2013 (17)

Serum albumin level	5 year survival rates	P value
<20 g/LVS. ≥20 g/L	90% VS. 60%	0.44
<25 g/LVS. ≥2 g/L	90% VS. 59%	0.10
<30 g/LVS. ≥30 g/L	43% VS. 63%	0.04*
<35 g/LVS. ≥35 g/L	49% VS. 69%	0.02*
<40 g/LVS. ≥40 g/L	58% VS. 62%	0.48
<45 g/LVS. ≥45 g/L	58% VS. 73%	0.17

* - significant value.

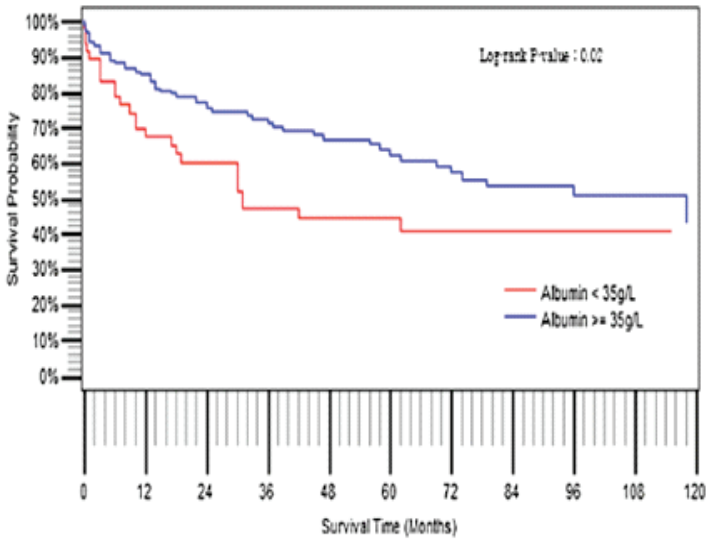

Figure 1. Kaplan-Meire survival curves for rectal cancer based on serum albumin level. . Reproduced from Chandrasinghe et al. 2013 (17)

Table 2. Percentage of each category of regression grade in rectal cancers receiving NCRT. Reproduced from Deen et al. 2023 (16)

Regression grade	Percentage
TRG 1	43.1% (Good)
TRG 2	12.7% (Good)
TRG 3	22.6% (Moderate)
TRG 4+5	21.6% (Poor)
Good vs. Moderate vs. Poor - Chi-Square=2.58; DF=2; P=0.28	

an adequate follow-up period to evaluate long-term survival.

Results

Preoperative albumin as a prognostic marker

A total of 226 (male - 123 (54%) and female – 103) patients were studied (median age – 59 years; range 19-88, median follow up 36; range 10-160). 35 g/L was the cut-off serum albumin value at which most significant differences in survival emerged (Table 1). Forty-five patients (20%) of this cohort had hypoalbuminaemia (serum albumin < 3.5 g/L) according to this cutoff. Preoperative serum albumin of less than 35 g/L was associated with a significantly poor overall survivals following surgery for rectal cancer. (P = 0.02; Figure 1).

Five-year overall survival rates between normo and hypoalbuminaemia groups were 69% versus 47%. The five-year disease free survival rate in the hypoalbuminaemia group was 69.7% compared to 83% in the normoalbuminaemia group (P = 0.02). Age, positive circumferential margin, peri-neural invasion, angio-invasion, lympho-vascular invasion, and advanced AJCC stage emerged as confounders in a univariable analysis while multi factorial model type III analysis of effects revealed that hypoalbuminaemia (P = 0.002), a positive circumferential margin (P = 0.002), and AJCC stages III and IV compared with I and II (P = 0.003), were significant. Two-way interaction terms between the said factors using Weibull hazard model confirmed those factors to be independent risk factors for poor survival in rectal cancer.

Tumour response to neoadjuvant chemoradiotherapy and its effect on survival patterns in rectal cancer

Studying 153 patients with low or mid rectal cancer who received NCRT for locally advanced rectal carcinoma TRG 1 or TRG 2 was reported in 58.5% of the specimens. In total, 78.4% of patients showed tumour regression (TRG 1 - TRG 3) compared to 21.6% with either minimal or no tumour regression (TRG 4 + 5) (16) .A median pathological tumour stage (T) of 2 was observed in good TRG, whereas poor TRG was associated with a median pathological T stage of 3 (Chi-square 16.6; DF = 2; P = 0.0002). Percentage response to NCRT was comparable between good (TRG 1 + 2), moderate (TRG 3) and poor (TRG 4 + 5) - (Chi-Square = 2.58; DF = 2; P = 0.28, Table 2). In all, 131 (79 male, 52 female; median age 57, interquartile range 47–62 years) patients who underwent low or ultra-low anterior resection of the rectum post-NCRT; 4 (3%) developed anastomotic leaks. Median follow-up at the time of analysis was 15 months (interquartile range 6–45 months).

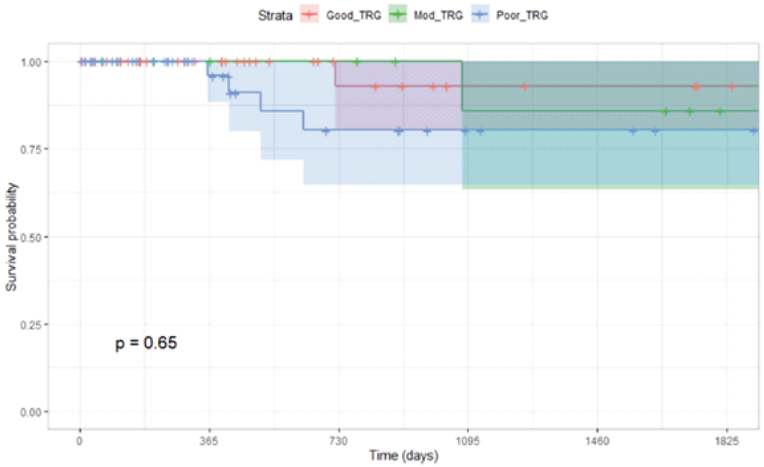

Figure 2. Local recurrence free survival of rectal cancers based on tumour regression. Reproduced from Deen et al 2023 (16)

Local recurrence rate was 6.8% (9 of 131) and there was no significant difference in overall survival (Figure 2) or disease-free survival related to TRG. The 5-year disease-free survival rates for good, moderate and poor TRG did not differ significantly either (65%, 83% and 67% ; Chi-square − 0.01; DF – 2; P = 0.99).

Optimum lymph node harvest from colorectal cancer specimens based on survival advantage

Out of a total of 131 patients (male – 56%, colon-55, rectal – 76, mean follow-up - 4.1 years; SD- 3.4), 61 had stage II and 70 had stage III cancer. The most significant survival benefit was seen with 14 or more nodes for both colon and rectal cancers (Table 3). For the total population of stages II and III CRCs, the maximum survival benefit was observed with 14 or more nodes (Figure 3). When stages II and III cancers were separately analysed, a similar observation was made (stage II, p= 0.07; stage III, p=0.03).

Lower risk of death (Hazard ratio - 0.37, 95 % CI, 0.18–0.77; p=0.007) was observed when more than 14 lymph nodes harvested. Advanced age, male sex, LVI, and preoperative CEA levels were the other significant factors associated with survival in an initial multivariable analysis. The lymph node yield remained significant with a hazard ratio of 0.19 (95 % CI, 0.066–0.593; p=0.004) after adjusting for the above mentioned factors using multiple regression analysis with stepwise selection

A significantly lower lymph node yield was observed in those who had NCRT (NCRT- 8; range, 5–20 vs. no-NCRT- 11; range, 5–45; p=0.0128) (Table 4). Analysing the patients

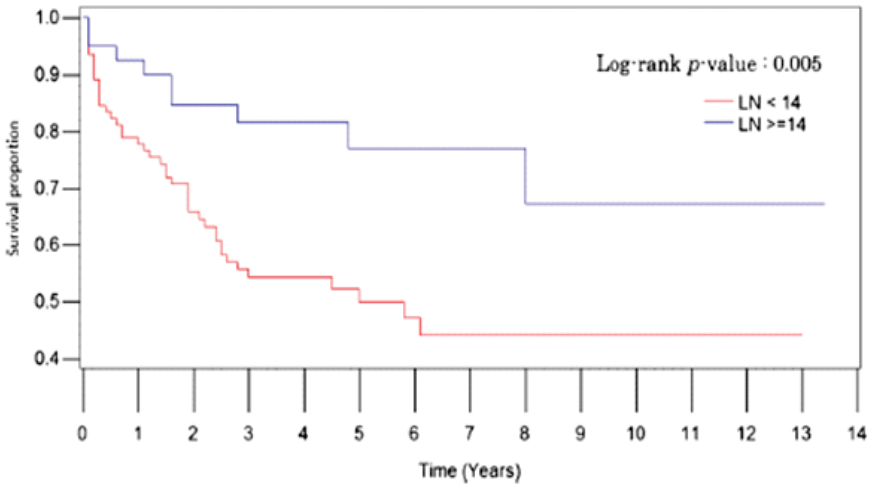

Figure 3. Kaplan-Miere curves for colorectal cancers based on lymph nodes harvested. Reproduced from Chandrasinghe et al 2014 (18)

Table 3. Overall survival comparison in colon and rectal cancers based on ascending numbers of lymph nodes harvested from specimens. Reproduced from Chandrasinghe et al 2014 (18)

Lymph node groups	Rectal cancer; mean survival (SE) in years	*p*-value	Colon cancer; mean survival (SE) in years	*p*-value
<6 vs. ≥6	4.0 (1.38) and 3.4 (0.28)	0.759	1.9 (0.35) and 6.5 (0.44)	0.356
<7 vs. ≥7	3.7 (0.77) and 3.4 (0.30)	0.729	1.4 (0.53) and 6.6 (0.44)	0.125
<8 vs. ≥8	3.2 (0.56) and 3.6 (0.32)	0.445	1.6 (0.33) and 6.5 (0.48)	0.580
<9 vs. ≥9	3.6 (0.48) and 3.5 (0.35)	0.988	1.6 (0.22) and 6.6 (0.47)	0.505
<10 vs. ≥10	3.4 (0.44) and 3.6 (0.37)	0.628	2.2 (0.27) and 6.9 (0.46)	0.103
<11 vs. ≥11	3.3 (0.40) and 3.8 (0.39)	0.295	2.3 (0.22) and 6.8 (0.51)	0.426
<12 vs. ≥12	3.1 (0.36) and 4.3 (0.43)	0.050	3.8 (0.43) and 7.2 (0.42)	0.091
<13 vs. ≥13	3.2 (0.35) and 3.7 (0.36)	0.033	4.0 (0.35) and 7.0 (0.60)	0.093
<14 vs. ≥14	3.2 (0.34) and 3.7 (0.38)	0.032	3.9 (0.33) and 7.5 (0.59)	0.085
<15 vs. ≥15	3.4 (0.32) and 3.6 (0.46)	0.230	3.9 (0.33) and 7.5 (0.59)	0.085
<16 vs. ≥16	3.5 (0.31) and 3.6 (0.52)	0.340	4.0 (0.31) and 7.4 (0.67)	0.128
<17 vs. ≥17	3.5 (0.32) and 3.5 (0.52)	0.340	4.1 (0.29) and 7.3 (0.85)	0.331
<18 vs. ≥18	3.6 (0.77) and 3.3 (0.30)	0.344	4.2 (0.26) and 6.9 (1.30)	0.856

receiving NCRT in the same patient population, the median number of lymph nodes harvested in patients with a good and moderate regression (TRG 1 + 2 + 3) was 6 compared to a median of 8 in the poor regression (TRG 4 + 5) group (16).

Change in survival patterns in patients with CRC over time

In the pre – 2010 time period, there were 276 (65%) rectal cancer and 149 (35%) colon cancer (right colon – 68, left colon – 81) compared with 165 (57%) rectal cancers and 124 (43%) colon cancer s(right colon – 49, left colon – 76) in the post-2010 group.

Post-2010 period demonstrated a significantly better overall survival compared to pre-2010 (X2= 12.1; DF=1; P<0.001). There is also a significantly better disease free survival (DFS) (X2= 19; DF=1; P<0.0001) and overall survival (OS) (X2= 19.1; DF=1; P<0.001) in patients with rectal cancer in the post 2010 period compared to pre-2010. Both DFS (X2= 1.8; DF=1; P=0.2) and OS (X2= 0.1; DF=1; P=0.8) were comparable for colon cancers in the two time periods (Table 5).

Discussion

CRC. This was the first study to report preoperative serum albumin level as a marker of long-term outcome in rectal cancer (19) and has been later supported by evidence from other investigators (20–22). Toyiyama and colleagues have shown that stage II CRC with a low albumin level or a higher CRP faired worse and suggest that stage II CRC with a low GPI to be considered for adjuvant chemotherapy despite of the TNM stage (23). The importance of albumin in the local setting is that it is easily accessible at an affordable cost. More complex inflammatory markers of prognosis may be available with the limitation of cost and accessibility in a resource poor setting.

Although NCRT for rectal cancers has a clear benefit in DFS the response of the tumors to such treatment varies depending on many factors. Pathologists have developed various grading systems to classify the tumour response (24) and there is conflicting data on the variability of long-term outcome for different regression grades (25–27). The pattern of TRG has not been published previously for a Sri Lankan population and is important as a country with limited access to radiation treatment (28). Also the study reveals our local recurrence rates for low and mid rectal cancers to be 6.8%, which is comparable to global benchmarks (29–31). In an era where complete responders can be offered organ preservation, further studies on tumour regression patterns is of high importance.

The indirect benefit of nodal assessment on survival may be observed due to accurate staging of the disease. Nodal harvest from CRC specimens is a team work between the surgeon and the pathologist. Sound surgical technique to include maximal mesentery in the specimen coupled with dissection techniques to increase nodal harvest (24,25). A previous study by Siriwardene et al on the same patient population has demonstrated pro-forma based reporting to enhance the reporting standards (26). Description of a cutoff value for local population is important in developing local management guidelines in the future for CRC. Furthermore, this analysis elaborates on the effect of NCRT for a reduced nodal harvest. This effect was previously demonstrated for the first time in a local population by Wijesuriya et al (27). It will be necessary to adopt cost effective techniques such as pre-operative tattooing to increase the nodal harvest in this patient group (28,29).

Understanding the survival pattern of the local population is pertinent for deciding the future direction of the particular surgical service. A a long term outcome analysis of the local CRC population with prospectively collected data allows us to assess the quality of the care provided and compare with standards. The overall survival in CRC for this local population is 68%, which is comparable to that of the United States according to the National Cancer Institute data (30). Further the study provides evidence to the improvement in survival in rectal cancer patients probably owing to the continuous improvement preoperative imaging, neo-adjuvant treatment and perioperative care as opposed to colon cancer. This phenomenon has been observed in other populations as well (31). Hemminki and colleagues analyzing data of 5

Table 4. Effect of NCRT on median nodal harvest in CRC. Reproduced from Chandrasinghe et al 2014 (18)

	No NCRT	NCRT	
LN<14 (*n*)	73	18	Total=91
LN>14 (*n*)	38	02	Total=40
Median nodal harvest (range)	11 (5–45)	8 (5–20)	*p*=0.0128

NCRT neoadjuvant chemoradiation

Table 5. The overall survival from rectal and colon cancers in the pre and post 2010 time periods

	CRC population		**Rectal cancer**		**Colon cancer**	
Time	<2010	>2010	<2010	>2010	<2010	>2010
5-year OS	59%	68%	54%	69%	70%	69%

decades from a Finnish population suggest that the improvement in survival in rectal cancers can be attributed to a large number of small improvements and not a single breakthrough (31).

Future challenges and the way forward

Sri Lanka will also face few challenges in managing CRC in the near future. Several of these aspects have been looked into at North Colombo using our cohort. The global pandemic of young and early onset colorectal cancers (EOCRC) may have been an established phenomenon in the local setting. A 20% EOCRC and a 16% young cancer rate is observed in the North Colombo cohort (32,33). An aging population is another challenge that the developing is faced with. Due to this an increasing number of CRC in the elderly population is seen with unique challenges in management. The north Colombo cohort has demonstrated that the chronological perse is not a predictor of poor outcome form surgery for CRC (34,35)Application of novel technologies is also challenging in this region die to the scarcity of resources and may need to be adapted to make them feasible in the local setting (35)

The most important perspective provided by these studies is the significance of maintaining prospective data. In a setting such as Sri Lanka where a centralized data collection and storage is lacking, the point of first contact is the best opportunity to capture individual patient data. While the national Cancer Control Programme maintained registries provides national data, the accuracy of the data collection sources is questionable. This is evident by the discrepancies in the CRC incidence by around 33% in the year 2017 provided by the same institute in the National Cancer registry and the Pathology based Cancer register (36,37). The North Colombo CRC database is now maintained as a cloud based electronic database. The infrastructure to manage online databases is present in Sri Lanka and several authors have demonstrated how prospective data could elaborate the landscape of patient care for better decision making (38,39). All units managing CRC should be encouraged to maintain updated data, which can be collaborated, in large multicenter studies to develop homegrown data. It is also an appropriate time to consider regional data hubs to collect data from the South Asian region which homes close to a 25% of the global population at present.

This is a synopsis of the SAARC oration 2023 delivered at the Sri Lanka Surgical congress 2023.

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